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Original Article

The contribution of fucosyltransferases to cancer biology

A contribuição das fucosiltransferases para a biologia do câncer

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Abstract

Fucosyltransferases are enzymes that transfer L-fucose residues from a donor substrate to target molecules. These enzymes are encoded by genes known as FUTs (FUT1 to FUT-11), along with POFUT1 and 2. Changes in FUT expression have a significant role in cancer development and malignancy. This review delves into the biochemistry and biological functions of FUTs and their contributions to cancer. Broadly, FUTs play roles in cancer tumorigenesis, survival, and metastasis. Interactions between fucosylated glycans and various molecules associated with cancer, such as E-selectins and the epidermal growth factor receptor (EGFR), offer alternative pathways for cancer development. The review also highlights FUTs as potential biomarkers for cancer prognosis and diagnosis, along with their application as targets for therapy.

Keywords: fucosyltransferase, fucosylation, cancer, biomarkers.

Resumo

As fucosiltransferases são enzimas que catalisam a transferência de resíduos de L-fucose de um substrato doador para uma molécula receptora. Essas enzimas são codificadas por genes chamados FUTs (FUT1 a FUT-11) e POFUT1 e 2. Alterações na expressão de FUTs na fucosilação desempenham um papel importante no desenvolvimento do câncer e malignidade. Esta revisão explora alguns aspectos bioquímicos e funções biológicas das FUTs e suas contribuições no câncer. Em uma perspectiva ampla, as FUTs contribuem na tumorigênese, sobrevivência e metástase do câncer. Interações entre glicanos fucosilados e uma variedade de outras moléculas associadas ao câncer, como E-selectinas e receptor do fator de crescimento epidérmico (EGFR), apresentam vias alternativas para o desenvolvimento do câncer. Esta revisão também enfoca o fato de que as FUTs são potenciais biomarcadores para o prognóstico e diagnóstico do câncer, além de sua aplicação como alvos terapêuticos.

Palavras-chave: fucosiltrasnferases, fucosilação, câncer, biomarcadores.

1. Introduction

What determines the importance of FUTs expression in tumor biology? Their precise and influenced transcriptional and post-transcriptional regulation pathways coordinated by multifactorial stimuli related to immunological and developmental status of the tumor cell and its microenvironment. Glycosylation, a crucial post-translational modification of protein structures (Nothaft and Szymanski, 2010; Li et al., 2019), plays a pivotal role in various cellular processes.

Dysregulation of glycosylation in cell surface and serum glycoproteins has been linked to carcinogenesis and cancer progression (Magalhães et al., 2017; Wang et al., 2019). In 1964, Hakomori and Jeanloz made a groundbreaking discovery by identifying lipid-linked fucose in human gastric adenocarcinoma (Hakomori and Jeanloz, 1964). This finding marked the onset of extensive research into fucosylation's involvement in cancer. Structural alterations in fucosylated glycoconjugates are observed in various diseases, including cancer (Vasconcelos et al., 2013; Nascimento et al., 2015, 2019; Albuquerque et al., 2018). Malignant tumors often exhibit abnormal fucosylated glycan expression with different localizations and functions (Yang et al., 2017; Noda et al., 2018; Ferdosi et al., 2018).

Changes in the expression of fucosyltransferases are important sources of information for translational research in the oncology area, especially about how glycocoding influences tumorigenesis and tumor progression also allow inferring therapeutic and diagnostic perspectives in the area.

2. Material and Methods

Data mining was conducted in Google, Google Scholar, Scielo, Science Direct and PubMed platforms. Descriptors included "Fucosyltrasnferases", "Glycosylation", "Fucosylation", individual combinations of "FUTs (1-13)", "POFUT1", "POFUT2", Boolean descriptors "AND" and

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"OR". "Cancer" descriptor was constant in all searches. Selected articles presented a relationship between one or more fucosyltransferases and their impact on biological and clinical aspects of any type of cancer. There was no restriction regarding date of publication. Articles selected presented titles containing terms related to fucosyltransferases and cancers. Those initially discussing fucosylated molecules without mentioning fucosyltransferases were excluded. Selected articles emphasized the connection between enzymes and cancer in their abstracts, excluding those focusing solely on fucosylated molecules. Further research was conducted to enhance the theoretical foundation during the narrative review development.

