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Insights into protein fucosylation in insects

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With 3 figures and 3 tables

Abstract: Fucosylation, or the attachment of a fucose moiety to a glycan or protein by the action of fucosyltransferases, happens extensively in all living organisms. It plays a vital role in multiple biological processes from development to immunity, and is thought to be highly associated with the occurrence of many human diseases. While the general principles of fucosylation are similar in all organisms, most insects synthesize less processed fucosylated glycans compared to humans. Recent studies in insects show that disruption of fucosylation causes developmental defects leading to lethality, suggesting an essential role in insects. However, because of the limited information available, the molecular mechanisms behind these phenotypes remain unresolved. This review provides an overview on insect fucosylation, including the principle and function of fucosylation, the phylogenesis of the fucosyltransferases, and the diversity and abundance of fucosylated glycans. To provide a better understanding of the different roles of fucosylation in insects, knowledge on fucosylation in mammals or other invertebrates is discussed. As the dynamic requirement for fucosylation in insects needs more research to elucidate the underlying mechanisms, we hope this overview of fucosylation could provide new insights into its role in insects for future studies.

Keywords: post-translational modification; fucosyltransferases; fucosylated glycans; insect development; insect immunity

1 Introduction

Post-translational modification (PTM) of proteins by oligosaccharides occurs commonly in all eukaryote organisms, it is estimated that more than half of all proteins are glycosylated (Apweiler et al. 1999). N-glycosylation and O-glycosylation are two major and common types of protein glycosylation. In N-glycosylation, a dolychol-linked precursor sugar chain ($Glc_3Man_9GlcNAc_2$) is attached to an asparagine (Asn) residue of nascent polypeptides in the endoplasmic reticulum (ER) in an Asn-X-Ser/Thr consensus sequence (with X any amino acid except Pro) (Stanley et al. 2022). After attachment, the resulting N-glycans are sequentially processed by a number of enzymes in the ER and Golgi apparatus to generate different glycans (Rini et al. 2022). Briefly, the first step is the stepwise removal of the three glucoses from $Glc_3Man_9GlcNAc_2$ to form a high mannose glycan ($Man_9GlcNAc_2$), this processing is important for protein quality control and correct folding. If the protein is misfolding, the glycan will be reglucosylated for another round of folding. Correctly folding proteins are subsequently transported to the Golgi apparatus where the α-1,2-mannoses are trimmed, generating $Man_5GlcNAc_2$. The $Man_5GlcNAc_2$ structure can be further modified with one GlcNAc to produce hybrid glycans ($GlcNAcMan_5GlcNAc_2$) or trimmed to form paucimannose glycan ($Man_{3–4}GlcNAc_2$). Once substituted by GlcNAc, the glycan can be further modified with other sugar moieties at the core and antenna. One of these modifications is the addition of fucose residues, or fucosylation, catalyzed by fucosyltransferases (FucTs) (Fig. 1A–B). In O-glycosylation, monosaccharides are sequentially attached to a serine or threonine residue of polypeptides (Holdener & Haltiwanger 2019). Many O-linked glycans are initiated with the addition of a GalNAc-moiety and are subsequently extended with Gal, GlcNAc, Fuc, or Sia-residues (Brockhausen et al. 2022). In addition, fucose moieties can be directly attached to a serine or threonine residue of the polypeptide, this O-fucosylation is catalyzed through the action of O-FucTs (Fig. 1C). In the human genome, thirteen genes encoding FucTs were identified and expected to be involved in fucosylation (de Vries et al. 2001, Schneider et al. 2017). Based on the linkage by which the fucose is added, these enzymes can be classified into α-1,2-, α-1,3/4-, and α-1,6-FucTs as well as O-FucTs (Li et al. 2018). In the genome of the nematode *Caenorhabditis elegans*, 40 genes encoding FucTs (20 α-1,2-FucTs, 17 α-1,3/4-FucTs, one α-1,6-FucT, and two O-FucTs) are identified (https://wormbase.org, version WS287). However, in the genome of the

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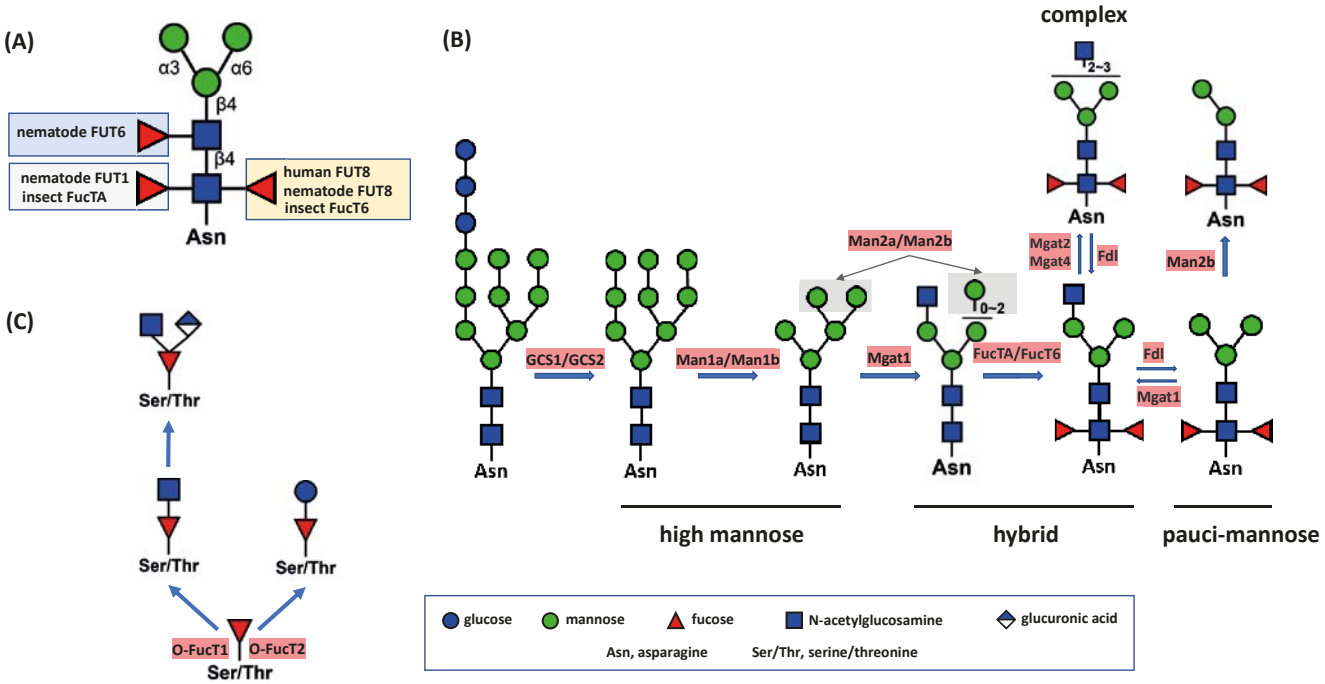

