Review

The modulatory roles of T cell glycosylation in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex and challenging disorder. At present, abnormal T cells are considered to be the key point in the pathogenesis of SLE, including the losing central immune tolerance of self-reactive T cells in the thymus, breaking of regulatory T cell balances, and the overactivation of pro-inflammatory T cells. The alterations of T-cell receptor proteins are closely related to these abnormal changes. Glycosylation is one of the most ubiquitous steps of protein post-translational modification. Especially the modifications of N-glycans and O-glycans on T-cell surfaces have been found to regulate apoptosis and downstream signalling in SLE. Accordingly, this review summarises the aberrant modulate effects of T cell glycosylation in SLE and provides new insights into understanding the pathogenesis and some potential therapeutic targets of this chronic autoimmune disease.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by multiple autoantibody production and abnormal immune-related pathologies (1, 2). This heterogeneous disease results in variable clinical manifestations and involves specific tissue and organ (3). Gene polymorphisms and epigenetic modifications provide the susceptibility for the loss of peripheral immune tolerance. Strong evidence points to the abnormal B cells and the secretion of autoantibodies as the pathogenesis centre of SLE (4-7). Some clinical trials indicated that B-cell inhibitor is a new target for the treatment of SLE (3, 8-10). However, the anti-CD20 monoclonal antibody (Rituximab) failed to deliver satisfactory clinical effects in active lupus disease (11, 12), which demonstrates that other immune pathways play an important role in SLE. As another major category of adaptive immunity, the role of T cells in the pathogenesis of SLE cannot be ignored. T cells subsets are altered in SLE and secret pro-inflammation cytokines in the serum. T follicular helper (Tfh) cells, as members of T helper (Th) cells, assist B cell differentiation by CD40L expression and other costimulatory factors. Moreover, Tfh cells promote immunoglobulin production, isotype switching, and B cell somatic hypermutation in germinal centre (13) by producing IL-21, which behaves like a checkpoint for self-reactive B cells (14, 15). T helper cell subset producing IL-17 (T_h17) is found in kidneys and skin lesions of patients with SLE (16, 17). Other T cell subsets such as double-negative T cells are considered to be the source of IL-17, also the pro-inflammation cytokines like IL-1 and IFN-γ, which promote B cell differentiation and antibody production (18, 19). Therefore, T cells play a crucial role in the pathogenesis of SLE by communicating with other immune cells, alerting the expression of receptors on the cell surface and the downstream signalling (20).

One of the mechanisms of T cell tolerance deficiency is first described as the abnormal signalling pathways through the T-cell receptor (TCR) on the cell surface (21, 22), especially the interaction between extracellular matrix and their protein ligands (23, 24). Glycosylation, as the most common post-translational modification, affects protein functions, including protein maturation, enzyme activity, and the contact between cell and others (cell or extracellular matrix) (25). Also, glycans display different structures even on the same protein, which is considered to reflect the biochemical condi-

tions of a cell or an organ under the pressure of stimulus (26). Actually, the glycoproteins bonded to the TCR take part in the initial inflammation process and influence the function of T cells. For example, the apoptosis mediated by lectin (one kind of glycoprotein) is downregulated in proinflammatory T cells, such as T_h17, which accelerate the pathogenic cytokines infiltrations (27). One of the difficulties in understanding SLE pathogenesis is how T cells alter their phenotype when contact with variable peptides or cytokines. The studies of glycoproteins on T cells will open another gate for a deep understanding of SLE. In this review, we focus on the researches about the disturbed glycosylation patterns on T cells and how they affect the abnormal pathways in cell signalling responses in SLE.

Glycosylation

– The synthesis of N-glycosylation and O-glycosylation

Post-translational modifications are crucial process to ensure the normal biological function of proteins and lipids, which occurs in the endoplasmic reticulum (ER) and Golgi apparatus of eukaryotes. Both proteins and lipids, including sphingolipids, participate in cell signal transduction via adding various lengths sugar chains under the action of a series of glycohydrolases and glycosyltransferases (28). At present, seventeen types of monosaccharides and two major types of glycosylation have been found in mammalian glycoconjugates (29).