3. Fucosyltransferase Features and Roles in Cancer Biology

There are thirteen fucosyltransferase genes called FUTs, classified from FUT1 to FUT11, and POFUT1 (FUT12) and POFUT2 (FUT13) (Schneider et al., 2017). POFUT1 encodes GDP-fucose protein-O-fucosyltransferase 1, catalyzing α-L-fucose transfer to protein receptors' serine hydroxyl group. FUT1 and FUT2 perform glycan α1,2-fucosylation, FUT3-7 and FUT9-11 α1,3-fucosylation. FUT3 and FUT5 also do α1,4-fucosylation, while FUT8 handles α1,6-fucosylation. These enzymes are crucial for the final stage of cellular glycosylation. They are located in the Golgi apparatus (Seelhorst et al., 2014) or in the endoplasmic reticulum (Shan et al., 2019; Lira-Navarrete et al., 2011). The genetic and biochemical characteristics of this family of enzymes are diverse, as shown in Table 1. Since the early 2000s, it is known that fucosyltransferases transfer α-L-fucose from GDP-fucose to target molecules like N-Acetyl-glucosamine residues (GlcNAc) (Vries et al., 2001) (Figure 1).

Fucosyltransferases and fucosylation products in the same or different tissues are often co-expressed, albeit with varying expression levels (Vries et al., 2001; Ezeabikwa et al., 2021). Their interaction with cell receptors and downstream signaling pathways is pivotal for tumorigenesis. Numerous cancers exhibit varying levels of FUT expression (Gene Expression Profiling Interactive Analyses, accessed June 10th, 2023), FUTs involves complex mechanisms, including transcriptional and/or post-transcriptional regulation, polymorphisms, and epigenetic triggers, suggesting potential alternative therapeutic targets, as discussed ahead.

FUT1, targeting LAMP-1 and LAMP-2, impacts the expression of Lewis Y antigen (LeY) and H2 antigens. LeY is elevated in ER+/PR+/HER- breast cancer cells (MCF-7, T47D) and low in triple-negative MDA-MB-231 cells. Negative regulation of FUT1 relocates LAMP-1 and LAMP-2, increasing autophagy, mTOR signaling, and autolysosome formation (Tan et al., 2016). These events have crucial implications in different cancers, such as ovarian cancer,