Fig. 1. Schematic of N-fucosylation. **(A)** Core fucosylation in insect, nematode, and human. The core of N-glycans is commonly comprised of $Man_3GlcNAc_2$. Nematode FUT1 and FUT6, α-1,3-fucosyltransferase. Nematode and human FUT8, α-1,6-fucosyltransferase. **(B)** Fucosylation-related N-glycosylation pathway in insects. GCS1/GCS2, glucosidases I and II. Man1a/Man1b, mannosidases class I. Man2a/Man2b, mannosidases class II. Mgat1/2/4, mannosyl (α-1,3-)-glycoprotein β-1,2-N-acetylglucosaminyltransferase 1/2/4. FucTA, α-1,3-fucosyltransferase. FucT6, α-1,6-fucosyltransferase. Fdl, N-acetylhexosaminidase. High mannose glycans carry five to nine mannose residues, $Man_{5-9}GlcNAc_2$. Pauci-mannose (also called short mannose) glycans carry two to four mannose, $Man_{2-4}GlcNAc_2$. Hybrid glycans includes one of branches substituted by GlcNAc. Complex glycans contain the branch substituted by two or more GlcNAc. **(C)** O-fucosylation in insects. O-FucT1 is involved in the left pathway while O-FucT2 is involved in the right pathway. Data adapted from Li et al. (2020).

insect model *Drosophila melanogaster*, only seven FucTs (four α-1,3-FucTs, one α-1,6-FucT, and two O-FucTs) are identified (https://flybase.org, version FB2023_01 released on February 15, 2023).

Fucosylation gained attention because of its involvement in the occurrence of many human diseases, including inflammation, cancers, and tumors, and its role in the immune response (Fujita et al. 2021b, Li et al. 2018, Tong et al. 2022, Tu et al. 2017, Wang et al. 2023, Wu et al. 2022). Alteration in the fucosylation profile is clinically used as an indicator for diseases. For example, the expression of FucTs or the fucosylation profile of proteins can be used as prognostic marker and therapeutic target for cancer patients (Geng et al. 2004, Loong et al. 2021, Luo et al. 2023). The fucosylation of antibodies also plays an important role in the treatment or diagnosis of diseases (Bournazos et al. 2021, Wang & Ravetch 2019). The "less or more" fucosylation is a dynamic balance and is required depending on physiological conditions (e.g. individuals or diseases). Non-fucosylated antibodies show protective immunity against malaria and HIV, however, it increases the severity of COVID-19 and dengue fever patients (Larsen et al. 2021, Oosterhoff et al. 2022, Šuštić et al. 2022). In addition to its role in diseases and immunity, fucosylation also plays a crucial role in development. In many organisms, such as mice, zebrafish, and nematodes, mutation of α-1,6-FucT (FUT8) resulted in growth defects and death (Hayashiji et al. 2022, Wang et al. 2006a, Wang et al. 2005). In insects, the knowledge generated in the model *Drosophila melanogaster* reveals that fucosylation is needed for normal insect development and the loss of fucosylation is accompanied with serious consequences, such as reduced growth and lethality (Rendić et al. 2010, Yamamoto-Hino et al. 2015). α-1,6-FucT (FucT6) has been reported to be essential for the development of *Nilaparvata lugens*, where the silencing of *FucT6* caused a failure of embryonal katatrepsis and nymphal ecdysis events, resulting in a complete lethality in embryos and nymphs (Yang et al. 2022, 2023). However, these phenotypes are not observed in the studies in *D. melanogaster, Tribolium castaneum* and *Leptinotarsa decemlineata* (Liu et al. 2022, Walski et al.

2016, Yamamoto-Hino et al. 2015). These discrepancies in phenotypes suggest that FucT6 plays a different role in different insect species, and that conclusions from one species cannot be readily translated to other insects. Therefore, knowing the role of FucTs in a variety of species is needed. In this review, we discuss FucTs and the general principles of fucosylation, summarizing the recent advances in the study of fucosylation in insects, aiming to better understand the role of fucosylation in insects.

2 Fucosylation and biosynthesis of fucosylated glycans

Fucosylation has been summarily discussed in a few recent reviews regarding insect glycosylation (Li et al. 2020, Ten Hagen et al. 2022, Walski et al. 2017), however, the information in these reviews was mainly limited to the model insect *D. melanogaster*. As a model *D. melanogaster* has received more attentions on both N-glycosylation and O-glycosylation (Katoh & Tiemeyer 2013, Nishihara 2020, Ten Hagen et al. 2009). Among the FucTs, FucTA (α-1,3-fucosyltransferase) and FucT6 (α-1,6-fucosyltransferase) are known to catalyze core α-1,3- and α-1,6-fucosylation, respectively, and FucTC (α-1,3-fucosyltransferase) is involved in terminal α-1,3-fucosylation. The exact enzyme activity of FucTB and FucTD (α-1,3-fucosyltransferases), however, remains unclear (Fabini et al. 2001, Kurz et al. 2016, Rendić et al. 2007, Rendić et al. 2006). In a previous study, Roos et al. (2002) characterized the *Drosophila* FucTs involved in the synthesis of fucosylated glycans. This study revealed that while genes encoding α-1,3-FucTs and α-1,6-FucTs were found, no genes encoding α-1,2-FucTs and α-1,4-FucTs were identified, suggesting insect fucosylation is different from other invertebrates, such as nematodes, and vertebrates. While the knowledge of insect fucosylation is still limited, the information obtained in vertebrate systems on biosynthesis and function of fucosylated glycans can be helpful for the understanding of insect fucosylation (Becker & Lowe 2003, Ma et al. 2006, Schneider et al. 2017).

