A role for partial epithelial-to-mesenchymal transition in enabling stemness in homeostasis and cancer

Jeroen Verstappe[1,2] and Geert Berx[1,2*]

[1]Molecular and Cellular Oncology Laboratory, Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium

[2] Cancer Research Institute Ghent (CRIG), Ghent, Belgium

*Corresponding Author contact information:

Prof. Dr. Geert Berx

Molecular and Cellular Oncology Laboratory, Ghent University

Technologiepark 71, 9052 Ghent , Belgium

Tel: +32.9.3313650

Email: geert.berx@ugent.be

Abstract

Stem cells have self-renewal capacities and the ability to give rise to differentiated cells thereby sustaining tissues during homeostasis and injury. This structural hierarchy extends to tumours which harbor stem-like cells deemed cancer stem cells that propagate the tumour and drive metastasis and relapse. The process of epithelial-to-mesenchymal transition (EMT), which plays an important role in development and cancer cell migration, was shown to be correlated with stemness in both homeostasis and cancer indicating that stemness can be acquired and is not necessarily an intrinsic trait. Nowadays it is experimentally proven that the activation of an EMT program does not necessarily drive cells towards a fully mesenchymal phenotype but rather to hybrid E/M states. This review offers the latest advances in connecting the EMT status and stem-cell state of both non-transformed and cancer cells. Recent literature clearly shows that hybrid EMT states have a higher probability of acquiring stem cell traits. The position of a cell along the EMT-axis which coincides with a stem cell-like state is known as the stemness window. We show how the original EMT-state of a cell dictates the EMT/MET inducing programmes required to reach stemness. Lastly we present the mechanism of stemness regulation and the regulatory feedback loops which position cells at a certain EMT state along the EMT axis.

Abbreviations

EMT, epithelial-to-mesenchymal transition; MET, mesenchymal-to-epithelial transition; EMP, epithelial-mesenchymal plasticity; EMT-TFs, EMT transcription factors; CSC, cancer stem cell; MaSC, mammary stem cell; iPSC, induced pluripotent stem cell; ESC, embryonic stem cell; TIC, tumour initiation capacity; MEF, mouse embryonic fibroblast; scRNAseq, single cell RNA sequencing; IFE, interfollicular epidermis; HF, hair follicle; NSCLC, non-small cell lung cancer; CTC, circulating tumour cell; CRC, colorectal cancer

Keywords

Epithelial-to-mesenchymal transition, hybrid EMT, cancer stem cells, adult stem cells, EMT-TF

Conflict of interest

The authors declare no conflicts of interest.

1. Introduction

Epithelial cells form the main lining between tissues and function as a protective barrier against microorganisms, mechanical stress, ultraviolet radiation, among others. These protective functions require tight layers of cells with little intracellular space which is mediated by several transmembrane cell-adhesion complexes including tight junctions, adherens junctions and desmosomes. However, several embryonic processes such as gastrulation, formation of the heart and neural crest delamination require cell migration and consequently, the loss of these transmembrane cell-adhesion complexes [1]. It was observed that the loss of cell-adhesion complexes and other epithelial hallmarks was coupled with the upregulation of several genes facilitating migration commonly expressed by mesenchymal cell types. This was deemed as an epithelial-to-mesenchymal transition (EMT) and has since been found to contribute to several other processes including wound healing, fibrosis [2], and cancer [1,3,4]. Early studies on the regulatory mechanism revealed that the transcription factor SNAI1 could directly bind to the E-cadherin promoter to repress its transcription [5,6]. Since then, next to SNAI1, a set of core transcription factors consisting of ZEB2 [7], ZEB1 [8], SNAI2 [9,10], TWIST1 [11] and E47 [12] have been identified as the main drivers of transcriptional programming during EMT. While many EMT processes in both embryogenesis, homeostasis and cancer employ these master regulators, several other EMT-inducing TFs have been added to this list including KLF8 [13], FOXC2 [14,15], HMGA2 [16], PRRX1 [17], Goosecoid [18] and brachyury [19]. EMT grants cells migratory capacities yet its reverse process, deemed mesenchymal-to-epithelial transition (MET), is required for cell differentiation during embryology or metastatic colonisation during cancer progression. Similar to EMT-inducing TFs, several epithelial gatekeepers have also been identified such as OVOL1/2 [20] and GRHL2 [21–23] which directly target *Vim*, *Snai2*, *Cdh1* and *Zeb1* and drive MET. Although a substantial portion of EMT-related literature focusses on these transcriptional networks, EMT is also regulated by post-translational modifications [24], miRNAs [25], long non-coding RNAs , post-transcriptional modifications [26], epigenetic regulators [27] and alternative splicing [28]. These regulatory levels do not function as separate agents but form a highly interconnected network to achieve these highly plastic cell states.

Up until recently, EMT was seen as an “all or nothing” process where cells either exist in an epithelial state or a mesenchymal state. However novel insights have shown that EMT does not necessarily present as a binary switch between two extremes yet can render cells a partial or hybrid phenotype that simultaneously hold epithelial and mesenchymal characteristics. This new concept, recently defined as epithelial-mesenchymal plasticity (EMP), grants cancer cells a higher adaptive potential depending on microenvironmental cues [29,30]. The acquisition of this high adaptive potential is strongly intertwined

with stem cell and cancer stem cell characteristics. Cancer stem cells (CSC) are thought to be a rare population of cells within the tumours that, just like normal stem cells, have self-renewal and differentiation capacity. It has been shown that these cells, but not the bulk of the tumour, have the capacity to regenerate the original tumour upon dissemination or transplantation [31,32]. Accumulating evidence demonstrates that the property of stemness in CSC can be acquired via EMP programmes and is thus not necessarily an intrinsic property [33]. The EMT-stemness interplay is not limited to cancer as adult stem cells in several tissues also display activation of an EMT/EMP-like programme.

In this review, we discuss EMP programmes within embryonic stem cells, adult stem cells and cancer stem cells. We will further discuss how stemness and EMP are regulated by separate modules that form a highly intertwined network connecting both regulatory circuits. In this review, we will use the term EMT when we discuss a progression towards a more mesenchymal state while the term MET will be used for the opposite process. EMP will be used to refer to the combination of EMT and MET programmes where cells can readily switch between cell states. The characteristic of stemness will be used in this review for both cancer cells and their non-pathological counterparts to describe their cell state. It will be used as a relative property to compare cell states with each other in which the degree of stemness is determined by their tissue or tumour reconstitution capacities and spheroid/organoid/colony forming capacities.

2. Stem cells

2.1. Reprogramming to iPSCs requires MET

Stem cells are functionally defined by two key characteristics; the ability for self-renewal and the ability to give rise to more differentiated progeny. In general, stem cells are subdivided in embryonic stem cells (ES) and adult stem cells. Embryonic stem cells (ESC) are pluripotent cells that make up the inner cell mass of blastocysts and have the potential to differentiate to the three primary germ layers: endoderm, ectoderm, and mesoderm. Using the transcription factors Oct-4, Klf4, C-Myc and Sox2 (OKMS), normal murine or human fibroblasts can be reprogrammed towards a pluripotent state called induced pluripotent stem cells (iPSC) which hold the same differentiation potential as ESC [34]. Although in many cases, EMT programmes drive stem cell properties as will be discussed later, the reprogramming of these mesenchymal fibroblasts towards iPSCs requires MET [35]. The ESC factors Oct-4, Sox2 and C-Myc induce MET through inhibition of the TGFβ-Snail axis whereas Klf4 drives expression of epithelial markers (Fig. *1*). MET induction is required during the early phase of reprogramming and can be enhanced by BMP signalling which was shown to attenuate Snail, Slug, Zeb1 and Zeb2 and conversely upregulate miR200a/b and miR205 [36]. Interestingly, a follow-up study found that sequential activation of Oct4/Klf4, C-Myc and Sox2 (OK+M+S) yielded a 600% higher iPSC formation efficiency as opposed to simultaneous expression

(OKMS) [37]. Surprisingly, this was coupled with a transient increase in *Slug* expression and decrease of *Cdh1*. These results showed that although MET is required for fibroblast reprogramming, a short EMT pulse significantly enhanced this process. Similarly, reprogramming of male germ stem cells, neural reprogramming of MEFs or C/EBPα mediated iPSC reprogramming from B-cells also required a sequential EMT-MET [38–40]. Conversely, inducing EMT via c-Jun blocked reprogramming and differentiates ESC towards the endoderm lineage [41].

As was mentioned earlier, ESC and iPSC can differentiate towards the three germ layers. Interestingly, ESC cells differentiating towards definitive ectoderm were shown to re-activate EMT marked by downregulation of CDH1 [42,43]. This was confirmed in a recent study where iPSCs were differentiated towards hepatocytes. Cells will undergo an EMT programme to form definitive ectoderm followed by hepatoblast differentiation upon which MET is required for terminal differentiation towards hepatocytes (Fig. 1) [44].

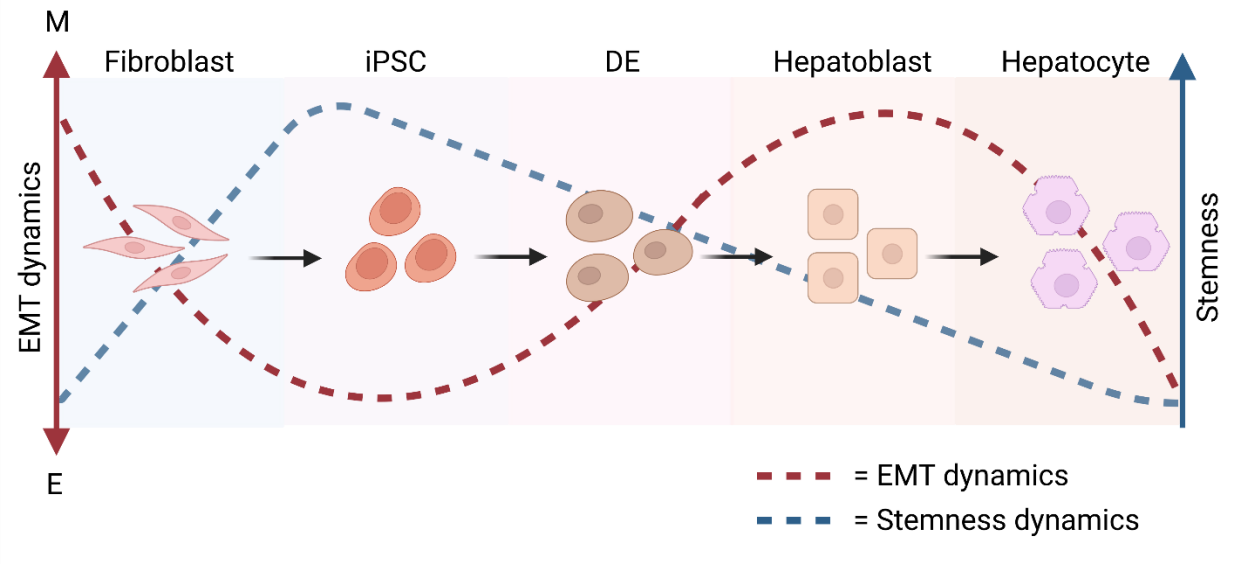

Fig. 1: Reprogramming of fibroblasts to iPSCs and differentiation towards hepatocytes requires alternating EMT-MET cycles. Reprogramming of normal fibroblasts towards induced pluripotent stem cells (iPSC) requires an MET programme. This process can be accelerated via a short EMT activation followed by MET. Differentiation of iPSCs towards hepatoblasts via definitive ectoderm (DE) reactivates EMT programmes which are again inhibited upon differentiation from hepatoblasts towards hepatocytes. This figure was created using Bio-render (https://biorender.com).

2.2. Mammary gland

In contrast to iPSC or ESC, adult stem cells only give rise to a small subset of differentiated cell types within one organ. They are multipotent and maintain cell turnover in tissues during homeostasis or injury. As they replenish tissues, they are identified based on tissue regeneration capacity after *in vivo* transplantation in immunocompromised mice or *in vitro* spheroid and organoid forming assays. Early stem

cell research in epithelial tissues was mainly performed on mammary glands which comprises ducts and alveoli and consist of a bilayered epithelium with a luminal inner layer and basal myoepithelial outer layer. The gold standard for identification of mammary stem cells (MaSCs) is their ability to reconstitute the mammary gland in cleared fat pads upon transplantation [45,46].

In the murine mammary gland, these MaSCs were identified as either Sca1+ [47], Cd49f^{high}Cd24^{med} [48–50], Cd29^{high}Cd24+ [49,51] or Cd49f^{high}Cd61+ [52]. All of these populations were shown to be enriched for basal markers (Krt14, Krt5) whereas luminal markers (Krt8, Krt18) were absent indicating that basal cells contain the bipotent cells responsible for mammary gland homeostasis and reside in a more undifferentiated state than luminal cells. Similar observations were made for human mammary gland cells where MaSCs were enriched via CD44+CD24- [53], CD49f^{high}EPCAM- [54] or ALDH+ [55].

The first association between normal stem cells and EMT was in murine Cd49f^{high}Cd24^{med} MaSCs which were shown to be enriched for N-cadherin and vimentin and attenuated for E-cadherin expression. This appeared to be mainly driven by Slug and to a lesser extent Twist1 [50,56]. Indeed, using a Slug promoter-YFP reporter construct, it was shown that Cd49^{high}Cd61+ MaSCs were Slug^{high} and that transient Slug expression in luminal progenitors but not differentiated luminal cells allowed organoid generation *in vitro* [52]. The crucial role of Slug in mammary gland morphogenesis and maintenance of the basal cell phenotype was underlined by several other studies [57,58]. Although Slug expression in differentiated luminal cells could not induce organoid forming MaSCs, transient co-expression of Slug and Sox9 was sufficient to reprogram differentiated luminal cells towards the MaSC phenotype which could reconstitute cleared mammary fat pads [52]. Initially, it was observed that Snail could replace Slug to induce MaSCs [52]. However, using *Snai1* or *Snai2-YFP* knockin mice demonstrated that only Slug was expressed in MaSCs and that Slug but not Snail was indispensable for *in vitro* organoid or *in vivo* gland forming capacities of MaSCs [59]. Nevertheless, Snail does seems to play a role in MaSC self-renewal by favouring symmetric cell division [60].

Despite initial reports showing that Zeb1 was either expressed by both luminal and basal MECs [57] or only in stromal fibroblasts but not in MECs [59], a CD29^{high}CD24+ subpopulation of Procr+ cells showed significant enrichment for *Zeb1* and other EMT-markers (*Zeb2*, *Vim*, *Cdh2*) [61]. Interestingly, in human single cell RNA sequencing (scRNAseq) data, high *ZEB1* levels were found in CD49f^{high}EPCAM- cells which showed strong overlap with the previously described Procr+ cluster [62] whereas murine scRNAseq data showed that only 15% of Zeb1^{high} basal MECS co-expressed *Procr* [63]. In basal MECs, Zeb1 functions as a gatekeeper for basal cell identity by maintaining a quiescent G0 state and steering self-renewal [63]. In

human MECs, ZEB1 also protects against oxidative stress via direct transcriptional activation of MSRB3 in MaSCs [64].

Although basal cells are bipotent upon isolation, lineage tracing demonstrated that during physiological conditions luminal and basal compartments are maintained by separate luminal and basal progenitors [65]. In contrast to the above-mentioned studies, MECs with increased aldehyde dehydrogenase activity (ALDH+), which were enriched in CD49f^{high}EPCAM^{high} luminal progenitor cells, were also enriched for MaSCs [55,66]. These cells show little overlap with the CD44+CD24- basal population, however, a population of CD44+CD24-ALDH+, which shows an intermediate EMT phenotype, displayed higher mammosphere forming capacity [67]. Adding to this, deletion of the epithelial gatekeeper *Ovol2* in Krt14+ basal cells impaired mammary gland morphogenesis during puberty [68]. Since Ovol2 reciprocally regulates Zeb1, a delicate balance between epithelial and mesenchymal programs seems to be necessary for proper MaSC function and consequently proper mammary gland morphogenesis [69]. This balance was further underlined by the observation that transient TWIST1 expression in CD24^{high} mammary epithelial cells markedly increased mammosphere capacity whereas constitutive TWIST1 expression did not form spheres [70].

2.3. *Skin*

Apart from its role in mammary gland stemness, Slug is also expressed by basal (Krt14+) cells from the interfollicular epidermis (IFE) and the hair placode during hair follicle development [71]. Similarly, in the human epidermis, SLUG was confined to the basal layer of the IFE and represses differentiation [72]. Although Snai1 has not been shown to be expressed by IFE or HF SCs, Krt14-driven Snail expression in the skin resulted in a higher number of Cd34+ keratinocytes reflected with a higher colony forming capacity than the Cd34+ cells from wild-type mice [73]. Also Twist1 seems to play a role in stem cell maintenance within the mouse epidermis since deletion of *Twist1* caused a decrease in Cd49f+Cd34+ hair follicle stem cells [74]. Moreover, these HF SCs expressed the early EMT marker tenascin C (TNC) [75] suggesting a partial EMT within these HF SCs [76]. Conversely, an *Ovol1/2* double knockout in Krt14+ IFE cells showed an expansion of the stem cell compartment which was accompanied by the induction of EMT [20].