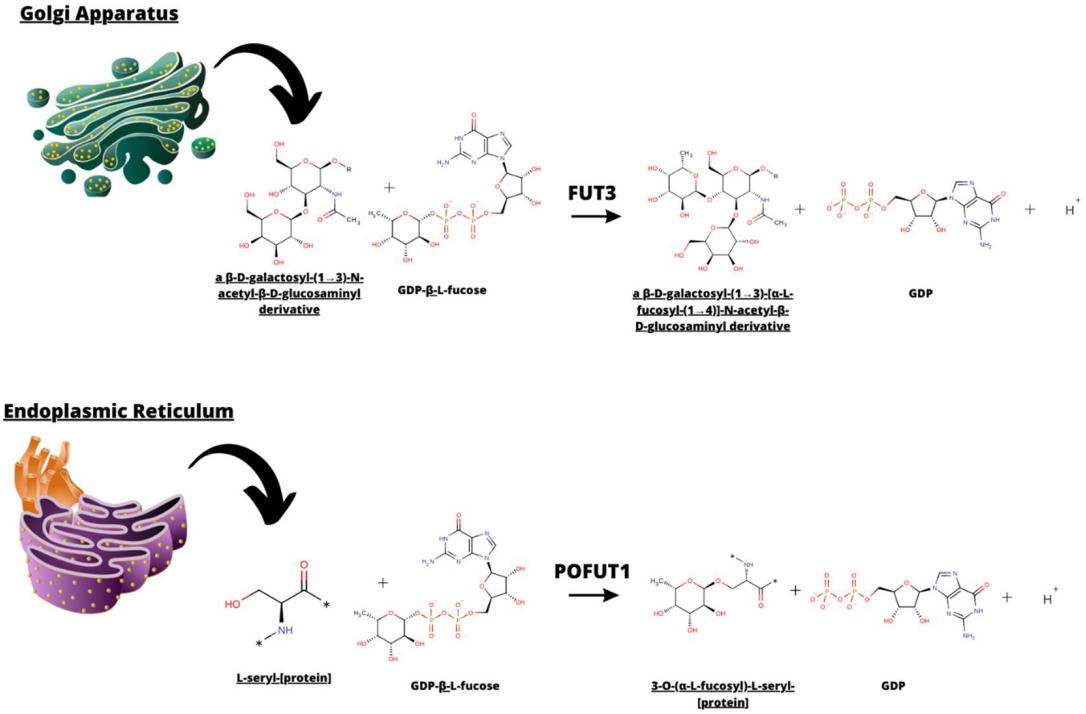

Figure 1. Fucosyltransferases 1-10, as well as FUT3, catalyses the addition of α-L-fucose by a GDP-β-L-fucose to an oligosaccharide preform, generating an α-L-fucosylated glycan, GDP and H^+. Alternatively, the O-fucosyltransferases, as well as POFUT1, catalyses the addition of the same α-L-fucose to a protein with a hydroxyl group in serine bonded to a threonine. The majority of fucosyltransferases are anchored in Golgi Apparatus, except the POFUT1 that is anchored in Endoplasmic Reticulum. Adapted from data available in UniProt (NIH, 2024a).

Table 1. Genetic and biochemistry features of the human fucosyltrasnferases.

Gene	Chromosome Location	Exons	Recommended Protein Name	Alternative Protein Name	Short Name	Catalytic activity
POFUT1	20q11.21	9	GDP-fucose protein O-fucosyltransferase 1	Peptide-O-fucosyltransferase 1	O-FucT-1	O-fucosylation of serine/threonine hydroxyl
POFUT2	21q22.3	16	GDP-fucose protein O-fucosyltransferase 2	Peptide-O-fucosyltransferase 2	O-FucT-2	O-fucosylation of serine/threonine hydroxyl
FUT1	19q13.33	5	Galactoside alpha-(1,2)-fucosyltransferase 1	Fucosyltransferase 1	Alpha(1,2) FT 1	α-1,2 fucosylation
FUT2	19q13.33	2	Galactoside alpha-(1,2)-fucosyltransferase 2	Fucosyltransferase 2	Alpha(1,2) FT 2 or SE2	α-1,2 fucosylation
FUT3	19p13.3	5	3-galactosyl-N-acetylglucosaminide 4- alpha-L-fucosyltransferase FUT3	Fucosyltransferase 3	FucT-III	α-1,3/4 fucosylation
FUT4	11q21	1	Alpha-(1,3)-fucosyltransferase 4	Fucosyltransferase 4	Fuc-TIV or FucT-IV	α-1,3 fucosylation
FUT5	19p13.3	2	4-galactosyl-N-acetylglucosaminide 3-alpha-L-fucosyltransferase FUT5	Fucosyltransferase 5	Fuc-TV or FucT-V	α-1,3/4 fucosylation*
FUT6	19p13.3	2	4-galactosyl-N-acetylglucosaminide 3-alpha-L-fucosyltransferase FUT6	Fucosyltransferase 6	Fuc-TVI or FucT-VI	α-1,3 fucosylation
FUT7	9q34.3	2	Alpha-(1,3)-fucosyltransferase 7	Fucosyltransferase 7	Fuc-TVII or FucT-VII	α-1,3 fucosylation
FUT8	14q23.3	15	Alpha-(1,6)-fucosyltransferase	Fucosyltransferase 8	Alpha1-6FucT	α-1,6 fucosylation
FUT9	6q16.1	5	4-galactosyl-N-acetylglucosaminide 3-alpha-L-fucosyltransferase 9	Fucosyltransferase 9	Fuc-TIX or FucT-IX	α-1,3 fucosylation
FUT10	8p12	10	Alpha-(1,3)-fucosyltransferase 10	Fucosyltransferase 10	Fuc-TX or FucT-X	α-1,3 fucosylation
FUT11	10q22.2	3	Alpha-(1,3)-fucosyltransferase 11	Fucosyltransferase 11	Fuc-TXI or FucT-XI	α-1,3 fucosylation