2.1 Terminal fucosylation

Terminal fucosylation in insects is not common and is largely dependent on the species. For example, in *D. melanogaster* no FucTs have been functionally proven to catalyze terminal fucosylation (Fabini et al. 2001, Rendic et al. 2006). However, in the honey bee *Apis mellifera* and the mosquito *Anopheles gambiae*, terminal fucosylation, yielding Lewis-type α-1,3-FucT structures, has been shown to be catalyzed by FucTC (Kurz et al. 2016, Rendić et al. 2007). In contrast to insects, terminal fucosylation in humans is more common and more complex, the antenna of both N-glycans and O-glycans can be modified with fucose moieties in an α-1,2-, α-1,3-, and α-1,4-linkage (Table 1). The addition of fucose in an α-1,2-linkage is catalyzed by α-1,2-FucTs (FUT1 and FUT2), while the introduction of fucose in an α-1,3-linkage is catalyzed by FUT4–7 and FUT9. FUT10 and FUT11 contain the characteristic α-1,3-FucT motif and share homology with α-1,3-FucT from *Drosophila*, suggesting these are putative fucosyltransferases, however, their function has not yet been defined (Ma et al. 2006). In addition to adding fucose in an α-1,3-linkage, FUT3 and FUT5 also add fucose in an α-1,4-linkage (Schneider et al. 2017) (Table 1).

2.2 Core fucosylation

The modification of the core structure of N-glycans in insects is catalyzed by FucT6 (α-1,6-FucT), adding fucose in an α-1,6-linkage, or/and by FucTA (α-1,3-FucT), adding fucose in an α-1,3-linkage (Fig. 1B), leading to up to two fucoses on the proximal GlcNAc residue of the core. Among the four α-1,3-FucTs identified in *D. melanogaster*, only FucTA is shown to play a role in core α-1,3-fucosylation (Fabini et al. 2001, Kurz et al. 2016, Rendić et al. 2006, 2007). Monofucosylation of the core in an α-1,3-linkage is rare, while fucosylation in an α-1,6-linkage is quite common. Difucosylation always occurs first in the α-1,6-linkage, as FucT6 cannot act at the core of α-1,3-fucosylated glycans while FucTA can be active at the core of α-1,6-fucosylated glycans (Kurz et al. 2016, Paschinger et al. 2005, Staudacher & Marz 1998). Noteworthy, core fucosylation appears to be different in *Manduca sexta*, where the fucose residue can be

Table 1. Lists of known fucosyltransferases in humans and insects (adapted from Schneider et al. 2017 and Ma et al. 2006).

FucT types	Addition site of fucose	Abbreviation in human genome	Abbreviation in *D. melanogaster* genome
α-1,2-fucosyltransferase	terminal α-1,2-linkage of N-glycan	FUT1, FUT2	
α-1,3-fucosyltransferase	α-1,3-linkage of N-glycan	FUT3-7, FUT9-11[1]	FucTA-D[2]
α-1,4-fucosyltransferase	terminal α-1,4-linkage of N-glycan	FUT3, FUT5	
α-1,6-fucosyltransferase	core α-1,6-linkage of N-glycan	FUT8	FucT6
O-fucosyltransferase	O-glycans	FUT12/POFUT1, FUT13/POFUT2	O-FucT1, O-FucT2

[1] α-1,3-fucosylation in the core of N-glycan is absent in humans.
[2] FucTA is the only enzyme catalyzing core α-1,3-fucosylation in *D. melanogaster.*

added to the distal GlcNAc of the core in an α-1,3-linkage. Such modification is also seen in other invertebrates, such as the nematode *C. elegans* whose N-glycans are more complex, with up to three (Yan et al. 2013) or even five fucose residues to the core (Yan et al. 2018). The presence of a GlcNAc residue on the core α-1,3-mannose has been thought to be a prerequisite for core α-1,6-fucosylation by α-1,6-FucT. However, recently, it was shown that human FUT8 (α-1,6-FucT, the sole enzyme catalyzing core fucosylation of human N-glycans) also can use N-glycans lacking an α-1,3-arm GlcNAc as substrate for core fucosylation (Yang et al. 2017). Similarly, in insects such as Lepidopteran larvae (e.g. *Trichoplusia ni* and *Lymantria dispar*), the high mannose N-glycan $Man_7GlcNAc_2$ was observed to be core α-1,6-fucosylated, supporting the hypothesis that α-1,6-FucT may have a relaxed substrate specificity and a GlcNAc residue on the core α-1,3-mannose is not absolutely required (Stanton et al. 2017). However, how FUT8 or FucT6 modulates such fucosylation is still unknown. Fucosylation of N-glycans in an α-1,6-linkage is conserved in all animal organisms and is the most preferred compared to any of the other linkages.

2.3 O-fucosylation

To date, there are two O-FucTs, O-FucT1 and O-FucT2, identified in the *D. melanogaster* genome. O-FucT1 is known to add fucose to properly folded epidermal growth factor-like (EGF) repeats with the consensus sequence C^2-X-X-X-X-Ser/Thr-C^3 (X is any amino acid and C^2 and C^3 are the second and third conserved cysteines of the EGF repeat), while O-FucT2 is responsible for the addition of fucose to thrombospondin type 1 repeats (TSRs) with the consensus sequence C^1-X-X-S/T-C^2 in TSRs group 1 and C^2-X-X-S/T-C^3 in TSRs group 2 (Haltiwanger et al. 2022). Compared to vertebrates, where O-fucoses comprise 50% of the O-glycome, the proportion of O-fucose in invertebrates is significantly lower (28%) (Thomès & Bojar 2021). In insects, studies on O-glycosylation are rare. The available data shows that O-GlcNAc-type O-glycans (also known as mucin type glycan) dominate the O-glycan profile (Brockhausen et al. 2022), while O-fucose comprises only a minor fraction of the insect O-glycome (Aoki et al. 2008, Li et al. 2020, Walski et al. 2017).

3 Phylogenetic analysis of FucTs

To better understand the phylogenetic relationship between the FucTs in insects, the protein sequences of *Drosophila* FucTs were used as queries for searches against the NCBI protein database, with the setting of max target sequence > 200 amino acid sequence and e-value cutoff of 1e-6, in other representative species across different insect orders. Homologs of α-1,3/6-FucTs and O-FucTs from human *Homo sapiens* (vertebrate) and nematode *C. elegans* (invertebrate) were included in the phylogenetic analysis. The generated tree clearly reveals the differentiation of an α-1,3-FucT, α-1,6-FucT, and O-FucT cluster, and the conservation of these enzymes in the different organisms (Fig. 2). There are apparent divergences between α-1,3-FucTs, revealing the discrepancies of insect FucTA, FucTB, and FucTC. Human FUT10 and FUT11 are evolutionarily incorporated into the insect FucTB clade, while other α-1,3-FucTs from human and nematode are evolutionarily related to insect FucTA and FucTC. Analysis of the phylogenetic tree suggests FucTA is probably evolved from FucTC. As no orthologs of the *D. melanogaster* FucTD could be identified in other insect species, it is assumed that FucTD is specific to *Drosophila*, and was excluded from the phylogenetic analysis. Surprisingly, *N. lugens* FucT6 and *Apis mellifera* FucT6 show a difference from other insects' FucT6 at amino acid level, locating them at the outer side of the insect α-1,6-FucT cluster. Compared with other insects, an expansion of α-1,3-FucT and α-1,6-FucT seems to be present in the hemipterous aphids. More research is still needed for confirmation of these observations.