2.4. *Prostate*

The prostate is a pseudostratified epithelium comprising secretory luminal, basal, and neuroendocrine cells. Originally, prostate stem cells were identified at the proximal region within the p63+ basal layer and marked as Sca1+Cd49f+Trop2+ or Sca1+Cd133+Cd44+Cd117+ [77,78]. Both of these separate stem cell populations were bipotent and gave rise to all three prostate epithelial lineages upon transplantation to

immunocompromised mice. Early studies showed enrichment of miR-200 [79] and E-cadherin [80] in the luminal cell layer. It should be noted that later studies demonstrated that whereas basal prostate cells had bipotent capacity in transplantation assays, they only contributed to the luminal lineage during development and a short postnatal period. Similar to the mammary gland, the luminal lineage is maintained by their own stem cell compartment in adult mice [81].

Using a Slug promoter – YFP construct, the previously identified Sca1+Cd49f+Trop2+ population was shown to be enriched for Slug activity. These cells also displayed higher organoid forming capacities yet the role for Slug in stem cell maintenance remains to be elucidated [82]. A second study identified a $Zeb1^{high}$ basal cell population which showed resistance to castration-mediated androgen deprivation. Similarly to $Slug^{High}$ cells, Sca1+Cd49f^{high}Zeb1+ displayed higher organoid forming capacity compared to Sca1+Cd49f^{high}Zeb1- cells and could give rise to all three prostate lineages [83]. Interestingly, the knockout of ZEB1 caused a rapid decrease of p63 expressing basal cells indicating that Zeb1 is required for stem cell maintenance.

2.5. Lungs and other epithelia

Lungs consist of a pseudostratified epithelium in the upper airways and simple epithelia in the alveolar ducts and alveoli in which basal cells [84,85] and alveolar type 2 cells [86] act as stem cells, respectively. Early studies showed that basal cells express the EMT-TF Slug [84,85,87] whereas its expression is absent in alveolar type 2 cells [88]. A recent single cell RNA sequencing study confirmed these findings [89]. Moreover, Slug expression was accompanied by higher vimentin expression indicating the activation of a Slug-mediated EMT programme [87]. Furthermore, loss of Slug in bronchospheres caused a loss of stemness markers such as OCT3/4 and CD133 and abolished sphere propagating potential [87]. Other EMT-associated TFs are not expressed in basal bronchial cells with the exception of low *TWIST1* levels but no functional role for TWIST1 has been described yet [90].

Similarly to the distal lung, Slug expression was not detected in other simple epithelia such as the gut and liver [88]. In the murine colon however, Snai1 is expressed in the nuclei of crypt base columnar cells [91] where it contributes to stem cell maintenance [92]. Furthermore, loss of Snai1 in the intestinal epithelial cells abolishes successful establishment of organoids further underlining its role in self-renewal [92]. Moreover, a recent study showed that miR200a/b/c were enriched at the top of the crypt [93].

The expression of EMT-TFs and activation of their respective downstream programme thus plays a role in adult stem cell maintenance. Most of the EMT-stemness interplay has been described in the mammary gland which suggests that predominantly cells residing in a hybrid E/M state hold stem cell capacity. In

adult stem cells of other tissues, an unambiguous role for EMT activation has been shown although the position of these cells along the EMT-axis is yet to be defined. Despite this, in the skin, lungs and prostate, Slug plays a vital role in stem cell maintenance. A recent study showed that Slug promotes a hybrid EMT-state as it acts as a weaker EMT-inducer compared to other EMT-TFs [94]. These findings demonstrate that adult stem cells reside in hybrid states yet the influence of perturbing this hybrid state on adult stem cell function remains to be elucidated.

3. Cancer stem cells

The concept that a small population of stem cells can repopulate tissues has been extended to cancer biology. Comparable to tissue homeostasis, cancers are thought to be propagated by only a small subset of cells deemed cancer stem cells (CSC). Analogous to normal stem cells, CSCs have the ability to self-renew and differentiate to various lineages and are thought to be responsible for relapse post-treatment and metastatic colonization. CSCs can, comparable to normal stem cells, be multipotent, where they give rise to cells within the same lineage or pluripotent able to differentiate into cell types of the three germ layers. The latter has been recently described where breast cancer cells endowed by EMT driven plasticity can be trans-differentiated towards adipocytes [95]. Within the context of cancer cell biology, the parameters, and assays to quantify stemness are less defined compared to normal stem cells. Often, the tumour initiation capacity based on limiting dilution assays and the *in vitro* colony/sphere formation assays [96] were extensively used to identify CSCs. This way, CD34+CD28- acute myeloid leukemia [97], CD133+ brain [98], CD133+ pancreatic [99], CD44+CD133+ colon [100,101] and CD44+CD24- breast [102] cancer cells were identified as tumour initiation cells (TICs).

Many research papers questioned the ontogeny of these CSCs as to whether they are derived from stem cells undergoing mutations or whether more differentiated cells that underwent transformation can regain stemness and repopulate the whole tumour. Here we discuss that activation of EMP can yield cancer cells higher stemness. This indicates that the property of stemness is not necessarily an intrinsic characteristic but acquirable [103].

3.1. EMT and cancer stem cells: a perfect correlation?

As EMP orchestrates phenotypic plasticity in normal and cancer cells, a growing body of evidence identified it as a potential driver for cancer stemness. The first associations between EMP and cancer stemness showed that the activation of an EMP programme driven by SNAI1, TWIST1 or TGF-β1 could induce the CD44+CD24- CSC state in breast cancer [50,56] whereas inhibition of an EMT-programme by miR-200c suppressed stemness [104–106]. [107][108]. Interestingly, a strong enrichment for CD44+CD24-

breast cancer cells was observed in residual disease from patients after treatment with letrozole or docetaxel [109]. EMT and cancer stemness have been implicated as a major driver in therapy resistance [110] which makes this axis an attractive target for therapeutic interventions [111,112]. Indeed, two studies performed drug screenings to selectively target the CSC breast cancer phenotype which identified salinomycin [113] and ML239 [114] respectively. In a similar fashion, anti-EMT drug or drug target screens aim to tackle the EMT-stemness interplay [115–117].

Apart from CD44+CD24- cells showing an enrichment in EMT phenotype, TICs in the MMTV-PyMT mouse model displayed a Snail^{high} phenotype. Interestingly, the authors compared Snail and Slug in the mammary gland and breast cancer and found that whereas cancer stemness was mainly dependant on Snail, MaSC identity was driven by Slug. In both cases, an EMT programme drives stemness yet the upstream driver can differ between normal stem cells and their neoplastic counterparts [59].

In prostate cancer, Sca-1+CD49f^{high} CSC displayed a basal Krt5+Trp63+ phenotype [107] and enrichment for EMT markers [108]. In pancreatic cancer, expression of Prrx1 [118] or intrinsic EMT [119] was also positively correlated with CSC behaviour and the expression of well-known stemness markers such as *ALDH1A1* or *NANOG*. Unsurprisingly, the loss of ZEB1 [120] or Slug [121] impaired sphere or TIC frequencies in PDAC. In the non-small cell lung cancer (NSCLC) cell lines A549 and LC31, TGF-β1 treatment also induced EMT, higher sphere forming capacities and higher TIC frequencies [122].

Although these studies laid a promising foundation that targeting EMT could hold the key in tackling the cancer stem cells, a more nuanced view of the EMT-stemness correlation seemed appropriate. Indeed, several studies showed that the activation of an MET programme as opposed to EMT could inflect stemness in cancer cells. In the claudin-low BT-549 cell line, silencing the EMT-inducing transcription factor *PRRX1* was required for tumour initiation, sphere formation and metastatic colonisation [17]. Moreover, in several mouse models for breast and pancreatic cancer, EMT seemingly had no effect on the metastatic burden or CTC number [123–125]. In early passage NSCLC cell cultures, cells with a more epithelial phenotype developed larger tumours upon transplantation in NOD/SCID mice [126] and similarly, epithelial prostate cancer Pc3 cells had higher spheroid forming capacity than the more mesenchymal Pc3 variant cells [127].

3.2. Partial EMT as a driver for stemness

Two conflicting lines of evidence either attribute stemness and metastasis as being unapologetically driven by EMT or show an opposite correlation between the activation of EMT and stemness. Recent advancements show that both might hold a partial truth.

First, the generation of mammospheres from sorted epithelial (CD44-CD24+) and mesenchymal (CD44+CD24-) fractions of HMLER cells and demonstrated that epithelial cells activate an EMT programme whereas mesenchymal cells inhibit an EMT programme to achieve a stem-like state [128]. Since mammosphere generation enriches for stem cells, this implies that both E and M cells shift towards a hybrid state to allow stemness. Similarly, using the epithelial marker ITGB4, ITGB4^{low} MDA-MB-231 cells and ITGB4^{high} SUM159 cells were enriched for CSCs [129]. Indeed, ITGB4^{low} MDA-MB-231 and ITGB4^{high} SUM159 cells reside in a similar EMT state and express similar ITGB4 levels. These results show that inhibition of EMT in more mesenchymal breast cancer subtypes but activation of EMT in epithelial subtypes is required to induce a CSC phenotype. Intermediate EMP phenotypes thus take the lead in tumour initiation over the extreme phenotypes along the EMP axis. This was also confirmed by stabilizing the intermediate states through the combined *SNAI1* expression and *ZEB1* knockout [130].

Moreover, a separate ALDH+ CSC population, which were spatially distinct from CD44+CD24-, was shown to have higher TIC frequency than ALDH- BC cells [55,66]. Gene expression analyses found that ALDH+ exhibited a more epithelial phenotype compared to CD44+CD24- cells but interestingly, a small subset of CD44+CD24-ALDH+ cells, displaying a hybrid EMT phenotype, was capable of initiating tumours with transplantation of as little as 20 cells once again strengthening the hybrid EMT-CSC axis [66]. In nasopharyngeal carcinoma ZEB1^{med}OVOL2^{low} cells displayed higher stemness properties then either ZEB1^{low}OVOL2^{high} or ZEB1^{high}OVOL2^{low} cells [131].

Together, abovementioned results show that intermediate EMP states display higher intrinsic TIC frequency. Within NSCLC, intermediate EMP states do not display this intrinsic TIC frequency yet upon TGFβ-mediated EMT they have the highest phenotypic plasticity to convert towards CD133+ CSC [132,133].

These results explain a clear link between partial EMT and tumour- or sphere- initiation capacity in isolation/transplantation studies, yet they offer no answers to the requirement for EMT during metastatic seeding. Spontaneous activation of EMT was recently demonstrated in a study where a Tenascin-C (Tnc) or Cdh2-driven inducible lineage tracing system was used within MMTV-PyMT mice [134]. The Tnc lineage

tracing system marks cells which have passed through a hybrid E/M state whereas Cdh2 marks cells which have undergone full EMT at a certain point. In spontaneous lung metastases from MMTV-PyMT mice, the majority of cells pass through a Tnc+ state yet almost never reach a Cdh2+ during the metastatic cascade [134]. This indicates that activation of a partial, but not full EMT programme is required at some point during metastatic dissemination. Similarly, in the KPC PDAC mouse model, the loss of *Zeb1* strongly decreased the metastatic burden as well as TIC frequency and stemness [135].

Although it was shown that non-CSCs can adopt a state of stemness upon reaching a hybrid E/M phenotype, the potential of cells to undergo EMT can already be imprinted in the cell of origin. Indeed, using two mouse models for cutaneous squamous cell carcinoma; Krt14creER/Kras^{G12D}/Trp53$^{fl/fl}$ (K14 mice) and Lgr5creER/Kras^{G12D}/Trp53$^{fl/fl}$ (Lgr5 mice), it was established that tumours originating from the interfollicular epidermis (K14 mice) were strongly differentiated whereas hair follicle-originating tumours (Lgr5 mice) were highly heterogeneous displaying both epithelial and mesenchymal compartments. Since enrichment of Sox2 was seen in the Epcam+ epithelial population of these Lgr5 mice-derived tumours, this CSC population might be restricted to only papillomas or well differentiated SCC of the skin. Interestingly, Epcam- epithelial cells from Lgr5 mice displayed higher tumour propagating and colony forming potential than Epcam+ mesenchymal cells [136]. In a subsequent study where 6 EMP transition states within the Lgr5 model were uncovered, partial EMP states displayed higher metastatic capacity but the activation of an EMP programme is sufficient to unlock their stemness properties as all Epcam- states displayed the same tumour initiation capacity (Fig. 3) [137]. Recently it was also shown that stable hybrid EMT states can persist as a consequence of deletion of the protocadherin Fat1. This was associated with a 10-fold higher tumour propagation potential [138]. Loss of FAT1 promotes the simultaneous activation of an epithelial programme through upregulation of SOX2 via inhibition of EZH2 mediated H3K27me3 histone modifications and a mesenchymal programme via the CAMK2-CD44-SRC axis to sustain a hybrid phenotype [138].

Another study using the DMBA/TPA driven skin cancer mouse model showed that transient, but not constitutive Twist1 expression strongly enhanced the number of lung metastasis [139]. Altogether these studies provide evidence that the activation of an EMT programme is required for stemness but that, contrary to breast cancer, both hybrid and fully mesenchymal exhibit similar tumour propagating capacities whereas partial EMT phenotypes pioneer during metastatic seeding.

Conversely, in a Pb-Cre+/−;PtenL/L;KrasG12D/+ prostate cancer mouse model equipped with a Vimentin-GFP sensor system, three EMT states were uncovered: GFP+EPCAM-, GFP+EPCAM+ and GFP-EPCAM+.

Although intermediate cells displayed higher sphere forming capacity and showed enrichment for the Sca-1+CD49f^{high} CSC phenotype, mesenchymal cells showed higher *in vivo* tumour initiating capacity and epithelial cells resulted in the largest metastatic burden [140].

Recent literature questioned whether the property type of stemness is intrinsic or acquirable [103]. These studies showed that modulation of EMT programmes can yield a stemness gain but also that the initial cell state can hold stemness properties. Moreover, these studies showed that cells residing in hybrid E/M phenotypes have higher stemness capacities than their epithelial and mesenchymal counterparts and offer explanations as to why both activation and inhibition of EMT can offer normal and cancer cells stemness properties. This aligns with the recently introduced "stemness window" (Fig. 2) [141]. The stemness window does not exclude the possibility that epithelial or mesenchymal cells have stem cell properties. However, the probability for cells acquiring stemness characteristics is higher upon residing in a hybrid E/M state. This explains why most adult stem cells have a more mesenchymal phenotype compared to their fully differentiated progeny but also why the reprogramming of highly mesenchymal fibroblasts to iPSC requires activation of a MET programme. Similarly, in the context of cancer, more mesenchymal-like cancers such as claudin-low type BC inhibit EMT programmes to unlock their stemness potential while differentiated luminal activate this.

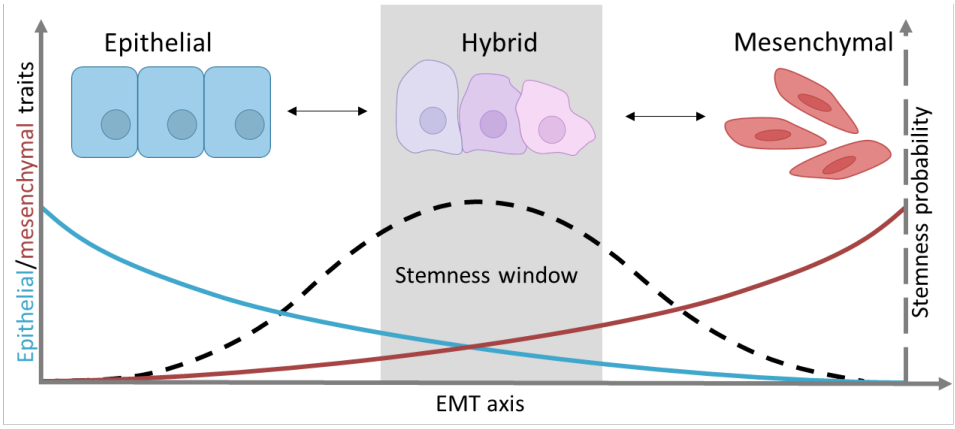

Fig. 2: A cells position along the EMT axis dictates its stemness potential
The balance between EMT- and MET-inducing programmes dictates the cells EMT phenotype. In agreement with experimental evidence which demonstrate that hybrid E/M cells display stronger stemness features, a stemness window was defined. Stemness characteristics follow a gaussian distribution along the EMP axis. While cells residing in either epithelial or mesenchymal cell states can exhibit stemness characteristics, the probability for hybrid cells to behave stem-like is the highest. The EMT window in which stemness probability is the highest is defined as the stemness window.

3.3. Collective strand migration

While single cancer stem cells were thought to disseminate through the blood and seed new tumours in distant locations, the observation that circulating tumour cells can present as clusters pressed researchers to revaluate this. Although single cell dissemination is one route via which cells can metastasize, collective dissemination might even be more potent for establishing metastases. Indeed, upon co-injecting MDA-MB 231 LM2 cells equipped with GFP or mcherry reporters in the fat-pad of mice, spontaneous lung metastases arose. Interestingly, only 2.6% of CTCs presented as clusters indicating that single cells are more potent to intravasate. However, 53% of lung nodules contained both GFP and mcherry positive cells suggesting a multiclonality and a higher potency of CTC clusters to establish metastatic outgrowths [142]. Similarly, injection of aggregates of breast cancer cells as opposed to single cells resulted in a higher metastatic burden (Fig. 3) [134,142,143]. Interestingly, intravenous injection of a mixture of TNC+ hybrid EMT cells and TNC- epithelial cells derived from MMTV-PyMT mice resulted in the highest tumour burden compared to combinations of fully epithelial, fully mesenchymal, and intermediate cells [134]. This role for cells in a hybrid EMT state during collective migration has been shown in the KPC PDAC mouse model where intermediate EMT (Cdh1+) cells preferably migrated as collective strands as opposed to fully mesenchymal cells (Cdh1-) which migrated as single cells [144]. Equivalent results were reported for the hybrid DFCI032, H1650, H1693 and HCC827 NSCLC cell lines which preferably migrated as collective clusters compared to single cell migration seen in mesenchymal NSCLC cells [145]. Although these studies do not fully support the CSC theory, a recent study showed that MCF7 cells in 3D cultures could also invade collectively. Interestingly leader cells co-expressed CDH1 and CDH2 as well as the stem-cell marker NANOG which is highly upregulated in CD44+CD24- CSC [146]. Maintenance of a partial EMT phenotype during collective migration is also important during development as Ovol2 is required for collective migration of terminal end buds during mammary ductal morphogenesis in mice [68]. A recent study revealed that in CTC clusters isolated from either breast cancer patients or xenografts, TF binding sites for the stemness factors OCT4, NANOG, SOX2 and SIN3A were hypomethylated [147].

