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REVIEW ARTICLE

N-Glycosylation in progression of skin cancer

Ling Tang[1,2,3,4] · Xiaoping Chen[4] · Xu Zhang[1,2,3] · Yeye Guo[1,2,3] · Juan Su[1,2,3] · Jianglin Zhang[1,2,3] · Cong Peng[1,2,3,4] · Xiang Chen[1,2,3,4]

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Abstract
Skin cancer can be classified as cutaneous malignant melanoma, basal cell carcinoma, and squamous cell carcinoma. Due to the high level of morbidity and mortality, skin cancer has become a global public health issue worldwide while the pathogenesis of skin cancer is still unclear. It is necessary to further identify the pathogenesis of skin cancer and find candidate targets to diagnose and treat skin cancer. A variety of factors are known to be associated with skin cancer including N-glycosylation, which partly explained the malignant behaviors of skin cancer. In this review, we retrieved databases such as PubMed and Web of Science to elucidate its relationship between glycosylation and skin cancer. We summarized some key glycosyltransferases and proteins during the process of N-glycosylation related to skin cancer, which was helpful to unmask the additional mechanism of skin cancer and find some novel targets of skin cancer.

Keywords Melanoma · NMSC · N-glycosylation · Glycosyltransferases

Introduction

Skin cancer is the most common of all human cancers with a proportion of 5% in Hispanics, 4% in Asians, and 2% in blacks, and has developed as a global public health issue around the world [1]. Three known representative types of skin cancer are cutaneous malignant melanoma, basal cell carcinoma, and squamous cell carcinoma, the latter two of which are also referred as non-melanocytic skin cancer (NMSC). Cutaneous malignant melanoma (CM) is the least common but most fatal form of skin cancer with about 200,000 new cases diagnosed worldwide each year. The key to treatment is early diagnosis and surgical resection [2]. NMSC is less malignant, but the incidence is much higher than that of melanoma. A giant problem for healthcare worldwide is springing up due to rising incidence [3]. More importantly, the etiology of skin cancer is not entirely clear.

Multiple risk factors such as environmental, genetic, or psychological factors are known to contribute to skin cancer. One of the most significant risk factors is ultraviolet radiation from sun exposure. The rate of progression in skin cancer falls with a 78% decline by reducing the time of sun exposure [4]. From the perspective of genetics, researchers identified a large number of risk alleles associated with NMSC and melanoma [5]. Furthermore, psychological factors are equally important for skin cancer. Cigarette, sex, age, income, and level of education were reported to be related with skin cancer [6].

Besides above the well-known factors, the post-translational modification (PTM) also promotes malignant manifestation of skin cancer [7]. Phosphorylation, ubiquitination, and glycosylation are main types of post-translational modification. Among these types of modification, Glycosylation is also of great importance and can be partly explained as the malignant phenotype of cancer. It is a process that produces glycosidic linkage from one saccharide to other saccharide. Two most common types of glycosylation are O-linked glycosylation and N-linked glycosylation. O-linked glycosylation is that proteins can be modified by

✉ Cong Peng
pengcongxy@csu.edu.cn

✉ Xiang Chen
chenxiangck@126.com

1 Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan, China

2 Hunan Key Laboratory of Skin Cancer and Psoriasis, Changsha, Hunan, China

3 Hunan Engineering Research Center of Skin Health and Disease, Changsha, Hunan, China

4 Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha, Hunan, China

β-*N*-acetylglucosamine (GlcNAc) and attach to a serine or threonine residue. O-linked glycosylation affects protein–protein interactions and protein stability and activity, and regulates protein metabolism, organelle biogenesis, and transport [8]. N-glycosylation is the best-characterized form of protein glycosylation. Nearly one-fifth of proteins are reported to be glycosylated [9]. Changes of specific glycan structures are correlated with cancer and can be regarded as specific biomarkers in cancer [10]. However, the mechanisms of *N*-glycans in skin cancer especially melanoma are not understood clearly. Here, we try to provide a clear and updated overview of the roles of *N*-glycans in skin cancer, thus hoping to enrich the pathogenesis of skin cancer.