4 Fucose-containing glycans in insect

4.1 Fucosylated glycans across insect species

While insects account for 80% of all known living species, knowledge of their fucosylation is very limited. Thomès & Bojar (2021) collected a dataset of glycan structures assembled from public databases [GlyTouCan (Fujita et al. 2021a), GlyCosmos (Yamada et al. 2020), CSDB (Toukach & Egorova 2016)], together with glycan structures manually extracted from the peer-reviewed literature. The dataset is released and is freely accessible via https://github.com/BojarLab/glycowork. This database includes fucose-containing glycans from more than 20 insect species, distributed over six orders, including Hymenoptera, Hemiptera, Lepidoptera, Coleoptera, Diptera and Orthoptera (Fig. 3), and comprises at least 280 fucosylated glycans within insects. Among these species, *Apis mellifera* (Hymenoptera) has the largest number of fucosylated glycans (152), followed by *T. ni* (Lepidoptera) (75) and *L. dispar* (Lepidoptera) (51) as well as *Anopheles gambiae* (Diptera) (45) and *Aedes aegypti* (Diptera) (42) (Diptera). In the other species, the total number of fucose-containing glycans is relatively smaller. For example, 27 fucose-containing glycans have been found in *D. melanogaster* (Diptera), 12 in both *Bombyx mori* (Lepidoptera) and *N. lugens* (Hemiptera), nine in *T. castaneum* (Coleoptera), seven in *L. decemlineata* (Coleoptera), and five in *Locusta migratoria* (Orthoptera).

The binding of the fucose residue in the glycans appears to vary depending on species. The occurrence of monofucosylated glycans with their fucose unit in an α-1,6-linkage of N-fucosylated glycans is conserved in insects, and presence of core difucosylated N-glycan structures occurs exten-