One major question remains whether the interaction between cells promotes metastases or whether different cell types within the CTC clusters excel during the metastatic cascade. One recent study has shown that coculturing epithelial (CD44-CD24+) and mesenchymal (CD44+CD24-) HMLER cells results in higher mammosphere formation *in vitro* [148]. Moreover, whereas subcutaneous injections of epithelial or mesenchymal HCPC-1 cells did not result in spontaneous metastases, co-injection of these populations did [149]. The cooperation between E and M cells does require the potential for EMP since it was shown that mixing HMLER cells trapped in an E and M state did not yield enhanced tumorigenicity [130]. These

results underline that the crosstalk between cancer cell subsets is crucial in mediating tumorigenicity but do not exclude the different contribution of different cell types during metastasis.

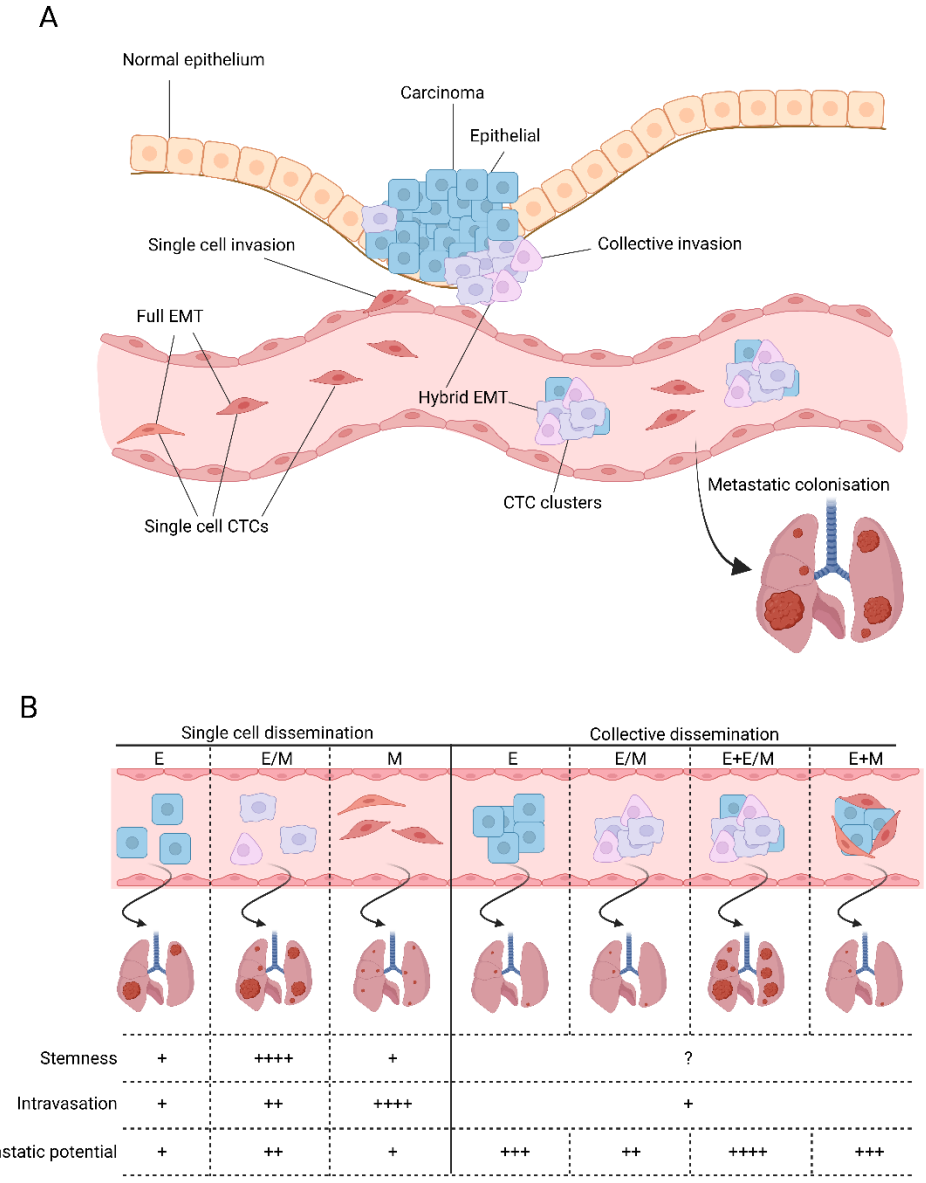

Fig. 3: The role of EMT during collective strand and single cell CTC formation, stemness and metastasis
(A) Activation of EMT in epithelial carcinoma cells pushes them towards mesenchymal or hybrid E/M phenotypes. Whereas mesenchymal phenotypes are more likely to disseminate as single cells, hybrid E/M cells retain some cell adhesion properties which promote collective migration and dissemination as CTC clusters in the bloodstream. **(B)** Tumour initiation studies performed on single cells showed a higher TIC frequency and consequently stemness of hybrid E/M cells. These studies have not been performed on aggregates. Nonetheless, mesenchymal cells are more invasive and have higher intravasation potency than other EMT phenotypes and cells migrating collectively. Despite this, cluster CTCs is much more potent at establishing macrometastases compared to single CTCs. This figure was created using Bio-render (https://biorender.com).

4. Feedback loops stabilize a hybrid EMT state and define the stemness window

In both adult stem cells and cancer stem cells, hybrid E/M states hold higher stem-like capacities. We previously discussed the "stemness window" [141] which entails that all cells along the EMP axis have the capacity to behave as CSCs yet the probability for CSC identity is the highest when cells reside in a hybrid E/M state. This implies that reaching this state of stemness requires stabilization of this intermediate phenotype. Interestingly, many new mathematical modeling studies uncouple EMT regulation from stemness regulation and postulate that this is regulated by two separate "circuits". These circuits are regulated by multiple feedback loops which form a highly interconnected network of transcription factors, miRNAs, long non-coding RNAs and epigenetic regulators. Interestingly, epithelial and mesenchymal inducers can operate as separate teams which results in a bimodal phenotype stability distribution [150]. This is in line with experimental evidence showing that hybrid states are often metastable [137] and explains why stemness in tumours is rare despite being acquirable.

4.1. EMT-TF-miRNA loops govern the EMT state

The best studied EMT-regulating feedback loops are the miR-200-ZEB1/2 and miR-34-SNAIL circuits. The miR-200 and miR-34 family members target the 3'UTR of *ZEB1/2* (Fig. 4) [120,151–154] and *SNAI1* [155–157] respectively. Both miRNA families contain E-boxes in their promoter regions which are directly targeted by both SNAIL and ZEB1/2 [155,157]. The mutational background of tumours also impacts the EMT state as both miRNA families are directly activated by P53 [158–163]. Hence loss of P53 enables cell plasticity and priming towards hybrid or full EMT phenotypes. These miRNA-TF feedback loops are widespread across cell types and cancers yet others exist as well. A miR-1199-5p-Zeb1 [164] and a miR145-ZEB2 [165] double negative feedback loop regulates EMT in both murine mammary gland cells and human prostate cancer cell lines.

4.2. A let-7-LIN28 feedback loop controls pluripotency genes and stemness

Members of the let-7 miRNA family directly target the 3'UTR of several genes important for self-renewal such as *HRAS*, *HMGA2* [166] and *OCT-4* [167] thereby reducing tumour initiation capacity in several epithelial cancers [168]. LIN28 on the other hand, enhances stemness and can drive reprogramming of somatic cells along with OCT4, SOX2 and NANOG [169] by antagonizing the let-7 miR family via direct inhibition of the precursor miRs [169]. Consequently, somatic reprogramming could also be achieved via OCT4, SOX2, NANOG and a let-7 miR sponge construct [170]. Similarly, in the human ovarian cancer cell line A2780 and breast cancer cell lines T47D and MCF7, LIN28 is directly responsible for the ALDH1+ CSC phenotype and induces a higher sphere formation through inhibition of the let-7 miRNA precursor [171]. Inflammatory signaling mediated by oncostatin M or proinflammatory macrophages also induces the

CD44+CD24- CSC phenotype in MCF-7 breast cancer cells via STAT3 signaling which is partially reversed through expression of let-7 [172,173]. Let-7, in turn reciprocally inhibits *LIN28* expression via binding its 3'UTR region (Fig. 4) [171]. LIN28 can directly activate *OCT4* or via downstream regulation through HMGA2 and ARID3B which directly upregulate the pluripotency genes *SOX2* and *OCT4* [170,174]. This regulatory loop is tightly intertwined with EMT-regulation as several let-7 members were downregulated in mesenchymal gemcitabine resistant pancreatic cancer cells [175] whereas LIN28 showed upregulation in mesenchymal breast cancer cell lines MDA-MB-231 and SK3RD cell lines [176]. Let-7i is directly regulated by both TWIST1 and BMI1 in HNSCC cells [177] and SNAI1 in several epithelial cancer cell lines (PANC-1, MCF7 and OVCAR8) [178]. Expression of miR-200b/c can also inhibit LIN28 in prostate cancer and NSCLC although a direct interaction remains to be demonstrated [179,180]. Moreover, HMGA2 acts as an EMT inducer as it directly targets the *SNAI1* promoter in TGFβ–mediated EMT [181]. Long non-coding RNAs (lncRNAs), and the H19 lncRNA in particular, can antagonize the let-7 family by acting as a miRNA sponge [182–185]. Interestingly, H19 overexpression has been linked to poor prognosis, invasion, and metastasis in several cancers [184,186]. Mechanistically, H19 can induce EMT by acting as a decoy for miR-200a/b/c and miR-138 in both breast cancer xenografts [182] and human colorectal cancer cell (CRC) lines [187]. Moreover, SOX2 or OCT-4 upregulate *H19* lncRNA levels which in turn enhances stemness creating a feedforward mechanism [188].

Despite that several of these EMT inducers activate pluripotency genes via the let-7 pathway, these can in turn reactivate epithelial markers. Klf4 for example is a potent inducer of *Cdh1* during MEF to iPSC reprogramming [35] which is further enhanced by OVOL2 [189].

4.3. Negative feedback loops between EMT-inducing and MET-inducing transcription factors dictate the hybrid state

Several transcription factors activating epithelial gene expression patterns are also integrated in this network governing plasticity and stemness. Grainyhead-like 2 (GRHL2) inhibits EMT and induces MET during both development [21,190] and cancer [191–193] where it directly activates epithelial markers such as Cdh1, Cldn4 and Rab25 [21,194]. GRHL2 forms a reciprocal feedback loop with ZEB1 in breast cancer where it competes with the ZEB1 activating TFs LBX1 and SIX1 (Fig. 4) [22,23]. In ovarian cancer GRHL2 does not bind directly to the ZEB1 promoter but directly activates the miR-200 family [195]. Similarly, Ovol2 which also activates an epithelial programme [189,196] is reciprocally regulated by Zeb1 as well [68,69,197]. Its paralog OVOL1 also directly binds the ZEB1 promoter to induce MET but no direct reciprocal relationship has been shown [198]. Although the induction of EMT often drives stemness,

GRHL2 can directly bind the OCT-4 promoter and activate its expression [199] and regulates self-renewal in PDAC by maintenance of the CD133+ CSC population [193].

4.4. Alternative splicing controls hybrid EMT and the stem-cell factor CD44

CD44 is a cell-surface glycoprotein and is a widespread marker for normal and cancer stem cells [200] and can exist in multiple isoforms among which are CD44v which contains the variable exons 8-10 and the standard isoform CD44s. The balance between these isoforms is regulated by epithelial splicing regulatory proteins 1 and 2 (ESRP1/2) [201] which are negatively regulated by ZEB1 and SNAIL through direct promoter interactions [202–204]. Following EMT, the CD44s isoform prevails over CD44v which in turn further enhances EMT through the interaction with hyaluronic acid encoded by *HAS2* [202,205]. *HAS2* is positively regulated by ZEB1 via a direct promoter interaction [205]. Using these studies in combination with mathematical modeling, the ZEB1-ESRP1-CD44-HAS2 axis was shown to promote a hybrid EMP state [206]. Moreover, deletion of *Fat1* in an SCC mouse model was shown to promote the hybrid EMT state via the Camk2–Cd44–Src axis and the activation of the pluripotency marker Sox2 [138].

4.5. NOTCH and oxidative stress regulate the "stemness window"

These EMP and stemness regulating feedback loops have been subjected to mathematical modeling which defined the miR-200-ZEB and miR-34-SNAIL interactions as the main drivers for positioning of cells along the EMT axis [207]. GRHL2 and OVOL1/2 act as phenotypic stability factors (PSF) in this network to stabilize the hybrid E/M cell state [69]. Importantly, these studies uncouple EMT from stemness and identify the let-7-LIN28 loop as the main driver of stemness. As we have discussed before the "EMP circuit" and "stemness circuit" are highly interconnected for the concept of a "stemness window" was introduced [141]. This implies that all cells along the EMP axis have the capacity to behave as CSC yet the probability for CSC identity is the highest when cells reside in a hybrid E/M state.

One major signaling pathway that was reported to control this balance was notch-jagged signaling. During Notch signaling, Notch binds to the transmembrane ligand Jagged or Delta of the neighboring cell. The former interaction stimulates lateral induction whereas the latter stimulates lateral inhibition. During lateral inhibition both neighboring cells will undergo different cell fates whereas they will activate the same pathways during lateral stimulation. Upon interaction, Notch is cleaved and the Notch intracellular domain (NICD) translocates to the nucleus and modulates the transcription of target genes via interaction with its cofactor CSL [208]. A recent study proposed that the Notch-Jag1 interaction drives the generation of cell clusters residing in the hybrid E/M state [209,210]. This was partly shown in MMTV-PyMT mice as Jag1 was one of the highest upregulated genes in hybrid E/M CTC clusters compared to mesenchymal

single CTCs [143]. Similarly, Notch signatures were shown to be upregulated in CSC populations across cancers [207]. Moreover, in CD133+CD44+ CSC from CRC patients, the balance between notch signalling and miR-34a regulates self-renewal. Indeed, miR-34a directly binds to the 3'UTR of *NOTCH* and minimizes the NICD levels in the daughter cells giving rise to KRT20+ differentiated progeny. Conversely, elevated levels of NOTCH, and consequently NICD stimulate symmetric division with two CSCs as daughter cells [211]. Regulation of NOTCH1 by miRNAs is not limited to CRC as both miR-141 and miR-200c, which are members of the miR-200 family, directly target *JAG1* in the Panc1 cell line [212] whereas miR-200b/c directly target *NOTCH1* in PC3 cells [179]. Unsurprisingly, the knockdown of ZEB1 decreased *NOTCH1*, *JAG1* and *MALM2/3* (notch coactivators) levels [212]. Importantly, although Notch signalling can promote EMT, Notch inhibitors, Numb and Numbl play a crucial role in maintaining a hybrid phenotype. In H1975 NSCLC cells which reside in a hybrid E/M state, knockdown of either Notch inhibitor pushes these cells towards a fully mesenchymal phenotype [213]. Similarly, in MCF10A cells the knockdown of NUMB initiated EMT although this was met with an increase in the pluripotency factors OCT4 and SOX2 expression and the shift towards a $CD44^{high}CD24^{low}$ CSC state indicating a context dependent relationship with stemness [214].

This Notch-EMT network is strongly intertwined with metabolic switching during EMP. Several studies demonstrate a clear positive correlation between the activation of an EMT programme and glycolysis [216,217], however TGF-b mediated EMT resulted in inhibition of pyruvate dehydrogenase kinase 4 (PDK4) and pyruvate kinase M2 in lung [218] and colon cancer respectively [219]. Since high glycolytic activity is also associated with pluripotency and a metabolic switch towards glycolysis takes place upon iPSC reprogramming, this might indicate that a hybrid E/M state favours glycolytic metabolism. This is partly supported by a recent EMT-glucose metabolism correlation study [220] and the observation of glycolysis being favoured during collective strand migration [221,222]. Metabolic reprogramming is directly correlated with Notch signaling as HIF-1α, which is a mediator of glycolysis and oxidative stress, can activate N1ICD which directly binds the SNAI1 promoter via CSL [215]. Similarly, Tgfβ1 mediated EMT was mediated via N2ICD and N4ICD binding to the SNAIL1 promoter via CSL in A549 lung carcinoma cells [223]. Novel studies however, have demonstrated a leading role for the ROS induced nuclear factor E2-related factor 2 (Nrf2). Under basal conditions, Nrf2 is suppressed through retention in the cytoplasm by Keap1. This interaction is disrupted by oxidative stress which causes Nrf2 to translocate to the nucleus and binds antioxidant-response elements (ARE) in the promoter region of target genes. In A549, TGFβ1 mediated EMT was fully dependent on ROS production and activation of NRF2. In this context, NRF2 activates the *NOTCH4* promoter through ARE binding [224]. Similarly, IL6 mediated EMT occurred through

NRF2 in PDAC cell lines AsPC-1, BxPC-3, and Panc-1 [225]. However, several studies revealed an anti-EMT function for Nrf2 as it could indirectly downregulate Snai1 during pulmonary fibrosis [226]. Moreover, miR-200a targets the Keap1 3'UTR to activate Nrf2 and prevent EMT [227]. Recent mathematical modelling studies confirmed that NRF2 can act as an EMT inhibitor or inducer depending on the cellular context as they predicted that NRF2 behaves as a hybrid stability factor which can dictate collective strand migration [228,229]. This role has been experimentally demonstrated in wounding where Nrf2 drives collective strand migration via EMT inhibition but further experimental evidence is required [230].