Biosynthesis of N-glycosylation

The process of N-glycosylation first starts with the synthesis of dolichol-linked precursor oligosaccharide complex. The precursor oligosaccharide complex synthesized, including 2 GlcNAc, 9 mannose, and 3 glucose molecules, is then transferred to the nascent polypeptide which is located in the lumen of endoplasmic reticulum membrane [11]. Three glucose residues at the end of the oligosaccharide complex are removed by glucosidase I and II before the nascent protein is delivered to the Golgi for further modification, which is regarded as a quality control step. Three preconditions are to be satisfied: A critical consensus motif (Asn-X-Ser/Thr motif) is the first one to be required [12]. Only if this consensus motif appeared on the polypeptide, the motif can be recognized and transferred to the side chain of asparagine residues; the second one is that a suitable three-dimensional structure of the protein is required; last but not least, the asparagine of proteins must be found in the luminal side of the endoplasmic reticulum.

The final step of the biosynthesis of N-glycosylation involves further addition and removal of sugar residues in the Golgi. Various complex and diverse glycans are formed by the catalysis of glycosyltransferases. Based on the modification of *N*-glycans, they can be classified into three major types: high-mannose, hybrid, and complex glycans. High mannose is full of single mannose residues attached to two *N*-acetylglucosamines. The hybrid oligosaccharides contain a mannose residue on one side of the branch, while on the other side an *N*-acetylglucosamine initiates a complex branch. The rest is the so-called complex glycans.

Proteins modified by *N*-glycans exert diverse functions in organisms. Any minor changes of oligosaccharide structures involve multiple physiological and pathological conditions such as cell growth, migration, differentiation, invasion, host–pathogen interactions, cell trafficking, and transmembrane signaling transduction [13]. However, diversity of *N*-glycans is the result of various glycosyltransferases. Therefore, several key glycosyltransferases associated with skin cancer were introduced.

Glycosyltransferases related to skin cancer

Glycosyltransferases play a key role in the modification of glycans by transferring various sugar chains to proteins during the biosynthesis of *N*-glycans. *N*-acetylglucosaminyltransferase V (GNT-V), *N*-acetylglucosaminyltransferase III (GNT-III), sialyltransferase (ST6GAL1), and α1,6-fucosyltransferase (FUT8) are of great significance during the formation of *N*-glycans. The aberrant expression of these glycosyltransferases was found in gastric cancer and small-cell lung cancer [14–16]. Furthermore, the crosstalk within various glycosyltransferases also leads to differential phenotypes (Fig. 1) [17]. The description about these

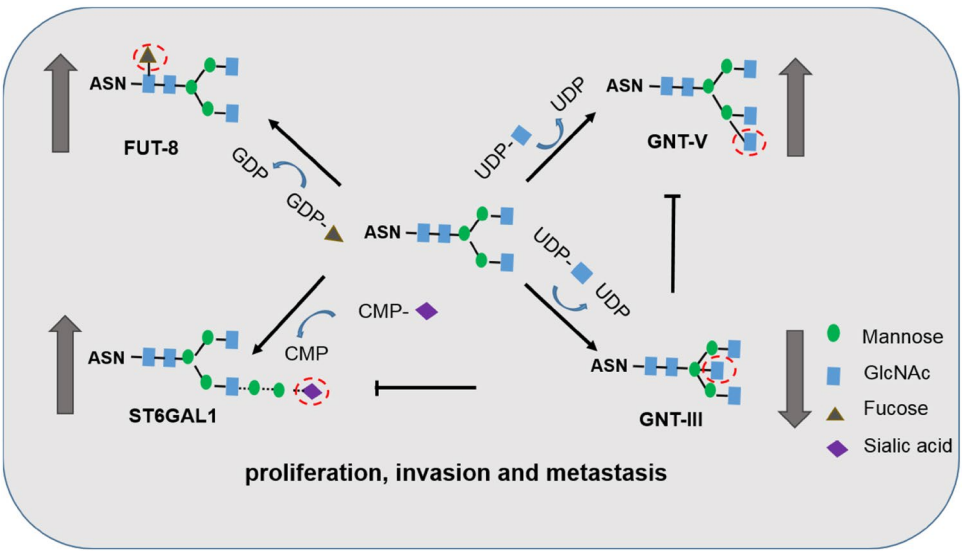

Fig. 1 The cross-talk between various glycosyltransferases. Any minor changes of one of these glycosyltransferases result in the abnormal expression of the other glycosyltransferase leading to the changes of biological function such as proliferation, invasion, and metastasis

glycosyltransferases such as GNT-III, GNT-V, STLGAL1, FUT-8 are as follows:

GNT-III

GNT-III catalyzes the transfer of GlcNAc to the β-mannose residue through the β1,4-linkage, to form the so-called bisecting GlcNAc structure. The enzyme activity of GNT-III is first identified in the early 1980s [18]. GNT-III is aberrantly regulated in cancer cells including ovarian cancer [19] and leukemia [20]. As a tumor suppressor gene, researchers injected the GNT-III-overexpressed B16 melanoma cells into mice and found a significantly less metastasis of melanoma cells in mouse lung [21]. It was described that overexpression of GNT-III in B16 melanoma cells upregulates the synthesis of cAMP and the phosphorylation of transcriptional factor CRE-binding protein, thus leading to a wide range of biological events such as proliferation, differentiation, and metastasis in melanoma [22]. Furthermore, Kariya et al. introduced the bisecting GlcNAc into Lm332 (GNT-III-Lm332) which reduced migration. lm332 is a large heterotrimeric glycoprotein that has been identified as a scattering factor, a regulator of cancer migration, and invasion as well as a prominent basement membrane component of the skin [23], since GNT-III-Lm332 could downregulate galectin-3-dependent keratinocyte motility by inhibiting Lm332-induced α3β1 and α6β4 integrin clustering and focal contact formation [24]. On the other hand, overexpressed GNT-III inhibits α2,3-sialylation, while the mechanisms need to be further addressed [25]. Data also showed that GNT-III inhibits the elongation of complex glycans by blocking the activity of *N*-acetylglucosaminyltransferase V (GNT-V). GNT-III itself and the cross-talk between various glycosyltransferases may become effective targets for skin cancer treatment and remain to be further elucidated.

GNT-V

GNT-V catalyzes the transfer of GlcNAc from UDP-GlcNAc to the 6-OH position of α-Man residue in the α6 arm of the core. Early evidence showed that GNT-V is activated in tumor cells and regulated by RAS-RAF-MAPK signal pathway [26]. Litynska et al. identified proteins bearing β1-6 branched *N*-glycans in human melanoma cell lines, WM35, WM239, and WM9, meanwhile they discovered a large number of substrates of the GNT-V such as integrins, Mac-2 binding protein, and melanoma cell adhesion molecule [27]. Later, the same team also found that β1-6 branching of glycoproteins increased the uveal melanoma cell motility [28]. Uveal melanoma cells bear more β1,6-branched glycans than CM cells, which may help uveal melanoma cells to migrate with a higher potential on fibronectin [17]. How β1,6-branched glycans affected these phenotypes in melanoma cells? Recent study has shown that it might affect their interaction with extracellular matrix proteins by activating focal adhesion kinase signaling in metastatic melanoma WM266-4 cells; the upregulated tyrosine phosphorylation of focal adhesion kinase enhanced its migration on vitronectin; and the co-localization of αvβ3 integrin with FAK indicated is responsible for melanoma cell migration [29]. Furthermore, as the characteristics of GNT-III cannot be extended, there existed a competitive inhibition between GNT-III and GNT-V; it means that the highly expressed GNT-III could inhibit the expression of GNT-V, the metastasis and invasion of cancer cells is inhibited because of the inhibition of the information of β1-6 branched *N*-glycans, while the GNT-V is in the leading position, the phenotype will be on the contrary [30]. Whether other mechanisms exist to cause an impact on the malignant phenotypes are not clear. However, it should be noted that GNT-V might be an alternative target in melanoma therapy. In fact, some of the researchers indeed designed and optimized methods in order to synthesize glycosyltransferase inhibitors [31, 32]. One of the literatures described that a small molecular inhibitor PST3.1a alters the β1,6-GlcNAc *N*-glycans by inhibiting the enzymatic activity of MGAT5 indicating that the development of small targeted inhibitors still prevails [33].