Table produced by authors based on the Uniprot and NCBI databases (NIH, 2024a, b).

where FUT1 promotes the overexpression of LeY, driving cell proliferation (Hao et al., 2017). FUT1 overexpression positively regulates 215 genes in ovarian carcinoma cells, including the TRIM46 oncogene (Gao et al., 2016). Another one, FUT2 is overexpressed in HCC, increasing levels of the tumor-associated Globo H antigen (Wu et al., 2014). Reduced levels of FUT1 inhibit tumor growth (Zhang et al., 2008) and proliferation in HER2-overexpressing breast cancer cells (Kawai et al., 2013), while FUT1 silencing decreases mTORC1 activity, a key regulator of growth and autophagy (Tan et al., 2016).

Many cancers may present aberrant expression of FUT3 and its upregulation leads to higher levels of Lewis antigens, associated with increased metastatic potential. But in gastric cancer, negative regulation of FUT3 reduces endothelial adhesion through interactions with sLe antigens and E-selectin (Padró et al., 2011). In invasive ductal breast cancer, FucT-III (FUT3) is absent, but FUT4, FUT5, FUT6, and FUT10-11 are present (Nascimento et al., 2015; Carrascal et al., 2018). FUT6 influences cell migration, invasion, and proliferation, promoting growth in HCC and cell adhesion in colon carcinoma (Li et al., 2016; Kanoh et al., 2003).

FUT5 plays a role in sLex and sLea antigen biosynthesis in gastric cancer cells (Carvalho et al., 2010), while FUT3 expression depends on promoter hypomethylation

(Serpa et al., 2006). Despite their similar mechanisms, FUT3 is more significant in cancer progression which high expression is linked to poor prognosis in clear cell renal carcinoma (ccRCC), predicting poor overall survival (OS) and relapse-free survival (RFS). It also influences various malignancy-related features (Meng et al., 2017).

Cell migration, invasion, and proliferation are cancer features influenced by FUT6 (Li et al., 2016). Aberrant FUT6 expression in HCC promotes cell growth, colony formation, Akt phosphorylation, and suppresses p21 expression (Guo et al., 2012). In colon carcinoma, FUT6 overexpression induces cellular adhesion (Kanoh et al., 2003).

FUT7 contributes to tumor cell adhesion and metastasis, cell proliferation, EMT, and inflammation (He et al., 2022; Liu et al., 2021; Liang et al., 2017). FUT7 is decreased in lung carcinoma, but in human lung cancer cells, FUT7 regulates sLex expression, promoting cell proliferation, migration, and invasion (Liu et al., 2008; Zhang et al., 2018). FUT7 seems to contribute to invasive potential of cancer cells. It content is decreased in lung carcinoma compared with tumour-adjacent tissues (Zhou et. al, 2017) and in human lung cancer cells lines FUT7 was involved in regulation of sLe^x expression and promotion of cell proliferation, migration and invasion (Liu et al., 2008; Zhang et al., 2018).

The α1,6-fucosylation, performed by FUT8, is crucial in tumor progression, associated with invasion and metastasis of prostate cancer and melanome (Agrawal et al., 2017) EMT, tumorigenesis, tumour growth, and poor prognosis (Wang et al., 2014b, 2015; Yang et al., 2017; Honma et al., 2015). MiR-198 represses tumor growth and metastasis in colorectal cancer by targeting fucosyltransferase 8 (Wang et al., 2014a). FUT9 influences tumorigenesis, proliferation, migration, and therapy, with low expression associated with poor survival in colorectal cancer (Auslander et al., 2017; Shi et al., 2017). Meanwhile FUT10 overexpression maintains stem cell populations, crucial in cancer malignancy (Kumar et al., 2013).