Recent studies have shown that Nrf2 can promote metastasis in lung adenocarcinoma mouse models via the indirect stabilization of the Bach1 transcription factor [231,232]. Interestingly, BACH1 has been identified as a novel EMT-inducing TF as BACH1 and HMGA2 co-occupied promoters of EMT related genes *VIM*, *SNAI2*, *SNAI1* and *TWIST1* to activate their transcription in the ovarian cancer cell line A2780, [233]. Comparable results were shown in PDAC cell lines where BACH1 bound to SNAI2, FOXA1 and CLDN3/4 [234]. Apart from its recent role as an EMT-inducer, BACH1 is also tightly connected to stemness regulation as let-7a/g can directly target the BACH1 3'UTR [235]. Moreover, BACH1 governs stemness in hESCs cells through directly interacting with NANOG, SOX2 and OCT-4 and stabilizing them through recruiting the deubiquitinating enzyme USP7 [236].

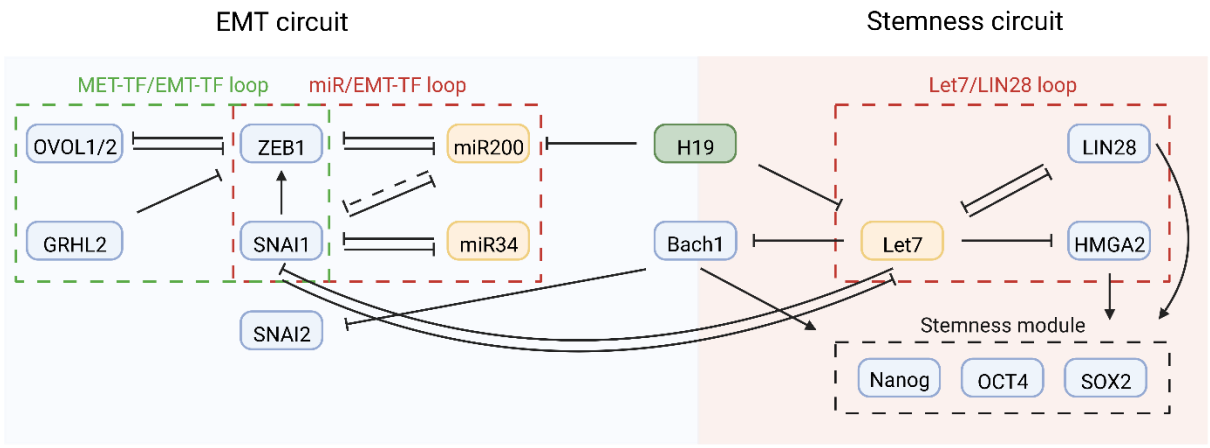

Fig. 4: EMT and stemness regulation form a highly interconnected network
The position of cells along the EMT axis dictates their probability for stemness with hybrid cells having the highest probability. Stabilization of a hybrid state requires the simultaneous activation of EMT- and MET- inducing programmes which are tightly regulated by several feedback loops. The ZEB1-miR200 and SNAI1-miR34 negative feedback loops form the central dogma for the determination of the EMT phenotype. The stemness balance is mainly regulated by a Let7-LIN28 negative feedback loop. These modules are highly interconnected and regulated by several other (post-) transcriptional, (post-) translational and epigenetic mechanisms. Solid and dashed lines depict direct and indirect regulation respectively.

5. Concluding remarks

While initial studies proposed a direct interaction between the activation of an EMT programme and the acquisition of stemness traits, novel findings have reevaluated this notion. In non-transformed stem cells and cancer stem cells, the activation of an EMT programme can certainly contribute to stemness traits yet a delicate balance between activation and inhibition of this process is required for stem cell capacity. Indeed, cells residing in hybrid EMT states, which co-exhibit epithelial and mesenchymal markers, have a higher probability of exhibiting stem cell traits compared to their fully epithelial and fully mesenchymal counterparts. This implies that to reach a "stem-like" state, cells will either activate an EMT or an MET programme which is dependent on their current position on the EMT-axis. In most epithelial tissues, achieving a stem cell state will require EMT activation, hence early reports showing a clear connection between these two phenomena. However, during reprogramming of highly mesenchymal fibroblasts or in mesenchymal-like cancer cells, MET allows these cells to re-enter a stem cell state. To reach- and maintain a hybrid state, both EMT and MET inducing programmes need to reach an equilibrium which is maintained by multiple feedback loops at the transcriptional, translational and epigenetic level. Altogether, a continuous EMP dynamic with stabilization of a hybrid E/M phenotype strongly enriches stem cells in normal and cancerous cell populations.

Acknowledgements

J.V. is supported by a personal PhD fellowship from Ghent University, Belgium. G. Berx's laboratory is supported by the Geconcerteerde Onderzoeksacties Ghent University (GOA022-21), Belgium, Kom Op Tegen Kanker (KoTK) (KotK_UGent/2018/11545/1), Belgium and Stichting tegen Kanker (F/2020/1437 & C/2020/1436), Belgium.

References

[1] M.A. Nieto, R.Y.Y.J. Huang, R.A.A. Jackson, J.P.P. Thiery, EMT: 2016, Cell. 166 (2016) 21–45.

[2] M.T. Grande, B. Sánchez-Laorden, C. López-Blau, C.A. de Frutos, A. Boutet, M. Arévalo, R.G. Rowe, S.J. Weiss, J.M. López-Novoa, M.A. Nieto, Snail1-induced partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease, Nat Med. 21 (2015) 989–997.

[3] A. Dongre, R.A. Weinberg, New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer, Nat Rev Mol Cell Biol. 20 (2019) 69–84.

[4] J.P. Thiery, H. Acloque, R.Y.J. Huang, M.A. Nieto, Epithelial-Mesenchymal Transitions in Development and Disease, Cell. 139 (2009) 871–890.

[5] E. Batlle, E. Sancho, C. Francí, D. Domínguez, M. Monfar, J. Baulida, A.G. de Herreros, The transcription factor Snail is a repressor of E-cadherin gene expression in epithelial tumour cells, Nat Cell Biol. 2 (2000) 84–89.

[6] A. Cano, M.A. Pérez-Moreno, I. Rodrigo, A. Locascio, M.J. Blanco, M.G. del Barrio, F. Portillo, M.A. Nieto, The transcription factor Snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression, Nat Cell Biol. 2 (2000) 76–83.

[7] J. Comijn, G. Berx, P. Vermassen, K. Verschueren, L. van Grunsven, E. Bruyneel, M. Mareel, D. Huylebroeck, F. van Roy, The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion, Mol Cell. 7 (2001) 1267–1278.

[8] A. Eger, K. Aigner, S. Sonderegger, B. Dampier, S. Oehler, M. Schreiber, G. Berx, A. Cano, H. Beug, R. Foisner, DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells, Oncogene. 24 (2005) 2375–2385.

[9] K.M. Hajra, D.Y.-S. Chen, E.R. Fearon, The SLUG zinc-finger protein represses E-cadherin in breast cancer., Cancer Res. 62 (2002) 1613–8.

[10] V. Bolós, H. Peinado, M.A. Pérez-Moreno, M.F. Fraga, M. Esteller, A. Cano, The transcription factor Slug represses E-cadherin expression and induces epithelial to mesenchymal transitions: a comparison with Snail and E47 repressors, J Cell Sci. 116 (2003) 499–511.

[11] J. Yang, S.A. Mani, J.L. Donaher, S. Ramaswamy, R.A. Itzykson, C. Come, P. Savagner, I. Gitelman, A. Richardson, R.A. Weinberg, Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis., Cell. 117 (2004) 927–39.

[12] M.A. Pérez-Moreno, A. Locascio, I. Rodrigo, G. Dhondt, F. Portillo, M.A. Nieto, A. Cano, A New Role for E12/E47 in the Repression of E-cadherin Expression and Epithelial-Mesenchymal Transitions, Journal of Biological Chemistry. 276 (2001) 27424–27431.

[13] X. Wang, M. Zheng, G. Liu, W. Xia, P.J. McKeown-Longo, M.C. Hung, J. Zhao, Krüppel-Like Factor 8 Induces Epithelial to Mesenchymal Transition and Epithelial Cell Invasion, Cancer Res. 67 (2007) 7184–7193.

[14] B.G. Hollier, A.A. Tinnirello, S.J. Werden, K.W. Evans, J.H. Taube, T.R. Sarkar, N. Sphyris, M. Shariati, S. v. Kumar, V.L. Battula, J.I. Herschkowitz, R. Guerra, J.T. Chang, N. Miura, J.M. Rosen, S.A. Mani, FOXC2 expression links epithelial-mesenchymal transition and stem cell properties in breast cancer, Cancer Res. 73 (2013) 1981.

[15] S.A. Mani, J. Yang, M. Brooks, G. Schwaninger, A. Zhou, N. Miura, J.L. Kutok, K. Hartwell, A.L. Richardson, R.A. Weinberg, Mesenchyme Forkhead 1 (FOXC2) plays a key role in metastasis and is associated with aggressive basal-like breast cancers, Proceedings of the National Academy of Sciences. 104 (2007) 10069–10074.

[16] H. Huldani, S.A. Jasim, K.N. Sergeenva, D.O. Bokov, W.K. Abdelbasset, R. Turakulov, M.E. Al-Gazally, B. Ahmadzadeh, Z.H. Jawhar, H. Siahmansouri, Mechanisms of cancer stem cells drug resistance and the pivotal role of HMGA2, Pathol Res Pract. 234 (2022) 153906.

[17] O.H. Ocaña, R. Córcoles, Á. Fabra, G. Moreno-Bueno, H. Acloque, S. Vega, A. Barrallo-Gimeno, A. Cano, M.A. Nieto, Metastatic Colonization Requires the Repression of the Epithelial-Mesenchymal Transition Inducer Prrx1, Cancer Cell. 22 (2012) 709–724.

[18] K.A. Hartwell, B. Muir, F. Reinhardt, A.E. Carpenter, D.C. Sgroi, R.A. Weinberg, The Spemann organizer gene, Goosecoid, promotes tumor metastasis, Proc Natl Acad Sci U S A. 103 (2006) 18969–18974.

[19] R.I. Fernando, M. Litzinger, P. Trono, D.H. Hamilton, J. Schlom, C. Palena, The T-box transcription factor Brachyury promotes epithelial-mesenchymal transition in human tumor cells, J Clin Invest. 120 (2010) 533.

[20] B. Lee, A. Villarreal-Ponce, M. Fallahi, J. Ovadia, P. Sun, Q.-C. Yu, S. Ito, S. Sinha, Q. Nie, X. Dai, Transcriptional Mechanisms Link Epithelial Plasticity to Adhesion and Differentiation of Epidermal Progenitor Cells, Dev Cell. 29 (2014) 47–58.

[21] M. Werth, K. Walentin, A. Aue, J. Schönheit, A. Wuebken, N. Pode-Shakked, L. Vilianovitch, B. Erdmann, B. Dekel, M. Bader, J. Barasch, F. Rosenbauer, F.C. Luft, K.M. Schmidt-Ott, The transcription factor grainyhead-like 2 regulates the molecular composition of the epithelial apical junctional complex, Development. 137 (2010) 3835–3845.

[22] B. Cieply, J. Farris, J. Denvir, H.L. Ford, S.M. Frisch, Epithelial-mesenchymal transition and tumor suppression are controlled by a reciprocal feedback loop between ZEB1 and Grainyhead-like-2, Cancer Res. 73 (2013) 6299–6309.

[23] B. Cieply, P. Riley IV, P.M. Pifer, J. Widmeyer, J.B. Addison, A. v. Ivanov, J. Denvir, S.M. Frisch, Suppression of the epithelial-mesenchymal transition by grainyhead-like-2, Cancer Res. 72 (2012) 2440–2453.

[24] X. Li, J. Yuan, C. Song, Y. Lei, J. Xu, G. Zhang, W. Wang, G. Song, Deubiquitinase USP39 and E3 ligase TRIM26 balance the level of ZEB1 ubiquitination and thereby determine the progression of hepatocellular carcinoma, Cell Death Differ. 28 (2021) 2315–2332.

[25] B. Dong, S. Li, S. Zhu, M. Yi, S. Luo, K. Wu, MiRNA-mediated EMT and CSCs in cancer chemoresistance, Exp Hematol Oncol. 10 (2021) 1–12.

[26] X. Lin, G. Chai, Y. Wu, J. Li, F. Chen, J. Liu, G. Luo, J. Tauler, J. Du, S. Lin, C. He, H. Wang, RNA m6A methylation regulates the epithelial mesenchymal transition of cancer cells and translation of Snail, Nat Commun. 10 (2019) 1–13.

[27] N. Skrypek, S. Goossens, E. de Smedt, N. Vandamme, G. Berx, Epithelial-to-Mesenchymal Transition: Epigenetic Reprogramming Driving Cellular Plasticity, Trends in Genetics. 33 (2017) 943–959.

[28] K. Horiguchi, K. Sakamoto, D. Koinuma, K. Semba, A. Inoue, S. Inoue, H. Fujii, A. Yamaguchi, K. Miyazawa, K. Miyazono, M. Saitoh, TGF-β drives epithelial-mesenchymal transition through δEF1-mediated downregulation of ESRP, Oncogene. 31 (2012) 3190.

[29] J. Yang, P. Antin, G. Berx, C. Blanpain, T. Brabletz, M. Bronner, K. Campbell, A. Cano, J. Casanova, G. Christofori, S. Dedhar, R. Derynck, H.L. Ford, J. Fuxe, A. García de Herreros, G.J. Goodall, A.-K. Hadjantonakis, R.J.Y. Huang, C. Kalcheim, R. Kalluri, Y. Kang, Y. Khew-Goodall, H. Levine, J. Liu, G.D. Longmore, S.A. Mani, J. Massagué, R. Mayor, D. McClay, K.E. Mostov, D.F. Newgreen, M.A. Nieto, A. Puisieux, R. Runyan, P. Savagner, B. Stanger, M.P. Stemmler, Y. Takahashi, M. Takeichi, E. Theveneau, J.P. Thiery, E.W. Thompson, R.A. Weinberg, E.D. Williams, J. Xing, B.P. Zhou, G. Sheng, Guidelines and definitions for research on epithelial–mesenchymal transition, Nat Rev Mol Cell Biol. 21 (2020) 1–12.

[30] I. Pastushenko, C. Blanpain, EMT Transition States during Tumor Progression and Metastasis, Trends Cell Biol. 29 (2019) 212–226.

[31] L. Vermeulen, F. de Sousa e Melo, D.J. Richel, J.P. Medema, The developing cancer stem-cell model: clinical challenges and opportunities, Lancet Oncol. 13 (2012) e83–e89.

[32] A. Kreso, J.E. Dick, Evolution of the cancer stem cell model, Cell Stem Cell. 14 (2014) 275–291.

[33] A. Singh, J. Settleman, EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer, Oncogene 2010 29:34. 29 (2010) 4741–4751.

[34] K. Takahashi, S. Yamanaka, Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors, Cell. 126 (2006) 663–676.

[35] R. Li, J. Liang, S. Ni, T. Zhou, X. Qing, H. Li, W. He, J. Chen, F. Li, Q. Zhuang, B. Qin, J. Xu, W. Li, J. Yang, Y. Gan, D. Qin, S. Feng, H. Song, D. Yang, B. Zhang, L. Zeng, L. Lai, M.A. Esteban, D. Pei, A mesenchymal-to-Epithelial transition initiates and is required for the nuclear reprogramming of mouse fibroblasts, Cell Stem Cell. 7 (2010) 51–63.

[36] P. Samavarchi-Tehrani, A. Golipour, L. David, H.K. Sung, T.A. Beyer, A. Datti, K. Woltjen, A. Nagy, J.L. Wrana, Functional Genomics Reveals a BMP-Driven Mesenchymal-to-Epithelial Transition in the Initiation of Somatic Cell Reprogramming, Cell Stem Cell. 7 (2010) 64–77.

[37] X. Liu, H. Sun, J. Qi, L. Wang, S. He, J. Liu, C. Feng, C. Chen, W. Li, Y. Guo, D. Qin, G. Pan, J. Chen, D. Pei, H. Zheng, Sequential introduction of reprogramming factors reveals a time-sensitive requirement for individual factors and a sequential EMT–MET mechanism for optimal reprogramming, Nat Cell Biol. 15 (2013) 829–838.