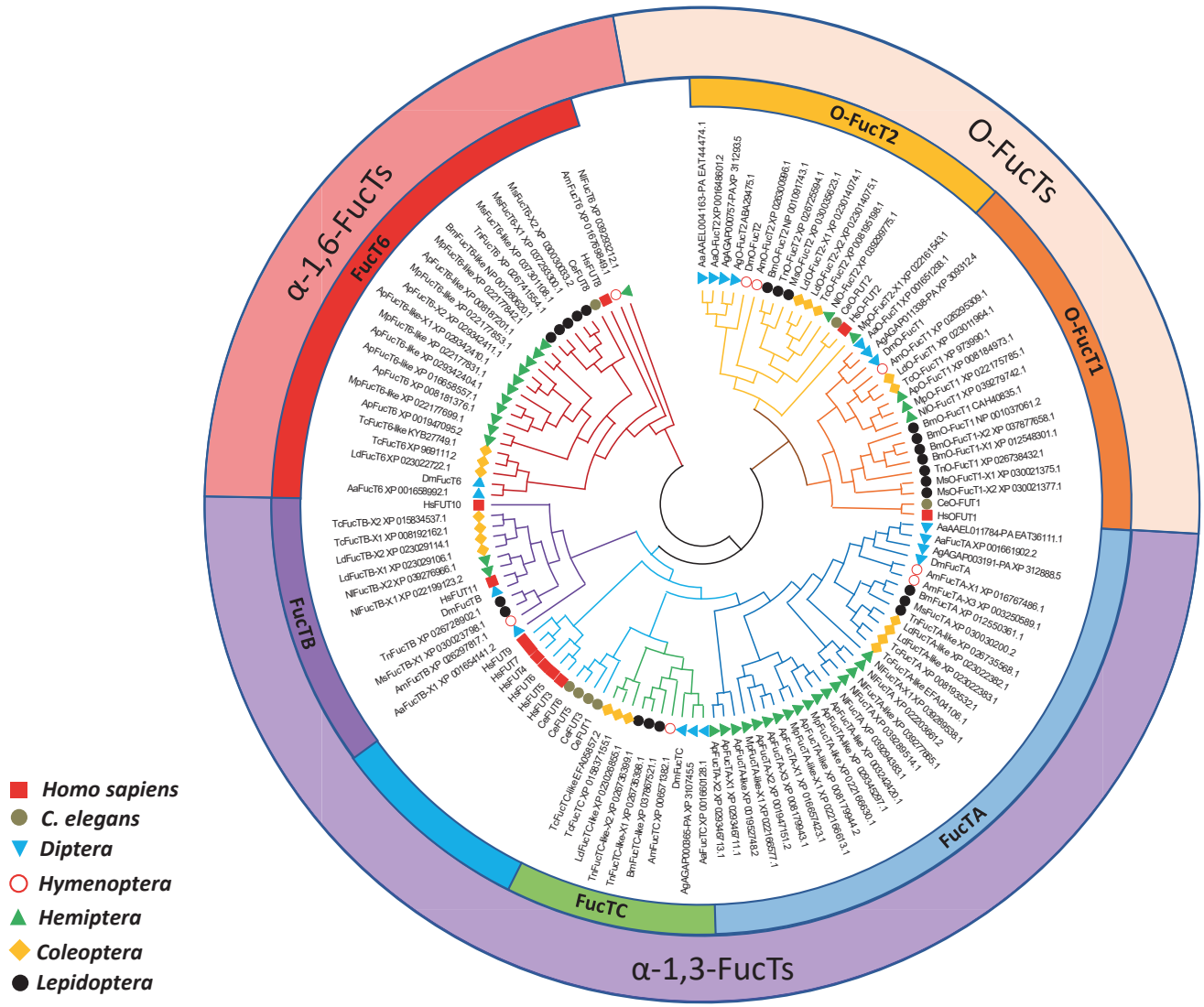

Fig. 2. Phylogenetic analysis of FucTs. *D. melanogaster* FucTs were downloaded from FlyBase (https://flybase.org) and used as queries searching against NCBI by BlastP with the setting of max target sequence > 200 amino acid and E-value cutoff of 1e-6, to find the homologs in other insect species, including Diptera (*A. aegypti* and *A. gambiae*), Hymenoptera (*N. lugens, Myzus persicae, Acyrthosiphon pisum*), Coleoptera (*T. castaneum* and *L. decemlineata*), Lepidoptera (*T. ni, B. mori*, and *M. sexta*), Orthoptera (*L. migratoria*, no homologs were found). The α-1,3/6-FucTs and O-FucTs from human *Home sapiens* and nematode *C. elegans* were downloaded from UniProt (https://www.uniprot.org) and included in the analysis as well. All sequences of FucTs were aligned by MUSCLE in MEGA 11 and the phylogenetic analysis was performed in Mega 11 using Maximum Likelihood method with the default settings. In the phylogenetic tree, insect FucTs were simplified using the abbreviation of species name, followed by FucT name (and isoform), and NCBI accession number.

sively in insects as well. However, the presence of one fucose unit at either the core or the antenna of N-glycans in an α-1,3-binding appears to be species-specific (Table 2). Of note, N-glycans of *M. sexta* (Lepidoptera) can even be modified with up to four fucose units in an α-1,3-linkage, two at the core and two at the antenna. In *T. ni* and *L. dispar*, core monofucosylation in an α-1,6-linkage is the most prevalent, and terminal fucosylation with a single fucose in an α-1,3 linkage is observed. Core α-1,6-monofucosylation is the most prevalent in mosquitos, while no terminal fucose was observed in the fucosylated glycans of *A. aegypti* and only two structures were found with one α-1,3 terminal fucose in that of *A. gambiae*. There is no terminal fucose found in the fucosylated glycans of *D. melanogaster, B. mori, N. lugens, L. decemlineata,* and *T. castaneum*. Noteworthy, in *Vespa crabro* and *Vespula germanica* glycans are observed modified with α-1,2-fucose (Garenaux et al. 2011), suggesting α-1,2-FucTs might be present in such species.

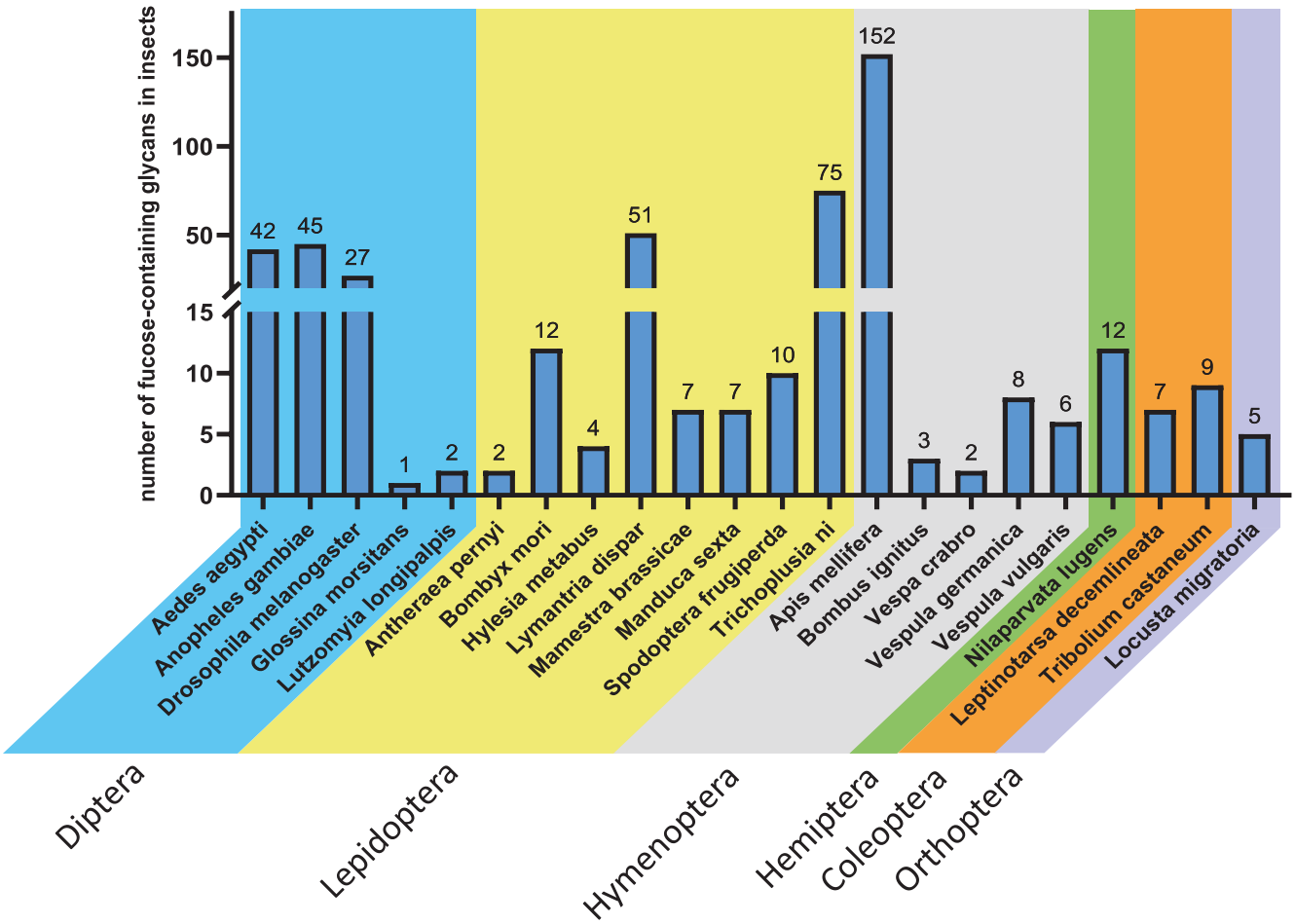

Fig. 3. Fucose-containing glycans in insects. Holometabolous insects: Diptera, Lepidoptera, Hymenoptera, and Coleoptera. Hemimetabolous insects: Hemiptera and Orthoptera. Data obtained from Thomès & Bojar (2021).