Functional analysis of the CancerSEA database showed that FUT3, FUT6, FUT8, FUT12 POFUT1 and POFUT2 are associated with differentiation, apoptosis, invasion, quiescence and hypoxia (Wang et al., 2023). POFUT1 overexpression showed to be an important factor to activation of Notch signalling and this feature was associated to poor prognostic in IDC and HCC progression (Ma et al., 2016; Wan et al., 2017).

FUTs are associated with the tumor microenvironment of colon adenocarcinoma. FUT1 regulated by miR-939-3p inhibits MUC2 expression. Fusobacterium nucleatum can affect the expression of FUTs by affecting their transcription factors and miRNA levels. Furthermore, Fusobacterium nucleatum promotes the progression of colon adenocarcinoma through the miR-939-3p/FUT1/MUC2 axis (Wang et al., 2023).

4. Translational Perspectives of Fucosyltransferases in Cancer

Translational medicine is the direct application of scientific discoveries to clinical practice, aiming to translate insights from basic research to enhance prevention, diagnosis, and treatment of diseases in clinical settings. In this context, there is data in the scientific literature that supports translational investigations in the area of oncology through the manipulation of fucosyltransferases (Table 2). An important therapeutic perspective in cancer may be create tools and/or protocols to regulate the inhibition of the enzymatic activity of fucosyltransferases and their genes expression. However, as a family of enzymes with redundant isoforms, it is challenging to predict whether the inhibition of a fucosyltransferase can have its activity reduced compensated by another fucosyltransferase that performs the same enzymatic activity.

Martin et al. (2021) proposed an L-fucose glycomimetic that markedly inhibits the creation of sLeX by FUT VI and FUT VII, but has no effect on the creation of LeX by FUT IX. Although these fucosyltransferases have the same alpha 1,3 fucosyltransferase activities, it was possible to obtain a selective suppression of sLex expression. In order to be able to apply this knowledge to other fucosyltransferases and thus regulate their activities, it is necessary to better understand how their enzymatic mechanism of action works in relation to GDP-fucose mimetic inhibitors, since it has been demonstrated that what the mentioned GDP mimetic -fucose surprisingly does not compete for the enzymatic binding site.

The overexpression of FUT1 and FUT2 contribute to cancer progression, by cellular proliferation (Labarriere et al., 1994; Isozaki et al., 2014; Zhou et al., 2017), tumorigenicity (Sun et al., 1995), cellular migration and invasion (Zhou et al., 2017), resistance to chemotherapy via overexpression of Lewis Y antigens (Gao et al., 2010; Che et al., 2016) and act as oncogenes or tumor suppressors (Raheja et al., 2014; Kannan et al., 2015). High FUT1 expression in HCC predicts poor prognosis and is associated with reduced relapse-free survival (RFS) and overall survival (OS) when combined with B3GALT5 (β-1,3-galactosyltransferase 5) (Kuo et al., 2017). Despite FUT8 overexpression, it does not influence malignancy features, as observed in NSCLC H1299 cells (Zhou et al., 2017).

Aberrant expression of FUT3 in various types of cancer is associated with higher levels of Lewis antigens, contributing to increased metastatic potential. In gastric cancer, negative regulation of FUT3 affects adhesion to the endothelium, highlighting its multifaceted role (Padró et al., 2011). Thus, therapeutic interventions that aim to reduce the expression or catalytic activity of FUT3 may be crucial to prevent the emergence of metastases in patients who overexpress this enzyme.

In colorectal cancer cell lines undergoing TGF-β-induced EMT, FUT3 and FUT6 knockdown reduced invasion and metastatic potential, as well as fucosylation of type I TβR and downstream molecule phosphorylation, indicating their role in TGF-β-mediated EMT (Hirakawa et al., 2014). In pancreatic cancer cells, FUT3 knockdown interrupted TGF-β-induced EMT (Zhan et al., 2018). Conversely, FUT3 was absent in cells overexpressing Kras (v12) or SNAIL, while FUT1 and FUT3 overexpression and increased prolactin content were linked to poor prognosis in lymph node metastasis (Breiman et al., 2016). High

Table 2. Fucosyltransferases and Expression Level and Biological and Clinical Impacts in Cancer