ST6GAL1

ST6GAL1, a sialyltransferase, is typically present in the Golgi and catalyzes the transfer of sialic acid monosaccharide to galactose-containing substrates. Increased protein expression of sialic acid is usually accompanied with malignant phenotypes [10]. A recent study showed that a high level of ST6GAL1 is related to atherosclerosis [34]. ST6GalI sialyltransferase also promoted chemoresistance in pancreatic ductal adenocarcinoma by abrogating gemcitabine-mediated DNA damage [35]. To evaluate the expression of sialylated derivatives on melanoma cells, researchers discovered that WM266-4 cells showed a high level of α2,3-linked sialic acid residues, whereas IGR-39 cells had lower expression of α2,6-linked sialic acid, and made a conclusion that melanoma progression is associated with the increased expression of α2,3-linked sialic acids on the cell surface, and these residues could promote melanoma cell interaction with fibronectin [36]. Over 100 melanoma cell lines were analyzed and identified to contain β1,6-branched glycans; however, researchers also found glycans containing a-2,6 and a-2,3-linked sialic acid in melanoma cells [37]. Furthermore, the expression of sialyltransferases was evaluated in actinic keratosis, keratoacanthoma, squamous cell carcinoma, and basal cell carcinoma, and they also found a high level of ST3Gal I and ST6Gal I, which is said to be associated with greater potential for invasion and metastasis [38]. Additional study reported that the removal of α2,6 sialic

acid either by enzymatic desialylation or by stably downregulating the ST6Gal-I by shRNA decreased the ability of adhesion and invasion [39]. The study on the mechanism of sialyltransferase in skin cancer is far from enough, putting an eye on ST6GAL1 will be of great value in tumor therapy.

FUT-8

The only enzyme known to generate a-1,6-fucosylated structure on the core of *N*-glycans, which belongs to a member of fucosyltransferases, is coded by FUT-8. It catalyzes the transfer of fucose to N-linked type complex glycopeptides. FUT8-mediated receptor core fucosylation was described to stimulate breast cancer cell invasion and metastasis by promoting TGF-β-induced epithelial–mesenchymal transition [40]. Gu et al. found a high level of FUT-8 in HCC mouse model treated with diethylnitrosamine and pentobarbital, and multiple large and vascularized nodules were induced; however, the formation of HCC in negative FUT-8 mouse model is little. They demonstrated that core fucosylation acts as a critical prognostic marker and therapeutic target for HCC [41]. In addition to influencing breast cancer and HCC, fucosyltransferases also contribute to melanoma invasive phenotype; they showed that the level of fucosyltransferases was significantly higher in melanoma cell lines from metastatic site than from primary cell line [42]. Research reported that protein kinase C-mediated activation of activating transcription factor 2 (ATF2) controlled the migration and invasion of melanoma cells through suppression of FUK protein fucosylation [43]. Recently, a more persuasive research published in the Journal of Cancer Cell showed that FUT-8 is upregulated, while FUT-1 and FUT-2 were downregulated in the serum of patients with metastasis melanoma with the help of lectin array and melanoma GEO datasets; they discovered that the knockdown of FUT-8 decreased the metastasis of melanoma in vivo and in vitro. Further research identified that protein expression of FUT-8 is strictly controlled by transcription factor TGIF2, and also, the core fucosylation impacted L1CAM cleavage, and L1CAM mediated the pro-invasive effects of FUT8, thus leading to the metastasis of melanoma [44]. Based on these, FUT-8 inhibitors were developed through a diversity-oriented synthesis [45]. Future studies focusing on the molecular mechanism of FUT-8 and its downstream targets might be a promising direction in the skin-related cancers.

Target proteins of N-glycosylation involved in skin cancer

As mentioned above, N-glycosylation is one of the most important post-transcription modifications. It is undeniable that diverse protein glycosylation plays critical roles in multiple cellular activities, including protein folding, stability and sorting, protein–protein interactions, signal transduction, and cell–cell communications. It is estimated that about 700 proteins need diverse glycan structures, including glycosyltransferases, glycosidases, and nucleotide sugar transporters [46]. Furthermore, approximately half of the human proteins are glycoproteins and most of them contain *N*-glycan structures [47]. More glycoproteins such as α-fetoprotein, prostate-specific antigen, carcinoembryonic antigen had been used in the clinic for the purpose of the early diagnosis and monitoring [48]. Owing to the complexity of protein glycosylation and its fundamental role in biological processes, minor alterations in carbohydrate structure can significantly impact the biological function such as proliferation, migration, metastasis, immune escape, and