Protein glycosylation includes N-glycans, O-glycans and proteoglycans (30). N-glycosylation occurs at Asn(N)-X-Ser/Thr motif that N-acetylglucosamine is connected to the nitrogen atom of asparagine residue by β-1N. This modification is catalysed by mannosidases, N-acetyl-glucosaminyltransferases (Mgat) I, II, IV, and V (31). Under the action of these enzymes, the substrate is transferred to the N-X-Ser/Thr motif and a series of enzymatic reactions take place to extend the sugar chains (32). Finally, the chains are capped by sialic acid and fucose via the action of sialytransferases and fucosyltransferases, respectively. The complex N-glycans sever as ligands of a series of lectins, including galectin (33), siglecs (34), and selectins (35), to regulate the homeostasis of the immune system.

O-glycosylation is the connection between N-acetylgalactose (GlcNAc)/N-acetylglucosamine (GalNAc) and functional hydroxyl groups catalysed by Polypeptide N-acetylgalactosaminyltransferase (ppGalNAcT), which is usually linked to serine and threonine residues to form a structure called Tn antigen (36). Among the O-glycosylated proteins, there is a kind of mucin formed by O-glycosylation residues and tandem repeats of serine and threonine, which exist on the cell surface and many secreted proteins (37). It has been reported that these glycans regulate the recognition, adhesion, and communication models when they interact with lectins in internal environment (37-39). In this review, we mainly discuss the research status of N-glycosylation and O-glycosylation on T cells in patients with SLE. Glycoconjugates in human cells are shown in Figure I.

– The biological function of N-glycosylation and O-glycosylation

In the thymus, thymocytes experience the negative and positive selection, then form the single positive peripheral T cells. Some studies found that the levels of N-glycans are decreasing during the maturation of thymocytes, suggesting that N-glycans participate in the development of these immune cells by regulating the interaction between TCR and MHC (major histocompatibility complex) (40). The Mgat is responsible for synthesis the N-glycan structure on proteins. The abnormal enzyme activities hinder the formation of N-glycans, which will affect recognition and binding to lectin receptors on the cell surface and cause a series of biological disorders. It is suggested that N-glycans participate in glucose metabolism, fat metabolism, signal transduction and apoptosis of immune cells in organisms. In Magt1-deficient mice, varying degrees of retardation or early postnatal death were observed due to the lack of a complete N-glycan sugar chain (41, 42). Some even showed symptoms similar to those caused by human Magt2 defects such as gastrointestinal, blood and bone diseases (43). The N-glycans on the protein are a lattice structure composed of many branches. Each branch binds precisely to the receptors on specific cells and produces completely different physiological effects. For example, both Mgat4a and Mgat5 are essential enzymes which make up the N-glycan antennas (44). The defective mice of the former showed hyperlipidaemia, obesity and insulin resistance, while the latter showed the opposite weight loss caused by hypoglycaemia and hyperinsulinaemia (45, 46). These studies identified the N-glycan as a key receptor in regulating cell signal and biological function.

O-glycosylation stabilises the folding of peptides or proteins in the ER and accelerates their secretion, most of which are functional enzymes(47). Therefore, O-glycosylation influences various tissues during the process of biological development. One study found that p.Thr192Met could inhibit the post-translational modification of matrix receptor by phosphorylated O-mannosyl glycans, which is common in muscles and central nervous system, resulting in muscle nerve symptoms (48). Stotter BR *et al*. (49) confirmed that mucin O-glycosylation plays a very important role in maintaining podocyte function. Studies also showed that the reduced mucin not only directly led to hyperphosphataemia caused by the glycosylation of fibroblast growth factor 23 (FGF23) (50), but also affected the composition and stability of oral microorganisms *in vitro* (51). Even in Alzheimer's disease, the reduced O-N-acetylglucosamine glycosylation was found to associate with the hyperphosphorylated tau protein in neuron cells, indicating that precise glycosylation of specific sites is an essential part of maintaining normal physiological activity (52). Similar to N-glycosylation, O-glycosylation can also bind to extracellular lectins, thus affecting cellular adhesion and inducing cell apoptosis (53, 54). The aberrant expression of glycosyltransferase enzymes promotes cell growth and metastasis, which play a critical role in tumour-related diseases (55). Table I shows the biological simi-