4.2 Abundance of fucosylated glycans in insect glycome

During the N-glycosylation pathway (Fig. 1B), the sugar moieties are sequentially removed from or added to the N-glycans generating high mannose, paucimannose, hybrid, and complex type glycans. Of which, paucimannose, hybrid and complex type glycans can be modified with fucoses by the α-1,3-FucTs and FucT6. Overall, insect N-glycans are dominated by high mannose and paucimannose (including fucosylated) glycans, accounting for > 85% of total N-glycome (Hagen et al. 2022, Scheys et al. 2019, Walski et al. 2016).

During the embryonic stage of *D. melanogaster*, the abundance of fucosylated glycans increases in the late embryo compared to the early embryo (Aoki et al. 2007). Overall, the N-glycome of *D. melanogaster* embryos is dominated by high mannose glycans, accounting for half of the total number of N-glycans while the fucosylated glycans comprise about 30% of the N-glycome (Aoki et al. 2007). In the larval stage, *D. melanogaster* has similar proportions in both high mannose and fucosylated glycans (Williams et al. 1991). In comparison, *T. castaneum* larvae carry more high mannose glycans (63%) and less fucosylated glycans (26%) (Walski et al. 2016). However, *N. lugens* nymphs carry as many fucosylated glycans (36%) as high mannose glycans (36%) (Scheys et al. 2019). In the adult stage, *D. melanogaster* carries more fucosylated glycans (41%) but still less than high mannose glycans (49%) (Fabini et al. 2001). In contrast, *T. castaneum* adults carry more fucosylated glycans (47%) than high mannose (38%) (Walski et al. 2016). Interestingly, *N. lugens* adults revealed an unexpected sex specificity in their N-glycome, where fucosylated glycans comprise only 8% of the N-glycome of females but 43% of the N-glycome of males. The N-glycan profiles of most insects including *A. mellifera*, *D. melanogaster*, and *N. lugens* revealed that monofucosylation with α-1,6-fucose is dominant in their N-glycome while difucosylated glycans account for only about 1% of total N-glycome (Fabini et al. 2001, Hykollari et al. 2019, Scheys et al. 2019). However, *T. castaneum* appears to have more difucosylated glycans in

Table 2. Summary of fucose in insect glycans. (1) Kurz et al. (2015), (2) Hykollari et al. (2018), (3) Hykollari et al. (2019), (4) Kim et al. (2003), (5) Ahn et al. (2019), (6) Kajiura et al. (2022), (7) Kubelka et al. (1994), (8) Aoki et al. (2007), (9) Aoki et al. (2008), (10) Kozak et al. (2021), (11) Cabrera et al. (2016), (12) Liu et al. (2019) (13) Hard et al. (1993), (14) Mondragon-Shem et al. (2020), (15) Stanton et al. (2017), (16) Abeytunga et al. (2008), (17) Stephens et al. (2004), (18) Scheys et al. (2019), (19) Scheys et al. (2020), (20) Gaunitz et al. (2013), (21) Li et al. (2021), (22) Walski et al. (2016), (23) Garenaux et al. (2011), (24) Kolarich et al. (2005).

Insect species	Core α-1,6	Core α-1,3	Core α-1,3 & α-1,6	Terminal α-1,3	O-fucose	References
A. aegypti	Yes	Yes	Yes	×	×	(1)
A. gambiae	Yes	Yes	Yes	Yes	×	(1)
A. mellifera	Yes	Yes	Yes	Yes[#]	–	(2), (3)
Antheraea pernyi	Yes	×	×	×	–	(4)
Bombus ignitus	Yes	×	×	×	–	(5)
B. mori	Yes	Yes	Yes	×	–	(4), (6), (7)
D. melanogaster	Yes	×	Yes	×	Yes[†]	(8), (9)
Glossina morsitans	Yes	×	×	×	–	(10)
Hylesia metabus	Yes	×	×	×	–	(11)
L. decemlineata	Yes	Yes	Yes	×	–	(12)
L. migratoria	Yes	×	×	×	–	(13)
Lutzomyia longipalpis	Yes	×	×	×	–	(14)
L. dispar	Yes	×	×	Yes	–	(15)
Mamestra brassicae	Yes	Yes	Yes	×	–	(7)
M. sexta	?	Yes[#]	×	Yes[#]	–	(16), (17)
N. lugens	Yes	×	Yes	×	–	(18), (19)
Spodoptera frugiperda	Yes	Yes	Yes	×	Yes[‡]	(7), (20)
T. castaneum	Yes	×	Yes	×	Yes[†]	(21), (22)
T. ni	Yes	×	Yes	Yes	Yes[‡]	(15), (20)
V. crabro	–	–	–	–	Yes[‡]	(23)
V. germanica	Yes	×	Yes	×	Yes[‡]	(23), (24)
Vespula vulgaris	Yes	×	Yes	×	–	(24)

"Yes" fucose found, "×" no fucose found, "–" unknown or no data available, "?" unclear, "[#]" two fucoses found, Column "terminal α-1,3" only includes N-linked α-1,3-fucose, "[†]" indicates only O-fucose found and "[‡]" indicates only terminal O-linked fucose found, α-1,2-fucose is found in the O-glycans of *V. crabro* and *V. germanica*.

its N-glycome, accounting for 9~14% of total N-glycome (Walski et al. 2016). Compared to the above-mentioned species, the N-glycans of *A. mellifera* are well understood, with the largest group of fucosylated glycans among all insects. In the larval stage of *A. mellifera*, fucosylated glycans are the most abundant and almost all glycans carry an α-1,6-fucose (Hykollari et al. 2019). Although the glycans in its royal jelly and venom are highly fucosylated with α-1,6-fucose and α-1,3-fucose, the total abundance of fucosylated glycans in these samples is lower than in whole larvae (Hykollari et al. 2019). An investigation of the N-glycan profile of the peritrophic membrane in the larva of the Colorado potato beetle, *Leptinotarsa decemlineata*, revealed that the fucosylated glycans are the most abundant group, accounting for about 37% of the total N-glycome. (Liu et al. 2019). Compared to the N-glycome, studies on the insect O-glycome are extremely limited. In *D. melanogaster* embryos, O-fucosylated glycans comprise 11~16% of the O-glycome (Aoki et al. 2008, Li et al. 2022). In contrast to *D. melanogaster*, *T. castaneum* embryos carry more O-fucosylated glycans, accounting for 27% of total O-glycome (Li et al. 2022). While in the larval and pupal stage of *T. castaneum*, the fraction is reduced to 13% and 7%, respectively. In the adult stage, this fraction is increased to 18%. Altogether, these results suggest that both N- and O-fucosylated glycans are dynamically changed during insect development, there is significant variation between species, between sexes, and between tissues.