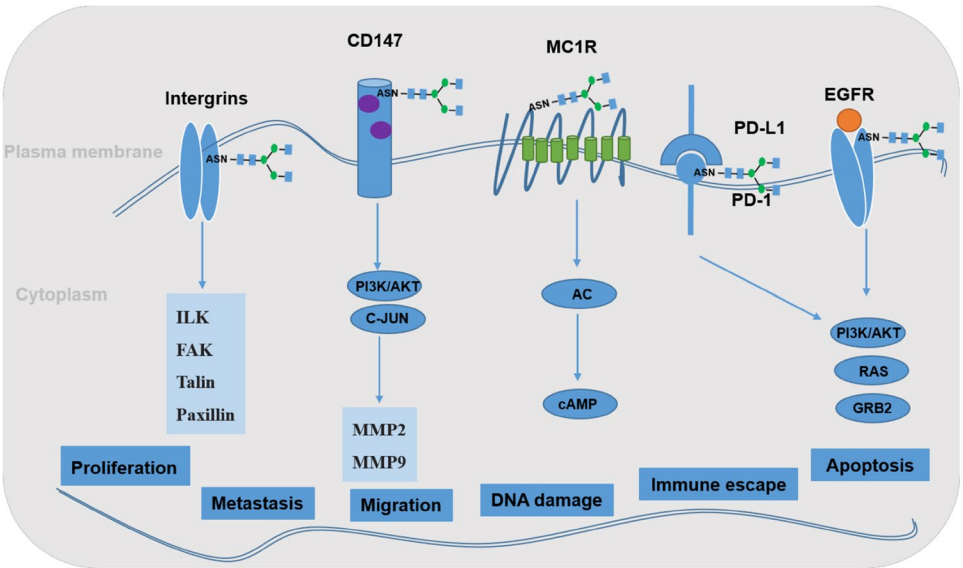

Fig. 2 Glycosylation of proteins involved in skin cancer. Several key glycoprotein-related skin cancer especially melanoma affecting a series of biological functions by inducing the changes of its downstream signaling pathways such as ILK, P13K/AKT, and AC

apoptosis. In this study, we mainly elucidate several key glycoproteins which are closely related to skin cancer (Fig. 2).

Integrins

Integrin is a heterodimeric transmembrane receptor which is widely presented on various cells consisting of 18 α-subunits and one of the eight β-subunits. Its biological function is associated with cell–extracellular matrix adhesion. More concretely, integrins act as a bridge to bind the extracellular ligand to the intracellular receptor, and activation of intracellular signals execute multiple functions including cell growth, cell differentiation, and survival by recruiting a series of effector molecules, such as Talin, Paxillin, ILK, FAK, and various GTPases [49]. The glycosylation of integrins causes cancer progression through its heterodimerization, ligand binding, complex formation with other membrane proteins. Early evidence suggested that the ability of cells to adhere to fibronectin and laminin decreased in a weakly metastatic glycosylation mutant as it was the result of the altered glycosylation of β1 integrins [50–52]. Researchers used tandem mass spectrometry to identify integrins as the largest group proteins in melanoma cells from different metastatic sites [27]. Therefore, it is essential to talk about integrins on the progress of melanoma. One of the reasons that integrins reduced the ability of cell adhesion and invasion is the result of the modification of GNT-III [53]. Some of these subunits like alpha v beta 3 integrin were thought to be characteristic of a particular stage of melanoma progression [54]. In order to shed light on the mechanism of the influence of N-glycosylation on adhesion, wound healing, and migration in human melanoma cell lines: primary WM35, metastatic WM9, WM239, and A375. It is confirmed that A375 and WM9 had the greatest migration ability and both expressed the highest level of α5β1 integrin [55]. Recently, Ewa Pochec used melanoma WM266-4 cells with overexpression of GNT-V and discovered that integrin on the surface of cell to extracellular matrix is a key activator of the focal adhesion kinase (FAK) signaling pathway [29]. Thus, we believe that focus on the glycosylation of integrin and itself will be benefit for clarifying the mechanism of skin cancer and even for other cancers.