[38] S. He, J. Chen, Y. Zhang, M. Zhang, X. Yang, Y. Li, H. Sun, L. Lin, K. Fan, L. Liang, C. Feng, F. Wang, X. Zhang, Y. Guo, D. Pei, H. Zheng, Sequential EMT-MET induces neuronal conversion through Sox2, Cell Discov. 3 (2017) 17017.

[39] B. di Stefano, J.L. Sardina, C. van Oevelen, S. Collombet, E.M. Kallin, G.P. Vicent, J. Lu, D. Thieffry, M. Beato, T. Graf, C/EBPα poises B cells for rapid reprogramming into induced pluripotent stem cells, Nature. 506 (2013) 235–239.

[40] J. An, Y. Zheng, C.T. Dann, Mesenchymal to Epithelial Transition Mediated by CDH1 Promotes Spontaneous Reprogramming of Male Germline Stem Cells to Pluripotency, Stem Cell Reports. 8 (2017) 446.

[41] J. Liu, Q. Han, T. Peng, M. Peng, B. Wei, D. Li, X. Wang, S. Yu, J. Yang, S. Cao, K. Huang, A.P. Hutchins, H. Liu, J. Kuang, Z. Zhou, J. Chen, H. Wu, L. Guo, Y. Chen, Y. Chen, X. Li, H. Wu, B. Liao, W. He, H. Song, H. Yao, G. Pan, J. Chen, D. Pei, The oncogene c-Jun impedes somatic cell reprogramming, Nat Cell Biol. 17 (2015) 856–867.

[42] K.A. D'Amour, A.D. Agulnick, S. Eliazer, O.G. Kelly, E. Kroon, E.E. Baetge, Efficient differentiation of human embryonic stem cells to definitive endoderm, Nat Biotechnol. 23 (2005) 1534–1541.

[43] A.M. Eastham, H. Spencer, F. Soncin, S. Ritson, C.L.R. Merry, P.L. Stern, C.M. Ward, Epithelial-Mesenchymal Transition Events during Human Embryonic Stem Cell Differentiation, Cancer Res. 67 (2007) 11254–11262.

[44] Q. Li, A.P. Hutchins, Y. Chen, S. Li, Y. Shan, B. Liao, D. Zheng, X. Shi, Y. Li, W.Y. Chan, G. Pan, S. Wei, X. Shu, D. Pei, A sequential EMT-MET mechanism drives the differentiation of human embryonic stem cells towards hepatocytes, Nat Commun. 8 (2017) 1–12.

[45] P.B. Blair, K.B. DeOme, Mammary Tumor Development in Transplanted Hyperplastic Alveolar Nodules of the Mouse, Proceedings of the Society for Experimental Biology and Medicine. 108 (1961) 289–291.

[46] C. Kuperwasser, T. Chavarria, M. Wu, G. Magrane, J.W. Gray, L. Carey, A. Richardson, R.A. Weinberg, Reconstruction of functionally normal and malignant human breast tissues in mice, Proc Natl Acad Sci U S A. 101 (2004) 4966–4971.

[47] B.E. Welm, S.B. Tepera, T. Venezia, T.A. Graubert, J.M. Rosen, M.A. Goodell, Sca-1pos Cells in the Mouse Mammary Gland Represent an Enriched Progenitor Cell Population, Dev Biol. 245 (2002) 42–56.

[48] J. Stingl, P. Eirew, I. Ricketson, M. Shackleton, F. Vaillant, D. Choi, H.I. Li, C.J. Eaves, Purification and unique properties of mammary epithelial stem cells, Nature. 439 (2006) 993–997.

[49] K.E. Sleeman, H. Kendrick, A. Ashworth, C.M. Isacke, M.J. Smalley, CD24 staining of mouse mammary gland cells defines luminal epithelial, myoepithelial/basal and non-epithelial cells, Breast Cancer Research. 8 (2006) R7.

[50] S.A. Mani, W. Guo, M.J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, M. Brooks, F. Reinhard, C.C. Zhang, M. Shipitsin, L.L. Campbell, K. Polyak, C. Brisken, J. Yang, R.A. Weinberg, The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells, Cell. 133 (2008) 704–715.

[51] M. Shackleton, F. Vaillant, K.J. Simpson, J. Stingl, G.K. Smyth, M.L. Asselin-Labat, L. Wu, G.J. Lindeman, J.E. Visvader, Generation of a functional mammary gland from a single stem cell, Nature. 439 (2006) 84–88.

[52] W. Guo, Z. Keckesova, J.L. Donaher, T. Shibue, V. Tischler, F. Reinhardt, S. Itzkovitz, A. Noske, U. Zürrer-Härdi, G. Bell, W.L. Tam, S.A. Mani, A. van Oudenaarden, R.A. Weinberg, Slug and Sox9 Cooperatively Determine the Mammary Stem Cell State, Cell. 148 (2012) 1015.

[53] M. Shipitsin, L.L. Campbell, P. Argani, S. Weremowicz, N. Bloushtain-Qimron, J. Yao, T. Nikolskaya, T. Serebryiskaya, R. Beroukhim, M. Hu, M.K. Halushka, S. Sukumar, L.M. Parker, K.S. Anderson, L.N. Harris, J.E. Garber, A.L. Richardson, S.J. Schnitt, Y. Nikolsky, R.S. Gelman, K. Polyak, Molecular Definition of Breast Tumor Heterogeneity, Cancer Cell. 11 (2007) 259–273.

[54] E. Lim, F. Vaillant, D. Wu, N.C. Forrest, B. Pal, A.H. Hart, M.L. Asselin-Labat, D.E. Gyorki, T. Ward, A. Partanen, F. Feleppa, L.I. Huschtscha, H.J. Thorne, S.B. Fox, M. Yan, J.D. French, M.A. Brown, G.K. Smyth, J.E. Visvader, G.J. Lindeman, Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers, Nat Med. 15 (2009) 907–913.

[55] C. Ginestier, M.H. Hur, E. Charafe-Jauffret, F. Monville, J. Dutcher, M. Brown, J. Jacquemier, P. Viens, C.G. Kleer, S. Liu, A. Schott, D. Hayes, D. Birnbaum, M.S. Wicha, G. Dontu, ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome, Cell Stem Cell. 1 (2007) 555.

[56] A.P. Morel, M. Lièvre, C. Thomas, G. Hinkal, S. Ansieau, A. Puisieux, Generation of Breast Cancer Stem Cells through Epithelial-Mesenchymal Transition, PLoS One. 3 (2008) 2888.

[57] M. Nassour, Y. Idoux-Gillet, A. Selmi, C. Côme, M.L.M. Faraldo, M.A. Deugnier, P. Savagner, Slug Controls Stem/Progenitor Cell Growth Dynamics during Mammary Gland Morphogenesis, PLoS One. 7 (2012).

[58] S. Phillips, A. Prat, M. Sedic, T. Proia, A. Wronski, S. Mazumdar, A. Skibinski, S.H. Shirley, C.M. Perou, G. Gill, P.B. Gupta, C. Kuperwasser, Cell-state transitions regulated by SLUG are critical for tissue regeneration and tumor initiation, Stem Cell Reports. 2 (2014) 633–647.

[59] X. Ye, W.L. Tam, T. Shibue, Y. Kaygusuz, F. Reinhardt, E. Ng Eaton, R.A. Weinberg, Distinct EMT programs control normal mammary stem cells and tumour-initiating cells, Nature. 525 (2015) 256–260.

[60] M.S. Ballard, A. Zhu, N. Iwai, M. Stensrud, A. Mapps, M.P. Postiglione, J.A. Knoblich, L. Hinck, Mammary stem cell self-renewal is regulated by Slit2/Robo1 signaling through Snail and mInscuteable, Cell Rep. 13 (2015) 290.

[61] D. Wang, C. Cai, X. Dong, Q.C. Yu, X.O. Zhang, L. Yang, Y.A. Zeng, Identification of multipotent mammary stem cells by protein C receptor expression, Nature. 517 (2014) 81–84.

[62] Q.H. Nguyen, N. Pervolarakis, K. Blake, D. Ma, R.T. Davis, N. James, A.T. Phung, E. Willey, R. Kumar, E. Jabart, I. Driver, J. Rock, A. Goga, S.A. Khan, D.A. Lawson, Z. Werb, K. Kessenbrock,

Profiling human breast epithelial cells using single cell RNA sequencing identifies cell diversity, Nat Commun. 9 (2018) 1–12.

[63] Y. Han, A. Villarreal-Ponce, G. Gutierrez, Q. Nguyen, P. Sun, T. Wu, B. Sui, G. Berx, T. Brabletz, K. Kessenbrock, Y.A. Zeng, K. Watanabe, X. Dai, Coordinate control of basal epithelial cell fate and stem cell maintenance by core EMT transcription factor Zeb1, Cell Rep. 38 (2022) 110240.

[64] A.P. Morel, C. Ginestier, R.M. Pommier, O. Cabaud, E. Ruiz, J. Wicinski, M. Devouassoux-Shisheboran, V. Combaret, P. Finetti, C. Chassot, C. Pinatel, F. Fauvet, P. Saintigny, E. Thomas, C. Moyret-Lalle, J. Lachuer, E. Despras, J.L. Jauffret, F. Bertucci, J. Guitton, A. Wierinckx, Q. Wang, N. Radosevic-Robin, F. Penault-Llorca, D.G. Cox, F. Hollande, S. Ansieau, J. Caramel, D. Birnbaum, A.M. Vigneron, A. Tissier, E. Charafe-Jauffret, A. Puisieux, A stemness-related ZEB1–MSRB3 axis governs cellular pliancy and breast cancer genome stability, Nat Med. 23 (2017) 568–578.

[65] A. van Keymeulen, A.S. Rocha, M. Ousset, B. Beck, G. Bouvencourt, J. Rock, N. Sharma, S. Dekoninck, C. Blanpain, Distinct stem cells contribute to mammary gland development and maintenance, Nature. 479 (2011) 189–193.

[66] S. Liu, Y. Cong, D. Wang, Y. Sun, L. Deng, Y. Liu, R. Martin-Trevino, L. Shang, S.P. McDermott, M.D. Landis, S. Hong, A. Adams, R. D'Angelo, C. Ginestier, E. Charafe-Jauffret, S.G. Clouthier, D. Birnbaum, S.T. Wong, M. Zhan, J.C. Chang, M.S. Wicha, Breast Cancer Stem Cells Transition between Epithelial and Mesenchymal States Reflective of their Normal Counterparts, Stem Cell Reports. 2 (2014) 78.

[67] J.A. Colacino, E. Azizi, M.D. Brooks, R. Harouaka, S. Fouladdel, S.P. McDermott, M. Lee, D. Hill, J. Madden, J. Boerner, M.L. Cote, M.A. Sartor, L.S. Rozek, M.S. Wicha, Heterogeneity of Human Breast Stem and Progenitor Cells as Revealed by Transcriptional Profiling, Stem Cell Reports. 10 (2018) 1596–1609.

[68] K. Watanabe, A. Villarreal-Ponce, P. Sun, M.L. Salmans, M. Fallahi, B. Andersen, X. Dai, Mammary Morphogenesis and Regeneration Require the Inhibition of EMT at Terminal End Buds by Ovol2 Transcriptional Repressor, Dev Cell. 29 (2014) 59.

[69] T. Hong, K. Watanabe, C.H. Ta, A. Villarreal-Ponce, Q. Nie, X. Dai, An Ovol2-Zeb1 Mutual Inhibitory Circuit Governs Bidirectional and Multi-step Transition between Epithelial and Mesenchymal States, PLoS Comput Biol. 11 (2015) 1004569.

[70] J.M. Schmidt, E. Panzilius, H.S. Bartsch, M. Irmler, J. Beckers, V. Kari, J.R. Linnemann, D. Dragoi, B. Hirschi, U.J. Kloos, S. Sass, F. Theis, S. Kahlert, S.A. Johnsen, K. Sotlar, C.H. Scheel, Stem-cell-like properties and epithelial plasticity arise as stable traits after transient twist1 activation, Cell Rep. 10 (2015) 131–139.

[71] A.E. Parent, K.M. Newkirk, D.F. Kusewitt, Slug (Snai2) Expression during Skin and Hair Follicle Development, Journal of Investigative Dermatology. 130 (2010) 1737–1739.

[72] D.S. Mistry, Y. Chen, Y. Wang, K. Zhang, G.L. Sen, SNAI2 Controls the Undifferentiated State of Human Epidermal Progenitor Cells, Stem Cells. 32 (2014) 3209–3218.

[73] B. de Craene, G. Denecker, P. Vermassen, J. Taminau, C. Mauch, A. Derore, J. Jonkers, E. Fuchs, G. Berx, Epidermal Snail expression drives skin cancer initiation and progression through enhanced cytoprotection, epidermal stem/progenitor cell expansion and enhanced metastatic potential, Cell Death Differ. 21 (2014) 310–320.

[74] J. Srivastava, O. Rho, R.M. Youssef, J. DiGiovanni, Twist1 Regulates Keratinocyte Proliferation and Skin Tumor Promotion, Mol Carcinog. 55 (2016) 941.

[75] M. Saxena, R.K.R. Kalathur, M. Neutzner, G. Christofori, PyMT-1099, a versatile murine cell model for EMT in breast cancer, Sci Rep. 8 (2018) 12123.

[76] S. Joost, A. Zeisel, T. Jacob, X. Sun, G. la Manno, P. Lönnerberg, S. Linnarsson, M. Kasper, Single-Cell Transcriptomics Reveals that Differentiation and Spatial Signatures Shape Epidermal and Hair Follicle Heterogeneity, Cell Syst. 3 (2016) 221–237.

[77] A.S. Goldstein, D.A. Lawson, D. Cheng, W. Sun, I.P. Garraway, O.N. Witte, Trop2 identifies a subpopulation of murine and human prostate basal cells with stem cell characteristics, Proc Natl Acad Sci U S A. 105 (2008) 20882–20887.

[78] K.G. Leong, B.E. Wang, L. Johnson, W.Q. Gao, Generation of a prostate from a single adult stem cell, Nature. 456 (2008) 804–808.

[79] L. Zhang, W. Zhao, J.M. Valdez, C.J. Creighton, L. Xin, Low-Density Taqman miRNA Array Reveals miRNAs Differentially Expressed in Prostatic Stem Cells and Luminal Cells, Prostate. 70 (2010) 297.

[80] J. Wang, H.H. Zhu, M. Chu, Y. Liu, C. Zhang, G. Liu, X. Yang, R. Yang, W.Q. Gao, Symmetrical and asymmetrical division analysis provides evidence for a hierarchy of prostate epithelial cell lineages, Nat Commun. 5 (2014) 1–13.

[81] X. Wang, M.K. de Julio, K.D. Economides, D. Walker, H. Yu, M.V. Halili, Y.P. Hu, S.M. Price, C. Abate-Shen, M.M. Shen, A luminal epithelial stem cell that is a cell of origin for prostate cancer, Nature. 461 (2009) 495.

[82] Z. Kahounová, J. Remšík, R. Fedr, J. Bouchal, A. Mičková, E. Slabáková, L. Binó, A. Hampl, K. Souček, Slug-expressing mouse prostate epithelial cells have increased stem cell potential, Stem Cell Res. 46 (2020) 101844.

[83] X. Wang, H. Xu, C. Cheng, Z. Ji, H. Zhao, Y. Sheng, X. Li, J. Wang, Y. Shu, Y. He, L. Fan, B. Dong, W. Xue, C. Wai Chua, D. Wu, W.Q. Gao, H. He Zhu, Identification of a Zeb1 expressing basal stem cell subpopulation in the prostate, Nat Commun. 11 (2020) 1–16.

[84] J.R. Rock, M.W. Onaitis, E.L. Rawlins, Y. Lu, C.P. Clark, Y. Xue, S.H. Randell, B.L.M. Hogan, Basal cells as stem cells of the mouse trachea and human airway epithelium, Proc Natl Acad Sci U S A. 106 (2009) 12771.

[85] N.R. Hackett, R. Shaykhiev, M.S. Walters, R. Wang, R.K. Zwick, B. Ferris, B. Witover, J. Salit, R.G. Crystal, The Human Airway Epithelial Basal Cell Transcriptome, PLoS One. 6 (2011).

[86] C.E. Barkauskas, M.J. Cronce, C.R. Rackley, E.J. Bowie, D.R. Keene, B.R. Stripp, S.H. Randell, P.W. Noble, B.L.M. Hogan, Type 2 alveolar cells are stem cells in adult lung, J Clin Invest. 123 (2013) 3025–3036.

[87] A. Tesei, W. Zoli, C. Arienti, G. Storci, A.M. Granato, G. Pasquinelli, S. Valente, C. Orrico, M. Rosetti, I. Vannini, A. Dubini, D. Dell'Amore, D. Amadori, M. Bonafè, Isolation of stem/progenitor cells from normal lung tissue of adult humans, Cell Prolif. 42 (2009) 298.

[88] A.E. Parent, C. Choi, K. Caudy, T. Gridley, D.F. Kusewitt, The developmental transcription factor slug is widely expressed in tissues of adult mice, Journal of Histochemistry and Cytochemistry. 52 (2004) 959–965.

[89] K.J. Travaglini, A.N. Nabhan, L. Penland, R. Sinha, A. Gillich, R. v. Sit, S. Chang, S.D. Conley, Y. Mori, J. Seita, G.J. Berry, J.B. Shrager, R.J. Metzger, C.S. Kuo, N. Neff, I.L. Weissman, S.R. Quake, M.A. Krasnow, A molecular cell atlas of the human lung from single-cell RNA sequencing, Nature. 587 (2020) 619–625.