Enzyme	Cancer	Expression Level and Biological and Clinical Impacts	References
FUT1	Liver	**High:** reduced RFS and OS.	Kuo et al. (2017)
	Breast	**Low:** inhibited tumor growth; decreased cell proliferation; reduced mTORC1 activity; increased autophagy and autolysosome formation; reduced LeY, stimulates EMT and lymph node metastasis.	Tan et al. (2016); Kawai et al. (2013); Zhang et al. (2008)
	Ovary	**High:** promoted LeY overexpression; upregulated 215 genes, especially TRIM46, and its proteins acts as oncogene or tumor suppressor.	Hao et al. (2017); Gao et al. (2016); Raheja et al. (2014); Kannan et al. (2015)
FUT2	Liver	**High:** increased Globo H antigen levels.	Wu et al. (2014)
	Lung	**Low:** decreased cell proliferation, migration and invasion; increased apoptosis.	Zhou et al. (2017)
FUT3	Breast	**High:** reduced OS and LeY expression; increases sLeX expression; stimulated EMT and lymph node metastasis.	Nascimento et al. (2015); Carrascal et al. (2018); Breiman et al. (2016)
	Kidney	**High:** reduced OS and RFS.	Meng et al. (2017)
	Colon/ Recto	**Low:** reduced invasion and metastatic potential.	Hirakawa et al. (2014)
	Stomach	**Low:** reduced adhesion to endothelium via interactions with sLeX antigens and E-selectin.	Padró et al. (2011)
	Pancreas	**Low:** interrupted TGF-β-induced EMT.	Zhan et al. (2018)
FUT4	Breast	**High:** increased LeY and cell proliferation and metastasis.	Zheng et al. (2017)
	Lung	**High:** promoted EMT	Wang et al. (2017)
	Colon/ Recto	**High:** decreased intratumoral CD3+ and CD8+ T cells; increased systemic inflammation and; increased invasiveness, metastasis and tumor aggressiveness.	Giordano et al. (2015); Li et al. (2017)
FUT5	Stomach	**Low:** reduced adhesion to endothelium via interactions with sLe antigens and E-selectin.	Padró et al. (2011)
FUT6	Colon/ Recto	**High: i**nduced cellular adhesion. **Low:** reduced invasion and metastatic potential.	Hirakawa et al. (2014); Kanoh et al. (2003)
	Liver	**High:** promoted cell growth, colony formation, Akt phosphorylation; suppresses p21 expression.	Guo et al. (2012)
	Breast	**High:** reduced cell migration, invasion, and proliferation. **Low:** increased cell migration, invasion, and proliferation.	Li et al. (2016)
FUT7	Lung	**High:** regulated sLeX expression; promoted cell proliferation, migration, invasion and monocyte-endothelial adhesion.	Zhang et al. (2018); Liu et al. (2008)
	Bladder	**High:** reduced OS and RFS; stimulates proliferation, migration, invasion and EMT; increased immune cells infiltration **Low:** inhibited the proliferation, migration, invasion and EMT.	Liu et al. (2021)
FUT8	Prostate	**High:** influenced invasion and metastasis, tumor growth and indicated poor prognosis.	Wang et al. (2014b)
	Skin	**High:** influenced invasion and metastasis.	Agrawal et al. (2017)
	Breast	**High:** promoted stemness and EMT.	Yang et al. (2017)
	Liver	**High:** promoted tumorigenesis.	Wang et al. (2015)
	Lung	**High:** associated to poor survival and prognosis.	Honma et al. (2015)
FUT9	Colon/ Recto	**High:** increased proliferation and migration; suppresses expansion of cells and inhibits tumor development (colon cancer). **Low:** associated to poor survival and tumor suppression.	Auslander et al. (2017); Shi et al. (2017)
FUT11	Kidney	**High:** considered a potential biomarker for ccRCC with a non-symptomatic disease course.	Zodro et al. (2014)
POFUT1	Colon/ Recto	**High:** Colon: promotes tumorigenesis and stemness. Recto: associated to treatment management. **Low:** reduces tumorigenesis.	Maftah and Germot (2019); Chabanais et al. (2018)
	Liver	**High:** associated to cancer progression	Ma et al. (2016)
	Breast	**High:** associated to poor prognostic	Wan et al. (2017)
	Stomach	**High:** correlated to aggressive tumor phenotypes and poor differentiation; considered a potential biomarker and therapeutic target.	Yokota et al. (2013); Dong et al. (2017)
POFUT2	Colon/ Recto	**High:** associated to poor prognosis in colon adenocarcinoma	Wang et al. (2023)