CD147

CD147 is a type I transmembrane glycoprotein belonging to a member of the immunoglobulin superfamily, known alias such as human extracellular matrix metalloproteinase inducer, hBasigin, M6, HAb18G, and basigin-1. It is widely expressed in various tissues and cells such as platelets and fibroblasts and involved in multiple physiology functions in developmental processes, wound healing, and nutrient transport [56]. CD147 is reported to promote the progression of malignant melanoma and other cancers [57]. CD147 promotes cell–matrix adhesion through regulation of focal adhesion kinase pathway [58], and CD147 silencing increased cellular ROS and destroyed the intrinsic antioxidant defenses in A375 [59]. As a matrix metalloproteinase inducer, CD147 increases the malignant phenotype through hypoxia-induced MMP2 activation [60], and also, the cleaved CD147 shed from the surface of malignant melanoma cells activates MMP2 which was produced by fibroblasts [61]. On the other hand, CD147 interacts with NDUFS6 encoding a subunit of mitochondrial respiratory chain complex I in regulating mitochondrial complex I activity and the mitochondrial apoptotic pathway in human malignant melanoma cells [62]. It is described as an independent prognostic biomarker to promote progression of malignant melanoma [57]. Repressing CD147 is described as a novel therapeutic strategy for malignant melanoma.

It is well known that CD147 is a heavy glycoprotein containing two glycoforms, which were classified as low-glycosylated (LG-CD147) and high-glycosylated (HG-CD147), representing ~ 32 kDa and ~ 45–65 kDa, respectively. An immature protein modified with a large number of mannose in the ER is LG-CD147, LG-CD147 further modified by a series of complexes glycans within the different glycosyltransferases became mature protein in the Golgi which is called HG-CD147 [63]. Furthermore, three known identified CD147 N-glycosylation sites were N44Q, N152Q, and N186Q. Among these, N152Q mutant plasmid was reported to retain in the endoplasmic reticulum and decrease MMP-induced activity by increasing the GNT-V of CD147 [64]. An in-depth research found that the modification of N-glycosylation at N152Q on CD147 is retained in the ER and strongly promoted invasion and migration [65]. Based on this, the same team developed CD147 monoclonal antibodies [66].

The latest research showed that β1,6-branched glycans enhanced the interaction of CD147 with integrin β1, and the regulation is involved in PI3K/Akt pathway [67]. The increased glycosylated CD147 is reported to activate matrix metalloproteinase-2/-9 (MMP-2 and MMP-9) [68]. Furthermore, β3GnT8 (β1,3-*N*-acetylglucosaminyltransferase), a key polylactosamine synthase is discovered to modulate the N-glycosylation patterns of CD147 and alter the polylactosamine structures by physically interacting with CD147 in a C-Jun-dependent manner [69]. However, little data is known about the relationship of the N-glycosylation of CD147 with skin cancer; hence much more should be done to bridge two of these.

Melanocortin 1 receptor (MC1R)

MC1R is a transmembrane G protein-coupled receptor which controls melanogenesis. It plays a key role in

melanocytes development, proliferation, and differentiation [70]. As a small G protein, the main role of MC1R is to activate adenylate cyclase and increase the activity of tyrosinase through activating cAMP signaling pathway; the is regarded as the rate-limiting step in melanin production [71]. Previous research reported that the carriers of MC1R variant had a 66% higher risk of developing melanoma compared with wild-type subjects which indicated a potential clinical diagnostic value [72]. Immunohistochemical staining also demonstrated that MC1R expression level in melanoma is much higher than normal tissues [73]. In addition, evidence demonstrated that MC1R gene is very significant in melanoma and might be an effective target to treat melanoma. Additionally, MC1R had been reported to have two putative N-glycosylation sites Asn15 and Asn29, and the N-glycosylation of MC1R has a strong effect on the availability of MC1R on plasma membrane. A reasonable explanation is that it might improve forward trafficking and decrease internalization [74]. However, little data about the functional role and mechanism of N-glycosylation of MC1R with melanoma have been reported; however, more evidence are needed to support this.

PD-1

PD-1, the programmed cell death (PD)-1 protein, is a 288-amino acid transmembrane receptor which is made up of three parts: the globular extracellular domain, a 20-amino acid transmembrane domain, and about 95 amino acids of intracellular domain. Within the intracellular domain, there is an immune receptor tyrosine-based inhibitory motif (ITIM) and an immune receptor tyrosine-based switch motif (ITSM) in the cytoplasmic tail. Once the PD-L1 ligand bind to PD-1 on the cell membrane, two phosphatases SHP-1 and SHP-2 bind to ITIM and ITSM motifs, respectively, thus inhibiting T-cell activation. PD-1 and PD-L1 are highly expressed in various tumor cells and tissues [75]. Numerous data showed that the upregulation of PD-1 and PD-L1 expression would induce immune suppression in tumor microenvironment, which is a crucial mechanism for tumor immune escape [76, 77]. PD-1 has been widely studied in various cancers including skin cancers [78].