[90] C. ben Brahim, C. Courageux, A. Jolly, B. Ouine, A. Cartier, P. de la Grange, L. de Koning, P. Leroy, Proliferation Genes Repressed by TGF-β Are Downstream of Slug/Snail2 in Normal Bronchial Epithelial Progenitors and Are Deregulated in COPD, Stem Cell Rev Rep. 17 (2021) 703–718.

[91] K. Horvay, F. Casagranda, A. Gany, G.R. Hime, H.E. Abud, Wnt Signaling Regulates Snai1 Expression and Cellular Localization in the Mouse Intestinal Epithelial Stem Cell Niche, Stem Cells Dev. 20 (2010) 737–745.

[92] K. Horvay, T. Jardé, F. Casagranda, V.M. Perreau, K. Haigh, C.M. Nefzger, R. Akhtar, T. Gridley, G. Berx, J.J. Haigh, N. Barker, J.M. Polo, G.R. Hime, H.E. Abud, Snai1 regulates cell lineage allocation and stem cell maintenance in the mouse intestinal epithelium, EMBO J. 34 (2015) 1319.

[93] S. Hisamori, J. Mukohyama, S. Koul, T. Hayashi, M.E. Rothenberg, M. Maeda, T. Isobe, L.E. Valencia Salazar, X. Qian, D.M. Johnston, D. Qian, K. Lao, N. Asai, Y. Kakeji, V.A. Gennarino, D. Sahoo, P. Dalerba, Y. Shimono, Upregulation of BMI1-suppressor miRNAs (miR-200c, miR-203) during terminal differentiation of colon epithelial cells, J Gastroenterol. 57 (2022) 407–422.

[94] A.R. Subbalakshmi, S. Sahoo, K. Biswas, M.K. Jolly, A Computational Systems Biology Approach Identifies SLUG as a Mediator of Partial Epithelial-Mesenchymal Transition (EMT), Cells Tissues Organs. 211 (2022) 109–122.

[95] D. Ishay-Ronen, M. Diepenbruck, R.K.R. Kalathur, N. Sugiyama, S. Tiede, R. Ivanek, G. Bantug, M.F. Morini, J. Wang, C. Hess, G. Christofori, Gain Fat—Lose Metastasis: Converting Invasive Breast Cancer Cells into Adipocytes Inhibits Cancer Metastasis, Cancer Cell. 35 (2019) 17-32.e6.

[96] G. Dontu, W.M. Abdallah, J.M. Foley, K.W. Jackson, M.F. Clarke, M.J. Kawamura, M.S. Wicha, In vitro propagation and transcriptional profiling of human mammary stem/progenitor cells, Genes Dev. 17 (2003) 1253–1270.

[97] T. Lapidot, C. Sirard, J. Vormoor, B. Murdoch, T. Hoang, J. Caceres-Cortes, M. Minden, B. Paterson, M.A. Caligiuri, J.E. Dick, A cell initiating human acute myeloid leukaemia after transplantation into SCID mice, Nature. 367 (1994) 645–648.

[98] S.K. Singh, C. Hawkins, I.D. Clarke, J.A. Squire, J. Bayani, T. Hide, R.M. Henkelman, M.D. Cusimano, P.B. Dirks, Identification of human brain tumour initiating cells, Nature. 432 (2004) 396–401.

[99] P.C. Hermann, S.L. Huber, T. Herrler, A. Aicher, J.W. Ellwart, M. Guba, C.J. Bruns, C. Heeschen, Distinct Populations of Cancer Stem Cells Determine Tumor Growth and Metastatic Activity in Human Pancreatic Cancer, Cell Stem Cell. 1 (2007) 313–323.

[100] C.A. O'Brien, A. Pollett, S. Gallinger, J.E. Dick, A human colon cancer cell capable of initiating tumour growth in immunodeficient mice, Nature. 445 (2006) 106–110.

[101] H. Naotsugu, O. Masahisa, S. Hiroyuki, M. Shinji, T. Fumiaki, M. Koshi, K. Yukio, I. Hiroshi, M. Masaki, CD133+CD44+ population efficiently enriches colon cancer initiating cells, Ann Surg Oncol. 15 (2008) 2927–2933.

[102] M. Al-Hajj, M.S. Wicha, A. Benito-Hernandez, S.J. Morrison, M.F. Clarke, Prospective identification of tumorigenic breast cancer cells, Proc Natl Acad Sci U S A. (2003).

[103] L. Laplane, E. Solary, Towards a classification of stem cells, Elife. 8 (2019).

[104] Y. Shimono, M. Zabala, R.W. Cho, N. Lobo, P. Dalerba, D. Qian, M. Diehn, H. Liu, S.P. Panula, E. Chiao, F.M. Dirbas, G. Somlo, R.A.R. Pera, K. Lao, M.F. Clarke, Down-regulation of miRNA-200c Links Breast Cancer Stem Cells with Normal Stem Cells, Cell. 138 (2009) 592.

[105] D. Iliopoulos, H.A. Hirsch, G. Wang, K. Struhl, Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells via IL6 secretion, Proc Natl Acad Sci U S A. 108 (2011) 1397–1402.

[106] D. Iliopoulos, M. Lindahl-Allen, C. Polytarchou, H.A. Hirsch, P.N. Tsichlis, K. Struhl, Loss of miR-200 inhibition of Suz12 leads to Polycomb-mediated repression required for the formation and maintenance of cancer stem cells, Mol Cell. 39 (2010) 761.

[107] D.J. Mulholland, L. Xin, A. Morim, D. Lawson, O. Witte, H. Wu, LSC Stem/Progenitors Are Tumor Initiating Cells in the Pten Null Prostate Cancer Model, Cancer Res. 69 (2009) 8555.

[108] D.J. Mulholland, N. Kobayashi, M. Ruscetti, A. Zhi, L.M. Tran, J. Huang, M. Gleave, H. Wu, Ptenloss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells, Cancer Res. 72 (2012) 1878.

[109] C.J. Creighton, X. Li, M. Landis, J.M. Dixon, V.M. Neumeister, A. Sjolund, D.L. Rimm, H. Wong, A. Rodriguez, J.I. Herschkowitz, C. Fan, X. Zhang, X. He, A. Pavlick, M.C. Gutierrez, L. Renshaw, A.A. Larionov, D. Faratian, S.G. Hilsenbeck, C.M. Perou, M.T. Lewis, J.M. Rosen, J.C. Chang, Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features, Proc Natl Acad Sci U S A. 106 (2009) 13820–13825.

[110] T. Shibue, R.A. Weinberg, EMT, CSCs, and drug resistance: the mechanistic link and clinical implications, Nat Rev Clin Oncol. 14 (2017) 611–629.

[111] S. Tanabe, S. Quader, H. Cabral, R. Ono, Interplay of EMT and CSC in Cancer and the Potential Therapeutic Strategies, Front Pharmacol. 11 (2020).

[112] S. Jonckheere, J. Adams, D. de Groote, K. Campbell, G. Berx, S. Goossens, Epithelial-Mesenchymal Transition (EMT) as a Therapeutic Target, Cells Tissues Organs. 211 (2022) 157–182.

[113] P.B. Gupta, T.T. Onder, G. Jiang, K. Tao, C. Kuperwasser, R.A. Weinberg, E.S. Lander, Identification of Selective Inhibitors of Cancer Stem Cells by High-Throughput Screening, Cell. 138 (2009) 645–659.

[114] L.C. Carmody, A.R. Germain, L. VerPlank, P.P. Nag, B. Muñoz, J.R. Perez, M.A.J. Palmer, Phenotypic High-Throughput Screening Elucidates Target Pathway in Breast Cancer Stem Cell–Like Cells, SLAS Discovery. 17 (2012) 1204–1210.

[115] K. Polireddy, R. Dong, P.R. McDonald, T. Wang, B. Luke, P. Chen, M. Broward, A. Roy, Q. Chen, Targeting Epithelial-Mesenchymal Transition for Identification of Inhibitors for Pancreatic Cancer Cell Invasion and Tumor Spheres Formation, PLoS One. 11 (2016) e0164811.

[116] Q. Li, C. Chen, A. Kapadia, Q. Zhou, M.K. Harper, J. Schaack, D. v. Labarbera, 3D Models of Epithelial-Mesenchymal Transition in Breast Cancer Metastasis: High-Throughput Screening Assay Development, Validation, and Pilot Screen, SLAS Discovery. 16 (2011) 141–154.

[117] Y. Zhang, J.L. Donaher, S. Das, X. Li, F. Reinhardt, J.A. Krall, A.W. Lambert, P. Thiru, H.R. Keys, M. Khan, M. Hofree, M.M. Wilson, O. Yedier-Bayram, N.A. Lack, T.T. Onder, T. Bagci-Onder, M. Tyler, I. Tirosh, A. Regev, J.A. Lees, R.A. Weinberg, Genome-wide CRISPR screen identifies PRC2 and KMT2D-COMPASS as regulators of distinct EMT trajectories that contribute differentially to metastasis, Nat Cell Biol. 24 (2022) 554–564.

[118] M. Reichert, S. Takano, J. von Burstin, S.-B. Kim, J.-S. Lee, K. Ihida-Stansbury, C. Hahn, S. Heeg, G. Schneider, A.D. Rhim, B.Z. Stanger, A.K. Rustgi, The Prrx1 homeodomain transcription factor plays a central role in pancreatic regeneration and carcinogenesis., Genes Dev. 27 (2013) 288–300.

[119] F. Wang, L. Ma, Z. Zhang, X. Liu, H. Gao, Y. Zhuang, P. Yang, M. Kornmann, X. Tian, Y. Yang, Hedgehog Signaling Regulates Epithelial-Mesenchymal Transition in Pancreatic Cancer Stem-Like Cells., J Cancer. 7 (2016) 408–17.

[120] U. Wellner, J. Schubert, U.C. Burk, O. Schmalhofer, F. Zhu, A. Sonntag, B. Waldvogel, C. Vannier, D. Darling, A. zur Hausen, V.G. Brunton, J. Morton, O. Sansom, J. Schüler, M.P. Stemmler, C. Herzberger, U. Hopt, T. Keck, S. Brabletz, T. Brabletz, The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs, Nat Cell Biol. 11 (2009) 1487–1495.

[121] Q. Ding, Y. Miyazaki, K. Tsukasa, S. Matsubara, M. Yoshimitsu, S. Takao, CD133 facilitates epithelial-mesenchymal transition through interaction with the ERK pathway in pancreatic cancer metastasis, Mol Cancer. 13 (2014) 1–11.

[122] G. Pirozzi, V. Tirino, R. Camerlingo, R. Franco, A. la Rocca, E. Liguori, N. Martucci, F. Paino, N. Normanno, G. Rocco, Epithelial to mesenchymal transition by TGFβ-1 induction increases stemness characteristics in primary non small cell lung cancer cell line, PLoS One. 6 (2011).

[123] K.R. Fischer, A. Durrans, S. Lee, J. Sheng, F. Li, S.T.C. Wong, H. Choi, T. el Rayes, S. Ryu, J. Troeger, R.F. Schwabe, L.T. Vahdat, N.K. Altorki, V. Mittal, D. Gao, EMT is not required for lung metastasis but contributes to chemoresistance, Nature. 527 (2015) 472.

[124] Y. Chen, V.S. LeBleu, J.L. Carstens, H. Sugimoto, X. Zheng, S. Malasi, D. Saur, R. Kalluri, Dual reporter genetic mouse models of pancreatic cancer identify an epithelial-to-mesenchymal transition-independent metastasis program, EMBO Mol Med. 10 (2018).

[125] X. Zheng, J.L. Carstens, J. Kim, M. Scheible, J. Kaye, H. Sugimoto, C.C. Wu, V.S. Lebleu, R. Kalluri, Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer, Nature. (2015).

[126] V. Tiran, J. Lindenmann, L. Brcic, E. Heitzer, S. Stanzer, N.G. Tabrizi-Wizsy, E. Stacher, H. Stoeger, H.H. Popper, M. Balic, N. Dandachi, Primary patient-derived lung adenocarcinoma cell culture challenges the association of cancer stem cells with epithelial-to-mesenchymal transition, Scientific Reports 2017 7:1. 7 (2017) 1–11.

[127] T. Celià-Terrassa, Ó. Meca-Cortés, F. Mateo, A.M. de Paz, N. Rubio, A. Arnal-Estapé, B.J. Ell, R. Bermudo, A. Díaz, M. Guerra-Rebollo, J.J. Lozano, C. Estarás, C. Ulloa, D. Álvarez-Simón, J. Milà, R. Vilella, R. Paciucci, M. Martínez-Balbás, A.G. de Herreros, R.R. Gomis, Y. Kang, J. Blanco, P.L. Fernández, T.M. Thomson, Epithelial-mesenchymal transition can suppress major attributes of human epithelial tumor-initiating cells, J Clin Invest. 122 (2012) 1849.

[128] A. Grosse-Wilde, A.F. D'Hérouël, E. McIntosh, G. Ertaylan, A. Skupin, R.E. Kuestner, A. del Sol, K.A. Walters, S. Huang, Stemness of the hybrid Epithelial/Mesenchymal State in Breast Cancer and Its Association with Poor Survival, PLoS One. 10 (2015).

[129] B. Bierie, S.E. Pierce, C. Kroeger, D.G. Stover, D.R. Pattabiraman, P. Thiru, J.L. Donaher, F. Reinhardt, C.L. Chaffer, Z. Keckesova, R.A. Weinberg, Integrin-β4 identifies cancer stem cell-enriched populations of partially mesenchymal carcinoma cells, Proc Natl Acad Sci U S A. 114 (2017) E2337–E2346.

[130] C. Kröger, A. Afeyan, J. Mraz, E.N. Eaton, F. Reinhardt, Y.L. Khodor, P. Thiru, B. Bierie, X. Ye, C.B. Burge, R.A. Weinberg, Acquisition of a hybrid E/M state is essential for tumorigenicity of basal breast cancer cells, Proc Natl Acad Sci U S A. 116 (2019) 7353–7362.

[131] X.K. Qi, H.Q. Han, H.J. Zhang, M. Xu, L. Li, L. Chen, T. Xiang, Q.S. Feng, T. Kang, C.N. Qian, M.Y. Cai, Q. Tao, Y.X. Zeng, L. Feng, OVOL2 links stemness and metastasis via fine-tuning epithelial-mesenchymal transition in nasopharyngeal carcinoma, Theranostics. 8 (2018) 2202.

[132] F. Andriani, G. Bertolini, F. Facchinetti, E. Baldoli, M. Moro, P. Casalini, R. Caserini, M. Milione, G. Leone, G. Pelosi, U. Pastorino, G. Sozzi, L. Roz, Conversion to stem-cell state in response to microenvironmental cues is regulated by balance between epithelial and mesenchymal features in lung cancer cells, Mol Oncol. 10 (2016) 253.

[133] A. Eramo, F. Lotti, G. Sette, E. Pilozzi, M. Biffoni, A. di Virgilio, C. Conticello, L. Ruco, C. Peschle, R. de Maria, Identification and expansion of the tumorigenic lung cancer stem cell population, Cell Death Differ. 15 (2007) 504–514.

[134] F. Lüönd, N. Sugiyama, R. Bill, L. Bornes, C. Hager, F. Tang, N. Santacroce, C. Beisel, R. Ivanek, T. Bürglin, S. Tiede, J. van Rheenen, G. Christofori, Distinct contributions of partial and full EMT to breast cancer malignancy, Dev Cell. 56 (2021) 3203-3221.e11.

[135] A.M. Krebs, J. Mitschke, M.L. Losada, O. Schmalhofer, M. Boerries, H. Busch, M. Boettcher, Di. Mougiakakos, W. Reichardt, P. Bronsert, V.G. Brunton, C. Pilarsky, T.H. Winkler, S. Brabletz, M.P. Stemmler, T. Brabletz, The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer, Nat Cell Biol. 19 (2017) 518–529.

[136] M. Latil, D. Nassar, B. Beck, S. Boumahdi, L. Wang, A. Brisebarre, C. Dubois, E. Nkusi, S. Lenglez, A. Checinska, A. Vercauteren Drubbel, M. Devos, W. Declercq, R. Yi, C. Blanpain, Cell-Type-Specific Chromatin States Differentially Prime Squamous Cell Carcinoma Tumor-Initiating Cells for Epithelial to Mesenchymal Transition, Cell Stem Cell. 20 (2017) 191-204.e5.

[137] I. Pastushenko, A. Brisebarre, A. Sifrim, M. Fioramonti, T. Revenco, S. Boumahdi, A. van Keymeulen, D. Brown, V. Moers, S. Lemaire, S. de clercq, E. Minguijón, C. Balsat, Y. Sokolow, C. Dubois, F. de cock, S. Scozzaro, F. Sopena, A. Lanas, I. Salmon, J. Marine, T. Voet, P.A. Sotiropoulou, C. Blanpain, Identification of the tumour transition states occurring during EMT, Nature. 556 (2018) 463–468.

[138] I. Pastushenko, F. Mauri, Y. Song, F. de Cock, B. Meeusen, B. Swedlund, F. Impens, D. van Haver, M. Opitz, M. Thery, Y. Bareche, G. Lapouge, M. Vermeersch, Y.R. van Eycke, C. Balsat, C. Decaestecker, Y. Sokolow, S. Hassid, A. Perez-Bustillo, B. Agreda-Moreno, L. Rios-Buceta, P. Jaen, P. Redondo, R. Sieira-Gil, J.F. Millan-Cayetano, O. Sanmatrtin, N. D'Haene, V. Moers, M. Rozzi, J. Blondeau, S. Lemaire, S. Scozzaro, V. Janssens, M. de Troya, C. Dubois, D. Pérez-Morga, I. Salmon, C. Sotiriou, F. Helmbacher, C. Blanpain, Fat1 deletion promotes hybrid EMT state, tumour stemness and metastasis, Nature. 589 (2021) 448–455.