5 Fucosylation in development

5.1 In non-insect organisms

Fucosylation has been shown to play an essential role in the normal development of many organisms. For example, in

mice, disruption of FUT8 causes severe growth retardation, early death during postnatal development, and emphysema-like changes in the lung (Wang et al. 2005). In zebrafish, disruption of FUT8 results in obvious developmental defects, including a smaller body size, abnormal muscle structures, and mortality in earlier developmental stages (Hayashiji et al. 2022). In *C. elegans*, RNAi or overexpression of *pad-2* (O-fucosyltransferase) led to abnormal development, suggesting that *pad-2* is required for normal development of *C. elegans* (Menzel et al. 2004).

5.2 In insects

While the knowledge of fucosylation in insect development is almost entirely generated in the insect model *D. melanogaster*, a few recent studies generated in other insect species are able to bring a new insight into our understanding of the biological role of fucosylation. In *D. melanogaster*, disruption of FucTA caused mild defects in the wing and neural development (Rendić et al. 2010, Yamamoto-Hino et al. 2010) (Table 3). In contrast, no negative effects were observed when silencing *FucTA* in the beetles *T. castaneum* and *L. decemlineata* (Liu et al. 2022, Walski et al. 2016) (Table 3). Although silencing of *FucTA* in the hemimetabolous insect *N. lugens* did not yield any obvious phenotype, it did cause an increased mortality (Yang et al. 2022). In contrast to the relative mild effects of *FucTA* silencing, silencing of *FucT6* caused severe developmental defects in *N. lugens* leading to complete mortality (Yang et al. 2022, Yang et al. 2023) (Table 3). Specifically, RNAi-mediated silencing of *FucT6* in *N. lugens* nymphs led to a block of the next ecdysis event, trapping the insects in their old cuticle during nymphal transition (Yang et al. 2022). In addition, parental RNAi of FucT6 resulted in a failure of the katatrepsis event during *N. lugens* embryonal development (Yang et al. 2023). These phenotypes suggest an essential role of α-1,6-fucosylation in this insect. However, these observations are in grave contrast with the observations in holometabolous insect, where silencing of *FucT6* in *T. castaneum* and *L. decemlineata* did not cause any observed negative effects (Liu et al. 2022, Walski et al. 2016), while in *D. melanogaster*, some lethality was reported in one study but not in another (Liu et al. 2022, Walski et al. 2016, Yamamoto-Hino et al. 2015) (Table 3).

Table 3. Overview of the available phenotypes in insects with loss of fucosyltransferases. (1) Ten Hagen et al. (2022), (2) Walski et al. (2016), (3) Liu et al. (2022), (4) Yang et al. (2022), (5) Yamamoto-Hino et al. (2015), (6) Yang et al. (2023), (7) Mortimer et al. (2012), (8) Li et al. (2021).

Gene	Species	Treatment	Phenotype	Reference
α-1,3-FucTs				
FucTA	*D. melanogaster*	Mutation	Altered glycosylation in larval, pupal, and adult central nervous system	(1)
FucTA	*T. castaneum*	RNAi in 4th instar larva	No obvious effects	(2)
FucTA	*L. decemlineata*	RNAi in 3rd instar larva	No obvious effects	(3)
FucTA	*N. lugens*	RNAi in 3rd instar nymph	Increased mortality	(4)
FucTB	*D. melanogaster*	RNAi	Lethality	(5)
α-1,6-FucT				
FucT6	*N. lugens*	RNAi in 3rd instar nymph	Complete lethality in nymphs, > 60% insects show ecdysis defect.	(4)
FucT6	*N. lugens*	RNAi in adult	Increased mortality in females but not males; no effects on egg production of females.	(6)
FucT6	*N. lugens*	Parental RNAi	Complete lethality in embryos; abnormal embryo with posterior mislocalization of eyespots; low hatching rate of the eggs.	(6)
FucT6	*D. melanogaster*	Mutation in larvae	Impaired immune response to wasp infection	(7)
FucT6	*D. melanogaster*	RNAi	Lethal before adult eclosion or specific defects depending on studies	(5)
FucT6	*L. decemlineata*	RNAi in 3rd instar larva	No obvious effects	(3)
O-FucTs				
O-FucT1	*D. melanogaster*	Mutation	*Notch*-like defects in cellular differentiation	(1)
O-FucT1	*D. melanogaster*	RNAi	Lethality before adult eclosion or specific defects depending on studies	(5)
O-FucT1	*T. castaneum*	RNAi	Severe effects with an abnormal pupal and adult elytra and high mortality	(8)

However, it is worth to mention that embryonal effects were not investigated in the holometabolous studies. Studies on O-FucTs are limited to *D. melanogaster* and *T. castaneum*. In the former, deficiency of O-FucT1 led to *Notch*-like defects (Okajima & Irvine 2002, Sasamura et al. 2003) or mild effects on survival and wing development (Yamamoto-Hino et al. 2015). In the latter, silencing of *O-FucT1* caused severe defects on the pupal and adult development, while no negative effects were observed when silencing *O-FucT2* (Li et al. 2021).

Altogether, these results suggest that FucT6 plays a different role between insect species, and this might be related to the abundance of fucosylated glycans in the N-glycome of the juvenile development stage in the insects mentioned above (e.g., *D. melanogaster*, *T. castaneum*, and *N. lugens*). Though the biological role of FucT6 has not been analyzed in the embryonal stage of other insects, the strong effects and the significant upregulation of transcript levels in the late embryo (after the embryonal katatrepsis process) compared to the early embryo (before the embryonal katatrepsis process) suggests the involvement of FucT6 in the embryonal katatrepsis event and its indispensable role in the embryonic development of *N. lugens* (Yang et al. 2023). Similarly, the N-glycan profile of *D. melanogaster* embryos showed that fucosylated glycans are increased in the late embryonal stage compared to the early embryo, which suggests FucT6 might be involved in the embryonic development of *D. melanogaster* as well (Aoki et al. 2007).