Medicines targeting PD-1/PD-L1 have been successfully applied in clinical trials. Pembrolizumab and nivolumab are the first batch of this anti-PD-1 pathway family of checkpoint inhibitors to gain accelerated approval from the US Food and Drug Administration for the treatment of melanoma [79]. Research studies have reported that the application of this medicine prolonged patient's survival rate. Furthermore, the effect is much better when combined with other immune checkpoint inhibitors, such as Cytotoxic T-lymphocyte antigen-4 [80]. PD-1 is predicted to have four N-linked glycosylation sites in its extracellular immunoglobulin variable domain. A research discovered three glycosylation sites of PD-1: N192, N200, and N219. The immunosuppression activity of PD-L1 is stringently modulated by N-glycosylation, and their results indicated that the glycosylation pathways to the regulation of PD-L1 could lead to potential therapeutic strategies [81]. A preclinical study confirmed that the binding of nivolumab to PD-1 is likely to rely on the glycosylation of PD-1, since nivolumab bound only to glycosylated PD-1 expressed in a mammalian cell line but not to non-glycosylated PD-1 expressed in *E. coli*. However, recent research has shown that an N-terminal loop outside the IgV domain of PD-1 is not involved in recognition of PD-L1 but dominated the binding to nivolumab, while the PD-1 N-glycosylation is not involved in binding [82]. It's worth noting that the N-glycosylation of PD-1 has been brought much arouse great awareness in cancer therapy.

EGFR

Epidermal growth factor receptor (EGFR) is a transmembrane protein which plays multiple roles in physiological and pathological conditions such as proliferation, differentiation, and motility. Receptor tyrosine kinase is activated by its ligand EGF. EGFR forms a homodimer or a heterodimer with its family members and is autophosphorylated, and its downstream intracellular signal molecules such as PI3K, GRB2, and RAS gets activated and exhibits different physiological functions, and the activated EGFR gets internalized in endosomes. EGFR is known to be abnormally expressed in many human carcinomas including skin cancer [83]. Kanemura et al. discovered a higher level of serum EGFR in patients with early-stage malignant melanoma such as in situ and stage I tumors [84]. Recent literature reported that the inhibition of EGFR improves antitumor efficacy of vemurafenib in BRAF-mutant human melanoma in preclinical model [85]. EGFR is also a highly glycosylated protein in plasma membrane. The glycans on EGFR was demonstrated to participate in the regulation of EGFR function [86], the N-glycosylation of EGFR determined its conformation on the cell membrane [87]. A recent research discovered that N-glycosylation of the EGFR extracellular domain plays critical roles in the binding of growth factors and monoclonal antibodies [88]. Concretely, studies with site-directed mutants thought the glycans on Asn 420 and 579 prevented EGFR from independent dimerization [89, 90]. Moreover, Wong et al. revealed that sialylation and fucosylation suppress EGFR dimerization, autophosphorylation, and EGF-induced lung cancer cell invasion [91]. Their latest results confirmed that the sialylation of EGFR suppress its phosphorylation [92]. Researchers also found that sialylation of EGFR by ST6Gal-I sialyltransferase promotes EGFR activation and resistance to gefitinib-mediated cell death [93]. EGFR-targeted inhibitors were developed

hoping to cure tumor patients based on its critical role in organisms [94]. In fact, the EGFR monoclonal antibodies and tyrosine kinase inhibitors (TKI) have been approved for cancer therapy. However, two common problems brought by these EGFR-targeted inhibitors were adverse side effects and acquired resistance[95]. Therefore, N-glycosylation of the EGFR will be a good choice to take into consideration.

Conclusion

People all over the world are bothered by several skin-related diseases, and skin cancer is one of the most significant types for its high lethality. Researchers have been trying to find new target to prolong patients' survival. As reviewed, we hope to clarify the post-translational modification that contributed to parts of the aberrant phenomenon of skin cancer. Nevertheless, the specific mechanism of some key glycosyltransferases and their target proteins in skin cancer need to be further investigated. Furthermore, the crosstalk mechanism within various glycosyltransferases also remains undiscovered. Focusing on these aspects, more effective antibody or inhibitors are in urge to be developed.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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