[139] J.H. Tsai, J.L. Donaher, D.A. Murphy, S. Chau, J. Yang, Spatiotemporal Regulation of Epithelial-Mesenchymal Transition Is Essential for Squamous Cell Carcinoma Metastasis, Cancer Cell. 22 (2012) 725–736.

[140] M. Ruscetti, B. Quach, E.L. Dadashian, D.J. Mulholland, H. Wu, Tracking and functional characterization of epithelial-mesenchymal transition and mesenchymal tumor cells during prostate cancer metastasis, Cancer Res. 75 (2015) 2749–2759.

[141] S. Pasani, S. Sahoo, M.K. Jolly, Hybrid E/M Phenotype(s) and Stemness: A Mechanistic Connection Embedded in Network Topology, J Clin Med. 10 (2020) 1–19.

[142] N. Aceto, A. Bardia, D.T. Miyamoto, M.C. Donaldson, B.S. Wittner, J.A. Spencer, M. Yu, A. Pely, A. Engstrom, H. Zhu, B.W. Brannigan, R. Kapur, S.L. Stott, T. Shioda, S. Ramaswamy, D.T. Ting, C.P. Lin, M. Toner, D.A. Haber, S. Maheswaran, Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis, Cell. 158 (2014) 1110–1122.

[143] K.J. Cheung, V. Padmanaban, V. Silvestri, K. Schipper, J.D. Cohen, A.N. Fairchild, M.A. Gorin, J.E. Verdone, K.J. Pienta, J.S. Bader, A.J. Ewald, Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters, Proc Natl Acad Sci U S A. 113 (2016) E854–E863.

[144] N.M. Aiello, R. Maddipati, R.J. Norgard, D. Balli, J. Li, S. Yuan, T. Yamazoe, T. Black, A. Sahmoud, E.E. Furth, D. Bar-Sagi, B.Z. Stanger, EMT subtype influences epithelial plasticity and mode of cell migration, Dev Cell. 45 (2018) 681.

[145] M.J. Schliekelman, A. Taguchi, J. Zhu, X. Dai, J. Rodriguez, M. Celiktas, Q. Zhang, A. Chin, C.H. Wong, H. Wang, L. McFerrin, S.A. Selamat, C. Yang, E.M. Kroh, K.S. Garg, C. Behrens, A.F. Gazdar, I.A. Laird-Offringa, M. Tewari, I.I. Wistuba, J.P. Thiery, S.M. Hanash, Molecular portraits of epithelial, mesenchymal, and hybrid states in lung adenocarcinoma and their relevance to survival, Cancer Res. 75 (2015) 1789–1800.

[146] Q. Quan, X. Wang, C. Lu, W. Ma, Y. Wang, G. Xia, C. Wang, G. Yang, Cancer stem-like cells with hybrid epithelial/mesenchymal phenotype leading the collective invasion, Cancer Sci. 111 (2020) 467–476.

[147] S. Gkountela, F. Castro-Giner, B.M. Szczerba, M. Vetter, J. Landin, R. Scherrer, I. Krol, M.C. Scheidmann, C. Beisel, C.U. Stirnimann, C. Kurzeder, V. Heinzelmann-Schwarz, C. Rochlitz, W.P. Weber, N. Aceto, Circulating Tumor Cell Clustering Shapes DNA Methylation to Enable Metastasis Seeding, Cell. 176 (2019) 98.

[148] A. Grosse-Wilde, R.E. Kuestner, S.M. Skelton, E. MacIntosh, A. Fouquier d'Hérouël, G. Ertaylan, A. del Sol, A. Skupin, S. Huang, Loss of inter-cellular cooperation by complete epithelial-mesenchymal transition supports favorable outcomes in basal breast cancer patients, Oncotarget. 9 (2018) 20018.

[149] T. Tsuji, S. Ibaragi, K. Shima, M.G. Hu, M. Katsurano, A. Sasaki, G.F. Hu, Epithelial-mesenchymal transition induced by growth suppressor p12CDK2-AP1 promotes tumor cell local invasion but suppresses distant colony growth, Cancer Res. 68 (2008) 10377.

[150] K. Hari, V. Ullanat, A. Balasubramanian, A. Gopalan, M.K. Jolly, Landscape of epithelial–mesenchymal plasticity as an emergent property of coordinated teams in regulatory networks, Elife. 11 (2022).

[151] P.A. Gregory, A.G. Bert, E.L. Paterson, S.C. Barry, A. Tsykin, G. Farshid, M.A. Vadas, Y. Khew-Goodall, G.J. Goodall, The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, Nat Cell Biol. 10 (2008) 593–601.

[152] U. Burk, J. Schubert, U. Wellner, O. Schmalhofer, E. Vincan, S. Spaderna, T. Brabletz, A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells, EMBO Rep. 9 (2008) 582–589.

[153] C.P. Bracken, P.A. Gregory, N. Kolesnikoff, A.G. Bert, J. Wang, M.F. Shannon, G.J. Goodall, A Double-Negative Feedback Loop between ZEB1-SIP1 and the microRNA-200 Family Regulates Epithelial-Mesenchymal Transition, Cancer Res. 68 (2008) 7846–7854.

[154] S.-M. Park, A.B. Gaur, E. Lengyel, M.E. Peter, The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2., Genes Dev. 22 (2008) 894–907.

[155] H. Siemens, R. Jackstadt, S. Hünten, M. Kaller, A. Menssen, U. Götz, H. Hermeking, miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions., Cell Cycle. 10 (2011) 4256–71.

[156] P. Dong, Y. Xiong, H. Watari, S.J.B. Hanley, Y. Konno, K. Ihira, T. Yamada, M. Kudo, J. Yue, N. Sakuragi, MiR-137 and miR-34a directly target Snail and inhibit EMT, invasion and sphere-forming ability of ovarian cancer cells, J Exp Clin Cancer Res. 35 (2016).

[157] N.H. Kim, H.S. Kim, X.-Y. Li, I. Lee, H.-S. Choi, S.E. Kang, S.Y. Cha, J.K. Ryu, D. Yoon, E.R. Fearon, R.G. Rowe, S. Lee, C.A. Maher, S.J. Weiss, J.I. Yook, A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial-mesenchymal transition., J Cell Biol. 195 (2011) 417–33.

[158] V. Tarasov, P. Jung, B. Verdoodt, D. Lodygin, A. Epanchintsev, A. Menssen, G. Meister, H. Hermeking, Differential regulation of microRNAs by p53 revealed by massively parallel sequencing: miR-34a is a p53 target that induces apoptosis and G1-arrest, Cell Cycle. 6 (2007) 1586–1593.

[159] N. Raver-Shapira, E. Marciano, E. Meiri, Y. Spector, N. Rosenfeld, N. Moskovits, Z. Bentwich, M. Oren, Transcriptional activation of miR-34a contributes to p53-mediated apoptosis, Mol Cell. 26 (2007) 731–743.

[160] L. He, X. He, L.P. Lim, E. de Stanchina, Z. Xuan, Y. Liang, W. Xue, L. Zender, J. Magnus, D. Ridzon, A.L. Jackson, P.S. Linsley, C. Chen, S.W. Lowe, M.A. Cleary, G.J. Hannon, A microRNA component of the p53 tumour suppressor network, Nature. 447 (2007) 1130–1134.

[161] D.C. Corney, A. Flesken-Nikitin, A.K. Godwin, W. Wang, A.Y. Nikitin, MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth, Cancer Res. 67 (2007) 8433–8438.

[162] T.C. Chang, E.A. Wentzel, O.A. Kent, K. Ramachandran, M. Mullendore, K.H. Lee, G. Feldmann, M. Yamakuchi, M. Ferlito, C.J. Lowenstein, D.E.E. Arking, M.A. Beer, A. Maitra, J.T. Mendell, Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis, Mol Cell. 26 (2007) 745–752.

[163] G.T. Bommer, I. Gerin, Y. Feng, A.J. Kaczorowski, R. Kuick, R.E. Love, Y. Zhai, T.J. Giordano, Z.S. Qin, B.B. Moore, O.A. MacDougald, K.R. Cho, E.R. Fearon, p53-Mediated Activation of miRNA34 Candidate Tumor-Suppressor Genes, Current Biology. 17 (2007) 1298–1307.

[164] M. Diepenbruck, S. Tiede, M. Saxena, R. Ivanek, R.K.R. Kalathur, F. Lüönd, N. Meyer-Schaller, G. Christofori, miR-1199-5p and Zeb1 function in a double-negative feedback loop potentially coordinating EMT and tumour metastasis, Nature Communications 2017 8:1. 8 (2017) 1–14.

[165] D. Ren, M. Wang, W. Guo, S. Huang, Z. Wang, X. Zhao, H. Du, L. Song, X. Peng, Double-negative feedback loop between ZEB2 and miR-145 regulates epithelial-mesenchymal transition and stem cell properties in prostate cancer cells, Cell Tissue Res. 358 (2014) 763–778.

[166] F. Yu, H. Yao, P. Zhu, X. Zhang, Q. Pan, C. Gong, Y. Huang, X. Hu, F. Su, J. Lieberman, E. Song, let-7 Regulates Self Renewal and Tumorigenicity of Breast Cancer Cells, Cell. 131 (2007) 1109–1123.

[167] T.T. Liao, W.H. Hsu, C.H. Ho, W.L. Hwang, H.Y. Lan, T. Lo, C.C. Chang, S.K. Tai, M.H. Yang, Let-7 Modulates Chromatin Configuration and Target Gene Repression through Regulation of the ARID3B Complex, Cell Rep. 14 (2016) 520–533.

[168] B. Jin, W. Wang, X. xin Meng, G. Du, J. Li, S. zhe Zhang, B. hai Zhou, Z. hao Fu, Let-7 inhibits self-renewal of hepatocellular cancer stem-like cells through regulating the epithelial-mesenchymal transition and the Wnt signaling pathway, BMC Cancer. 16 (2016).

[169] J. Yu, M.A. Vodyanik, K. Smuga-Otto, J. Antosiewicz-Bourget, J.L. Frane, S. Tian, J. Nie, G.A. Jonsdottir, V. Ruotti, R. Stewart, I.I. Slukvin, J.A. Thomson, Induced pluripotent stem cell lines derived from human somatic cells, Science. 318 (2007) 1917–1920.

[170] C.S. Chien, M.L. Wang, P.Y. Chu, Y.L. Chang, W.H. Liu, C.C. Yu, Y.T. Lan, P.I. Huang, Y.Y. Lee, Y.W. Chen, W.L. Lo, S.H. Chiou, Lin28B/Let-7 regulates expression of Oct4 and Sox2 and reprograms oral squamous cell carcinoma cells to a stem-like state, Cancer Res. 75 (2015) 2553–2565.

[171] X. Yang, X. Lin, X. Zhong, S. Kaur, N. Li, S. Liang, H. Lassus, L. Wang, D. Katsaros, K. Montone, X. Zhao, Y. Zhang, R. Bützow, G. Coukos, L. Zhang, Double negative feedback loop between reprogramming factor LIN28 and microRNA let-7 regulates aldehyde dehydrogenase 1-positive cancer stem cells, Cancer Res. 70 (2010) 9463.

[172] L. Guo, C. Chen, M. Shi, F. Wang, X. Chen, D. Diao, M. Hu, M. Yu, L. Qian, N. Guo, Stat3-coordinated Lin-28–let-7–HMGA2 and miR-200–ZEB1 circuits initiate and maintain oncostatin M-driven epithelial–mesenchymal transition, Oncogene 2013 32:45. 32 (2013) 5272–5282.

[173] L. Guo, X. Cheng, H. Chen, C. Chen, S. Xie, M. Zhao, D. Liu, Q. Deng, Y. Liu, X. Wang, X. Chen, J. Wang, Z. Yin, S. Qi, J. Gao, Y. Ma, N. Guo, M. Shi, Induction of breast cancer stem cells by M1 macrophages through Lin-28B-let-7-HMGA2 axis, Cancer Lett. 452 (2019) 213–225.

[174] J. Lovnicki, Y. Gan, T. Feng, Y. Li, N. Xie, C.H. Ho, A.R. Lee, X. Chen, L. Nappi, B. Han, L. Fazli, J. Huang, M.E. Gleave, X. Dong, LIN28B promotes the development of neuroendocrine prostate cancer, J Clin Invest. 130 (2020) 5338.

[175] Y. Li, T.G. Vandenboom, D. Kong, Z. Wang, S. Ali, P.A. Philip, F.H. Sarkar, Up-regulation of miR-200 and let-7 by natural agents leads to the reversal of epithelial-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells, Cancer Res. 69 (2009) 6704.

[176] Y. Liu, H. Li, J. Feng, X. Cui, W. Huang, Y. Li, F. Su, Q. Liu, J. Zhu, X. Lv, J. Chen, D. Huang, F. Yu, Lin28 Induces Epithelial-to-Mesenchymal Transition and Stemness via Downregulation of Let-7a in Breast Cancer Cells, PLoS One. 8 (2013).

[177] W.H. Yang, H.Y. Lan, C.H. Huang, S.K. Tai, C.H. Tzeng, S.Y. Kao, K.J. Wu, M.C. Hung, M.H. Yang, RAC1 activation mediates Twist1-induced cancer cell migration, Nature Cell Biology 2012 14:4. 14 (2012) 366–374.

[178] H. Wang, E. Chirshev, N. Hojo, T. Suzuki, A. Bertucci, M. Pierce, C. Perry, R. Wang, J. Zink, C.A. Glackin, Y.J. Ioffe, J.J. Unternaehrer, The Epithelial–Mesenchymal Transcription Factor SNAI1 Represses Transcription of the Tumor Suppressor miRNA let-7 in Cancer, Cancers (Basel). 13 (2021) 1–18.

[179] D. Kong, S. Banerjee, A. Ahmad, Y. Li, Z. Wang, S. Sethi, F.H. Sarkar, Epithelial to Mesenchymal Transition Is Mechanistically Linked with Stem Cell Signatures in Prostate Cancer Cells, PLoS One. 5 (2010).

[180] H. Sato, K. Shien, S. Tomida, K. Okayasu, K. Suzawa, S. Hashida, H. Torigoe, M. Watanabe, H. Yamamoto, J. Soh, H. Asano, K. Tsukuda, S. Miyoshi, S. Toyooka, Targeting the miR-200c/LIN28B axis in acquired EGFR-TKI resistance non-small cell lung cancer cells harboring EMT features, Sci Rep. 7 (2017) 1–10.

[181] S. Thuault, E.J. Tan, H. Peinado, A. Cano, C.H. Heldin, A. Moustakas, HMGA2 and Smads Co-regulate SNAIL1 Expression during Induction of Epithelial-to-Mesenchymal Transition, J Biol Chem. 283 (2008) 33437.

[182] W. Zhou, X.L. Ye, J. Xu, M.G. Cao, Z.Y. Fang, L.Y. Li, G.H. Guan, Q. Liu, Y.H. Qian, D. Xie, The lncRNA H19 mediates breast cancer cell plasticity during EMT and MET plasticity by differentially sponging miR-200b/c and let-7b, Sci Signal. 10 (2017).

[183] A.N. Kallen, X.B. Zhou, J. Xu, C. Qiao, J. Ma, L. Yan, L. Lu, C. Liu, J.S. Yi, H. Zhang, W. Min, A.M. Bennett, R.I. Gregory, Y. Ding, Y. Huang, The imprinted H19 lncRNA antagonizes let-7 microRNAs, Mol Cell. 52 (2013) 101–112.

[184] C. Ma, K. Nong, H. Zhu, W. Wang, X. Huang, Z. Yuan, K. Ai, H19 promotes pancreatic cancer metastasis by derepressing let-7's suppression on its target HMGA2-mediated EMT, Tumor Biology. 35 (2014) 9163–9169.

[185] F. Peng, T.T. Li, K.L. Wang, G.Q. Xiao, J.H. Wang, H.D. Zhao, Z.J. Kang, W.J. Fan, L.L. Zhu, M. Li, B. Cui, F.M. Zheng, H.J. Wang, E.W.F. Lam, B. Wang, J. Xu, Q. Liu, H19/let-7/LIN28 reciprocal negative regulatory circuit promotes breast cancer stem cell maintenance, Cell Death & Disease 2017 8:1. 8 (2017) e2569–e2569.

[186] Y. Wu, Y. Zhou, J. He, H. Sun, Z. Jin, Long non-coding RNA H19 mediates ovarian cancer cell cisplatin-resistance and migration during EMT, Int J Clin Exp Pathol. 12 (2019) 2506–2515.

[187] W.C. Liang, W.M. Fu, C.W. Wong, Y. Wang, W.M. Wang, G.X. Hu, L. Zhang, L.J. Xiao, D.C.C. Wan, J.F. Zhang, M.M.Y. Waye, The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer, Oncotarget. 6 (2015) 22513.