6 Fucosylation in immune response

6.1 In humans

In humans, the study fucosylation has gotten much attention for its role in the antigenic epitopes of blood types and its involvement in many human diseases (Jajosky et al. 2023). For example, the formation of the H-type and Lewis-type antigens are associated with the introduction of terminal fucoses by α-1,2, α-1,3 and α-1,4-fucosyltransferaseses at the antenna of hybrid and complex type glycans (de Vries et al. 2001, Ma et al. 2006, Schneider et al. 2017). Furthermore, aberrant fucosylation has been extensively reported to be associated with many biological processes of disease occurrence, including inflammation, tumors, and cancers (Bastian et al. 2021, Caldwell et al. 2021, Domino et al. 2009, Fujita et al. 2021b). Recently, non-fucosylation of IgG-antibodies was reported to be related to the severity of symptoms in COVID-19 patients (Larsen et al. 2021). FUT4-mediated Lewis-type antigens play a crucial role in the progression and development of gastric cancer (Aziz et al. 2022). FUT8-mediated core fucosylation is essential for evoking a proper immune response (Sun et al. 2022). These results suggest the importance of fucosylation in the human immune system. Over the years, increasing studies also highlight the vital role of fucosylation-related immunotherapies (Adhikari et al. 2022, Liao et al. 2021, Oosterhoff et al. 2022). It is known that fucosylated N-glycans of insects and plants can be immunogenic in vertebrates. These epitopes can be recognized by immunoglobulin E (IgE) from patients allergic to plant foods and pollen, as well as by antisera generated against plant and insect glycoproteins. Minimizing fucosylation can reduce their binding to IgE antibodies (Palmberger et al. 2014). Of interest, it has been observed that terminal fucose is always present in those glycans causing health problems to people and animals (Boukouvala et al. 2022). Therefore, terminal fucosylated glycans might be an interesting marker in medicine to assess allergenic insects.

6.2 In insects

Compared to humans, the study of the role of fucosylation in insect immunity is seriously lagging behind. Among the FucTs is FucTA that produces core α-1,3-fucosylated N-glycans recognized by anti-horseradish peroxidase (HRP) antisera, providing a marker for neural tissue (Rendić et al. 2006). In *D. melanogaster*, it has been shown that knockdown of *FucTA* increased the susceptibility to *Candida* infection (Glittenberg et al. 2022). In addition, *FucT6*-mutant *D. melanogaster* larvae exhibit a somewhat impaired immune response to parasitoid wasp infection, leading to a decreased encapsulation rate (Mortimer et al. 2012). In our recent study on *N. lugens* (Yang et al. 2023), we observed that *FucT6*^{RNAi}-eggs were prone to be infected by fungi during embryonic development (data not shown). These observations suggest that similar to human immunity, fucosylation might have an important role in modulating the insect immune response, though further research is needed to elucidate the underlying molecular mechanisms of fucosylation in the defense against pathogens. In view of pest control, the negative effects on the insect immunity caused by a deficiency of fucosylation opens perspectives for novel strategies for future pest control. In such strategies, carbohydrate binding proteins, or lectins, with a specificity for fucosylated glycans, e.g., F-type lectins (Vasta et al. 2017, Vasta & Feng 2020) could be used to disrupt the insect immune response against parasitoids or fungal or microbial agents. The role of lectins in the insect immune system have recently been summarized (Chen et al. 2021, Ming et al. 2023). In addition to the model *D. melanogaster*, the study of honeybees is gaining more attention as its royal jelly is a natural antimicrobial agent (Fratini et al. 2016), while its venom is allergenic (Pucca et al. 2019).

7 Fucosylation in the regulation of cellular signaling

As many proteins, present at the surface of the cells, are glycosylated, it is no surprise that glycans, and indeed fucosylated glycans, play a role in cellular communication. For

example, studies in mice, reveal that FUT8-mediated core fucosylation regulates the biological function of the epidermal growth factor receptor (EGFR) by impacting the binding affinity of epidermal growth factor (EGF) to EGFR and the phosphorylation status of EGFR (Wang et al. 2006b). By modulating this interaction between EGF and its receptor, fucosylation can influence cell growth and division. In the Wnt/β-catenin signaling pathway, fucosylation modulates Wnt activity by regulating the endocytosis of lipoprotein receptor-related protein 6 (LRP6) (Hong et al. 2020). Similar to the effects of the fucosylated N-glycans, the modification of the EGF repeats of Notch with O-fucose is required for the activation of the Notch signaling pathway and endocytic transportation of Notch in mice (Ge & Stanley 2008) and *D. melanogaster* (Okajima & Irvine 2002, Sasamura et al. 2007). Collectively, fucosylated glycans have been shown to modulate cellular biological processes by e.g. affecting the binding affinity of ligands to receptors, altering the phosphorylation status of receptors or by influencing the endocytosis of the receptors, and thus regulating the downstream signaling cascades of the receptors.

8 Fucosylation in microbe-host interactions

Next to their role in communication, the presence of glycans at the surface of the cell makes them potent markers for cellular and pathogen-host interactions. For example, glycosylated glycans are important for the entry of SARS-CoV-2 viruses into their host cells, but at the same time they are also involved in the protection of the host cell from viral infection (Gong et al. 2021). Similarly, fucosylated glycans are required for the binding of the Cholera toxin to its receptors on the host cell surface (Wands et al. 2015). Also in insects, glycosylation-mediated microbe-host interactions have been studied, e.g. α-mannosidase II-a (Man2a), a glycozyme involved in the trimming of lower arm mannoses on the core N-glycans (Fig. 1B), was reported to be involved in the interaction between mosquito (*Aedes aegypti*) and dengue virus (DENV) (Sigle et al. 2022). Similarly, the O-fucosyltransferase (POFUT2) in the parasite *Plasmodium falciparum* was reported to play an important role in its transmission to mosquitoes and infection of the human host (Lopaticki et al. 2017). From this aspect, investigating fucosylation (or glycosylation as a whole) in those pathogenic vectors is of great significance to elucidate its roles in microbe-host interaction.

9 Conclusion

Protein fucosylation plays pivotal roles from development to immunity in insects. Disruption of FucT activity can lead to serious consequences in insects as well as in non-insect species. While some phenotypes after disruption of fucosyltransferase activity seem to be conserved between mammals and insects, and knowledge from the former can help to understand the processes in the latter, some phenotypes are not found in other animals. For example, the phenotype observed during molting, a process absent in mammals, suggests a unique role in insects. The diversity of fucosylation and differential abundance of fucosylated glycans in insect species, developmental stages, and tissues suggest a dynamic requirement for fucosylation, but also poses challenges for its study. In addition, these differences between species in abundance and type of fucosylation and in phenotypes upon disruption suggests that information generated from one species cannot always be easily translated to another species. As the limited knowledge of fucosylation in insects is hampering the insight into the mechanisms behind observed phenotypes in insects, more research is needed to elucidate the underlying mechanisms of fucosylation in the future.

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