RFS = Relapse Free Survival; OS = Overall Survival; LeY = Lewis Y; EMT = Epithelial Mesenchymal Transition; sLeX = Sialyl Lewis X; ccRCC = Clear cell renal cell carcinoma.

FUT3 expression is a marker of lower overall survival of breast cancer patients (Nascimento et al., 2020).

Reduced levels of FUT1 have inhibitory effects on tumor growth, especially in breast cancer cells with HER2 overexpression, where proliferation is significantly affected. Silencing of FUT1 also influences the activity of mTORC1, a key regulator of growth and autophagy, highlighting its critical role in the tumor context (Zhang et al., 2008; Kawai et al., 2013; Tan et al., 2016). Gene editing or inhibition of the enzymatic activity of FUT1 are alternatives to be explored in the treatment of breast cancer. Furthermore, FUT1 should be investigated as a potential prognostic biomarker in breast cancer with HER2 overexpression. Increased expression of FUT1, POFUT1 and POFUT2 has been reported in colon adenocarcinoma leading to a poor prognosis, while patients with high expression of FUT2, FUT3, FUT6 had a more favorable prognosis (Wang et al., 2023). FUT11 high expression is a potential biomarker for ccRCC with a non-symptomatic disease course (Zodro et al., 2014).

FUT1 and POFUT2 could, independently, predict the prognosis of patients with colon adenocarcinoma (Wang et al., 2023). POFUT1 (FUT12) and POFUT2 emerge as potential biomarkers, although their role in cancer is poorly understood (Maftah and Germot, 2019). POFUT1 correlates with aggressive tumor phenotypes and poor differentiation, and its upregulation might serve as a potential biomarker and therapeutic target (Yokota et al., 2013; Dong et al., 2017). POFUT2 has not received much attention in cancer, but its high expression is linked, already, to poor prognosis in colon adenocarcinoma (Wang et al., 2023).

Epigenetic factors such as the expression of microRNAs are important factors for the gene regulation of fucosyltransferase expression. There are evidence that they are promising molecules for cancer treatment regarding their influence in tumor progression via fucosyltransferases expression. FUT4 is overexpressed in breast, lung, and colorectal cancer, impacting EMT, cell migration, invasion, proliferation, and metastasis (Zheng et al., 2017; Wang et al., 2017; Li et al., 2017). The miR-493-5p regulates breast cancer invasiveness and tumorigenicity by downregulating FUT4-mRNA (Zhao et al., 2016). Additionally, high levels of miR-200b decrease fucosylation and LeY biosynthesis, downregulating EGFR via FUT4 mRNA and inhibiting proliferation and metastasis in breast cancer through the PI3K/Akt signaling pathway (Zheng et al., 2017). The miR-106b targets FUT6-mRNA and its suppression increases FUT6 expression, reducing cell migration, invasion, and proliferation in breast cancer cell lines. Overexpression of FUT6 reverses these effects (Li et al., 2016). miR-106b high expression is also observed in many cancers as gastric and prostate ones (Cai et al., 2013; Yau et al., 2013).

5. Conclusion

FUTs family have proteins with redundant activity suggesting that fucosylation play a crucial role in modulating cellular molecular characteristics, impacting crucial physiopathological processes in the development and progression of cancer. FUTs rise as potential biomarkers in progression and prognosis, and as emerging potential therapeutic targets in cancer. So far, FUTs are correlated with relapse-free survival, overall survival, cell migration, invasion and metastasis, cellular death, proliferation and differentiation in cancer. However, indeed, very much are still to understand. The road ahead is long!

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