[188] N. Singh, V.R. Ramnarine, J.H. Song, R. Pandey, S.K.R. Padi, M. Nouri, V. Olive, M. Kobelev, K. Okumura, D. McCarthy, M.M. Hanna, P. Mukherjee, B. Sun, B.R. Lee, J.B. Parker, D. Chakravarti, N.A. Warfel, M. Zhou, J.J. Bearss, E.A. Gibb, M. Alshalalfa, R.J. Karnes, E.J. Small, R. Aggarwal, F. Feng, Y. Wang, R. Buttyan, A. Zoubeidi, M. Rubin, M. Gleave, F.J. Slack, E. Davicioni, H. Beltran, C. Collins, A.S. Kraft, The long noncoding RNA H19 regulates tumor plasticity in neuroendocrine prostate cancer, Nat Commun. 12 (2021) 1–20.

[189] K. Watanabe, Y. Liu, S. Noguchi, M. Murray, J.C. Chang, M. Kishima, H. Nishimura, K. Hashimoto, A. Minoda, H. Suzuki, OVOL2 induces mesenchymal-to-epithelial transition in fibroblasts and enhances cell-state reprogramming towards epithelial lineages, Sci Rep. 9 (2019) 1–12.

[190] E. Nikolopoulou, C.S. Hirst, G. Galea, C. Venturini, D. Moulding, A.R. Marshall, A. Rolo, S.C.P. de Castro, A.J. Copp, N. D.E. Greene, Spinal neural tube closure depends on regulation of surface ectoderm identity and biomechanics by Grhl2, Nat Commun. 10 (2019) 1–17.

[191] J. Xiang, X. Fu, W. Ran, Z. Wang, Grhl2 reduces invasion and migration through inhibition of TGFβ-induced EMT in gastric cancer, Oncogenesis. 6 (2017).

[192] S. Werner, S. Frey, S. Riethdorf, C. Schulze, M. Alawi, L. Kling, V. Vafaizadeh, G. Sauter, L. Terracciano, U. Schumacher, K. Pantel, V. Assmann, Dual Roles of the Transcription Factor Grainyhead-like 2 (GRHL2) in Breast Cancer, J Biol Chem. 288 (2013) 22993.

[193] H. Nishino, S. Takano, H. Yoshitomi, K. Suzuki, S. Kagawa, R. Shimazaki, H. Shimizu, K. Furukawa, M. Miyazaki, M. Ohtsuka, Grainyhead-like 2 (GRHL2) regulates epithelial plasticity in pancreatic cancer progression, Cancer Med. 6 (2017) 2686.

[194] K. Senga, K.E. Mostov, T. Mitaka, A. Miyajima, N. Tanimizu, Grainyhead-like 2 regulates epithelial morphogenesis by establishing functional tight junctions through the organization of a molecular network among claudin3, claudin4, and Rab25, Mol Biol Cell. 23 (2012) 2845.

[195] V.Y. Chung, T.Z. Tan, M. Tan, M.K. Wong, K.T. Kuay, Z. Yang, J. Ye, J. Muller, C.M. Koh, E. Guccione, J.P. Thiery, R.Y.J. Huang, GRHL2-miR-200-ZEB1 maintains the epithelial status of ovarian cancer through transcriptional regulation and histone modification, Sci Rep. 6 (2016) 1–15.

[196] K. Kitazawa, T. Hikichi, T. Nakamura, K. Mitsunaga, A. Tanaka, M. Nakamura, T. Yamakawa, S. Furukawa, M. Takasaka, N. Goshima, A. Watanabe, K. Okita, S. Kawasaki, M. Ueno, S. Kinoshita, S. Masui, OVOL2 Maintains the Transcriptional Program of Human Corneal Epithelium by Suppressing Epithelial-to-Mesenchymal Transition, Cell Rep. 15 (2016) 1359–1368.

[197] H. Roca, J. Hernandez, S. Weidner, R.C. McEachin, D. Fuller, S. Sud, T. Schumann, J.E. Wilkinson, A. Zaslavsky, H. Li, C.A. Maher, S. Daignault-Newton, P.N. Healy, K.J. Pienta, Transcription Factors OVOL1 and OVOL2 Induce the Mesenchymal to Epithelial Transition in Human Cancer, PLoS One. 8 (2013) 76773.

[198] C. Xu, T. Yan, J. Yang, OVOL1 inhibits oral squamous cell carcinoma growth and metastasis by suppressing zinc finger E-box binding homeobox 1, Int J Clin Exp Pathol. 12 (2019) 2801.

[199] W. Chen, J.K. Yi, T. Shimane, S. Mehrazarin, Y.L. Lin, K.H. Shin, R.H. Kim, N.H. Park, M.K. Kang, Grainyhead-like 2 regulates epithelial plasticity and stemness in oral cancer cells, Carcinogenesis. 37 (2016) 500.

[200] R. Bhattacharya, T. Mitra, S. Ray Chaudhuri, S.S. Roy, Mesenchymal splice isoform of CD44 (CD44s) promotes EMT/invasion and imparts stem-like properties to ovarian cancer cells, J Cell Biochem. 119 (2018) 3373–3383.

[201] C.C. Warzecha, T.K. Sato, B. Nabet, J.B. Hogenesch, R.P. Carstens, ESRP1 and ESRP2 Are Epithelial Cell-Type-Specific Regulators of FGFR2 Splicing, Mol Cell. 33 (2009) 591–601.

[202] B.T. Preca, K. Bajdak, K. Mock, V. Sundararajan, J. Pfannstiel, J. Maurer, U. Wellner, U.T. Hopt, T. Brummer, S. Brabletz, T. Brabletz, M.P. Stemmler, A self-enforcing CD44s/ZEB1 feedback loop maintains EMT and stemness properties in cancer cells, Int J Cancer. 137 (2015) 2566–2577.

[203] L.M. Reinke, Y. Xu, C. Cheng, Snail Represses the Splicing Regulator Epithelial Splicing Regulatory Protein 1 to Promote Epithelial-Mesenchymal Transition, J Biol Chem. 287 (2012) 36435.

[204] J.E. Larsen, V. Nathan, J.K. Osborne, R.K. Farrow, D. Deb, J.P. Sullivan, P.D. Dospoy, A. Augustyn, S.K. Hight, M. Sato, L. Girard, C. Behrens, I.I. Wistuba, A.F. Gazdar, N.K. Hayward, J.D. Minna, ZEB1 drives epithelial-to-mesenchymal transition in lung cancer, J Clin Invest. 126 (2016) 3219–3235.

[205] B.T. Preca, K. Bajdak, K. Mock, W. Lehmann, V. Sundararajan, P. Bronsert, A. Matzge-Ogi, V. Orian-Rousseau, S. Brabletz, T. Brabletz, J. Maurer, M.P. Stemmler, A novel ZEB1/HAS2 positive feedback loop promotes EMT in breast cancer, Oncotarget. 8 (2017) 11530.

[206] M.K. Jolly, B.T. Preca, S.C. Tripathi, D. Jia, J.T. George, S.M. Hanash, T. Brabletz, M.P. Stemmler, J. Maurer, H. Levine, Interconnected feedback loops among ESRP1, HAS2, and CD44 regulate epithelial-mesenchymal plasticity in cancer, APL Bioeng. 2 (2018) 031908.

[207] F. Bocci, M.K. Jolly, J.T. George, H. Levine, J.N. Onuchic, A mechanism-based computational model to capture the interconnections among epithelial-mesenchymal transition, cancer stem cells and Notch-Jagged signaling, Oncotarget. 9 (2018) 29906.

[208] S.J. Bray, Notch signalling: a simple pathway becomes complex, Nat Rev Mol Cell Biol. 7 (2006) 678–689.

[209] F. Bocci, L. Gearhart-Serna, M. Boareto, M. Ribeiro, E. Ben-Jacob, G.R. Devi, H. Levine, J.N. Onuchic, M.K. Jolly, Toward understanding cancer stem cell heterogeneity in the tumor microenvironment, Proc Natl Acad Sci U S A. 116 (2019) 148–157.

[210] M. Boareto, M.K. Jolly, A. Goldman, M. Pietilä, S.A. Mani, S. Sengupta, E. Ben-Jacob, H. Levine, J.N. Onuchic, Notch-Jagged signalling can give rise to clusters of cells exhibiting a hybrid epithelial/mesenchymal phenotype, J R Soc Interface. 13 (2016).

[211] P. Bu, K.Y. Chen, J.H. Chen, L. Wang, J. Walters, Y.J. Shin, J.P. Goerger, J. Sun, M. Witherspoon, N. Rakhilin, J. Li, H. Yang, J. Milsom, S. Lee, W. Zipfel, M.M. Jin, Z.H. Gümüş, S.M. Lipkin, X. Shen, A microRNA miR-34a Regulated Bimodal Switch targets Notch in Colon Cancer Stem Cells, Cell Stem Cell. 12 (2013) 602.

[212] S. Brabletz, K. Bajdak, S. Meidhof, U. Burk, G. Niedermann, E. Firat, U. Wellner, A. Dimmler, G. Faller, J. Schubert, T. Brabletz, The ZEB1/miR-200 feedback loop controls Notch signalling in cancer cells, EMBO J. 30 (2011) 770.

[213] F. Bocci, M.K. Jolly, S.C. Tripathi, M. Aguilar, S.M. Hanash, H. Levine, J.N. Onuchic, Numb prevents a complete epithelial–mesenchymal transition by modulating Notch signalling, J R Soc Interface. 14 (2017).

[214] J. Zhang, X. Shao, H. Sun, K. Liu, Z. Ding, J. Chen, L. Fang, W. Su, Y. Hong, H. Li, H. Li, NUMB negatively regulates the epithelial-mesenchymal transition of triple-negative breast cancer by antagonizing Notch signaling, Oncotarget. 7 (2016) 61036.

[215] C. Sahlgren, M. v. Gustafsson, S. Jin, L. Poellinger, U. Lendahl, Notch signaling mediates hypoxia-induced tumor cell migration and invasion, Proc Natl Acad Sci U S A. 105 (2008) 6392–6397.

[216] T. Shiraishi, J.E. Verdone, J. Huang, U.D. Kahlert, J.R. Hernandez, G. Torga, J.C. Zarif, T. Epstein, R. Gatenby, A. McCartney, J.H. Elisseeff, S.M. Mooney, S.S. An, K.J. Pienta, Glycolysis is the primary

bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells, Oncotarget. 6 (2015) 130.

[217] M. Masin, J. Vazquez, S. Rossi, S. Groeneveld, N. Samson, P.C. Schwalie, B. Deplancke, L.E. Frawley, J. Gouttenoire, D. Moradpour, T.G. Oliver, E. Meylan, GLUT3 is induced during epithelial-mesenchymal transition and promotes tumor cell proliferation in non-small cell lung cancer, Cancer Metab. 2 (2014) 11.

[218] Y. Sun, A. Daemen, G. Hatzivassiliou, D. Arnott, C. Wilson, G. Zhuang, M. Gao, P. Liu, A. Boudreau, L. Johnson, J. Settleman, Metabolic and transcriptional profiling reveals pyruvate dehydrogenase kinase 4 as a mediator of epithelial-mesenchymal transition and drug resistance in tumor cells, Cancer Metab. 2 (2014).

[219] A. Hamabe, M. Konno, N. Tanuma, H. Shima, K. Tsunekuni, K. Kawamoto, N. Nishida, J. Koseki, K. Mimori, N. Gotoh, H. Yamamoto, Y. Doki, M. Mori, H. Ishii, Role of pyruvate kinase M2 in transcriptional regulation leading to epithelial-mesenchymal transition, Proc Natl Acad Sci U S A. 111 (2014) 15526–15531.

[220] S. Muralidharan, S. Sahoo, A. Saha, S. Chandran, S.S. Majumdar, S. Mandal, H. Levine, M.K. Jolly, Quantifying the Patterns of Metabolic Plasticity and Heterogeneity along the Epithelial-Hybrid-Mesenchymal Spectrum in Cancer., Biomolecules. 12 (2022).

[221] D. Bhattacharya, A.P. Azambuja, M. Simoes-Costa, Metabolic Reprogramming Promotes Neural Crest Migration via Yap/Tead Signaling, Dev Cell. 53 (2020) 199-211.e6.

[222] S.J. DeCamp, V.M.K. Tsuda, J. Ferruzzi, S.A. Koehler, J.T. Giblin, D. Roblyer, M.H. Zaman, S.T. Weiss, A. Kılıç, M. de Marzio, C.Y. Park, N.C. Ogassavara, J.A. Mitchel, J.P. Butler, J.J. Fredberg, Epithelial layer unjamming shifts energy metabolism toward glycolysis, Sci Rep. 10 (2020) 18302.

[223] Y. Matsuno, A.L. Coelho, G. Jarai, J. Westwick, C.M. Hogaboam, Notch signaling mediates TGF-β1-induced epithelial–mesenchymal transition through the induction of Snai1, Int J Biochem Cell Biol. 44 (2012) 776–789.

[224] K. Yazaki, Y. Matsuno, K. Yoshida, M. Sherpa, M. Nakajima, M. Matsuyama, T. Kiwamoto, Y. Morishima, Y. Ishii, N. Hizawa, ROS-Nrf2 pathway mediates the development of TGF-β1-induced epithelial-mesenchymal transition through the activation of Notch signaling, Eur J Cell Biol. 100 (2021) 151181.

[225] Y.S. Wu, I. Chung, W.F. Wong, A. Masamune, M.S. Sim, C.Y. Looi, Paracrine IL-6 signaling mediates the effects of pancreatic stellate cells on epithelial-mesenchymal transition via Stat3/Nrf2 pathway in pancreatic cancer cells, Biochimica et Biophysica Acta (BBA) - General Subjects. 1861 (2017) 296–306.

[226] W. Zhou, X. Mo, W. Cui, Z. Zhang, D. Li, L. Li, L. Xu, H. Yao, J. Gao, Nrf2 inhibits epithelial-mesenchymal transition by suppressing snail expression during pulmonary fibrosis, Sci Rep. 6 (2016).

[227] G. Eades, M. Yang, Y. Yao, Y. Zhang, Q. Zhou, miR-200a Regulates Nrf2 Activation by Targeting Keap1 mRNA in Breast Cancer Cells, J Biol Chem. 286 (2011) 40725.

[228] F. Bocci, S.C. Tripathi, S.A. Vilchez Mercedes, J.T. George, J.P. Casabar, P.K. Wong, S.M. Hanash, H. Levine, J.N. Onuchic, M.K. Jolly, NRF2 activates a partial epithelial-mesenchymal transition and is maximally present in a hybrid epithelial/mesenchymal phenotype, Integrative Biology. 11 (2019) 251.

[229] S.A. Vilchez Mercedes, F. Bocci, M. Ahmed, I. Eder, N. Zhu, H. Levine, J.N. Onuchic, M.K. Jolly, P.K. Wong, Nrf2 Modulates the Hybrid Epithelial/Mesenchymal Phenotype and Notch Signaling During Collective Cancer Migration, Front Mol Biosci. 9 (2022) 279.

[230] R. Riahi, M. Long, Y. Yang, Z. Dean, D.D. Zhang, M.J. Slepian, P.K. Wong, Single cell gene expression analysis in injury-induced collective cell migration, Integrative Biology. 6 (2014) 192–202.

[231] C. Wiel, K. le Gal, M.X. Ibrahim, C.A. Jahangir, M. Kashif, H. Yao, D. v. Ziegler, X. Xu, T. Ghosh, T. Mondal, C. Kanduri, P. Lindahl, V.I. Sayin, M.O. Bergo, BACH1 Stabilization by Antioxidants Stimulates Lung Cancer Metastasis, Cell. 178 (2019) 330-345.e22.

[232] L. Lignitto, S.E. LeBoeuf, H. Homer, S. Jiang, M. Askenazi, T.R. Karakousi, H.I. Pass, A.J. Bhutkar, A. Tsirigos, B. Ueberheide, V.I. Sayin, T. Papagiannakopoulos, M. Pagano, Nrf2 Activation Promotes Lung Cancer Metastasis by Inhibiting the Degradation of Bach1, Cell. 178 (2019) 316-329.e18.

[233] W. Han, Y. Zhang, C. Niu, J. Guo, J. Li, X. Wei, M. Jia, X. Zhi, L. Yao, D. Meng, BTB and CNC homology 1 (Bach1) promotes human ovarian cancer cell metastasis by HMGA2-mediated epithelial-mesenchymal transition, Cancer Lett. 445 (2019) 45–56.

[234] M. Sato, M. Matsumoto, Y. Saiki, M. Alam, H. Nishizawa, M. Rokugo, A. Brydun, S. Yamada, M.K. Kaneko, R. Funayama, M. Ito, Y. Kato, K. Nakayama, M. Unno, K. Igarashi, BACH1 promotes pancreatic cancer metastasis by repressing epithelial genes and enhancing epithelial-mesenchymal transition, Cancer Res. 80 (2020) 1279–1292.

[235] J. Yun, C.A. Frankenberger, W.L. Kuo, M.C. Boelens, E.M. Eves, N. Cheng, H. Liang, W.H. Li, H. Ishwaran, A.J. Minn, M.R. Rosner, Signalling pathway for RKIP and Let-7 regulates and predicts metastatic breast cancer, EMBO J. 30 (2011) 4500.

[236] X. Wei, J. Guo, Q. Li, Q. Jia, Q. Jing, Y. Li, B. Zhou, J. Chen, S. Gao, X. Zhang, M. Jia, C. Niu, W. Yang, X. Zhi, X. Wang, D. Yu, L. Bai, L. Wang, J. Na, Y. Zou, J. Zhang, S. Zhang, D. Meng, Bach1 regulates self-renewal and impedes mesendodermal differentiation of human embryonic stem cells, Sci Adv. 5 (2019).