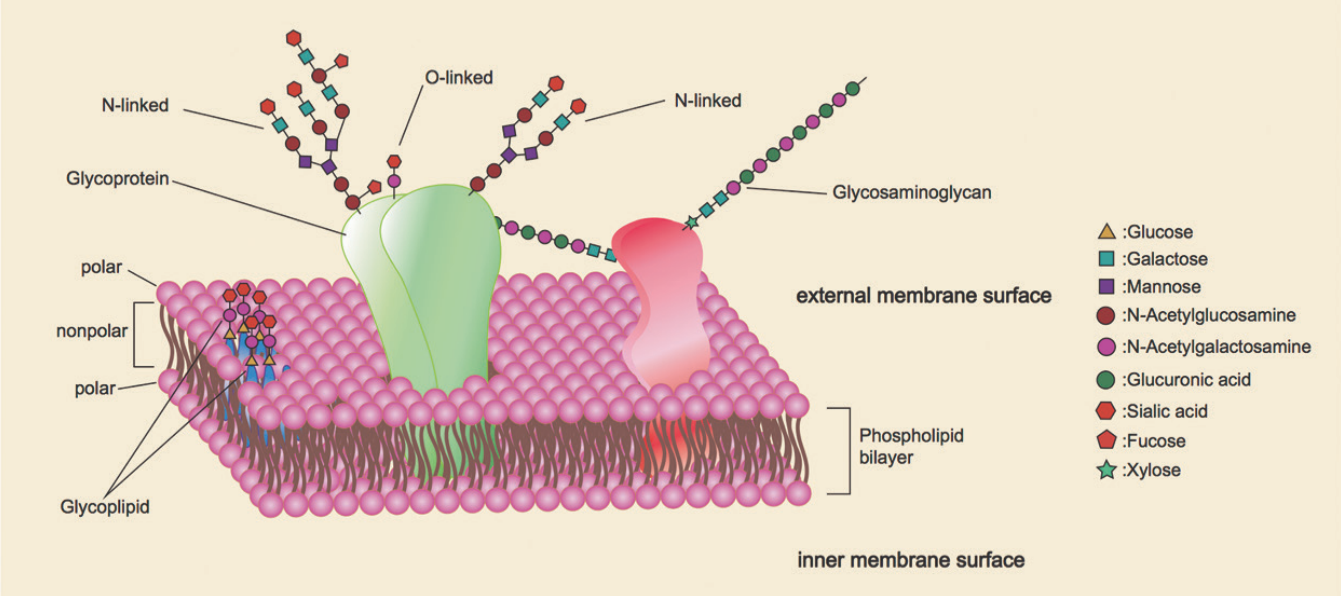

Fig. 1. Glycoconjugates in human cells.
Nine major types of monosaccharides attatched to glycoprotein, glycoplipid and glycosaminoglycan.

larities and differences between N-glycosylation and O-glycosylation.

T cells in SLE

SLE is a typical autoimmune disease caused by immune system overactivation with excessive production and deposition of autoantibodies (2). Also, it is a disease that influences together from the external environment to the internal environment (56). Adaptive immunity is still the core process of this disease. In human adaptive immune responses, T-cell subsets are the key components in inducing inflammation and maintaining immune balance (57).

There is a growing body of evidence to suggest that T cells are the centre in the pathogenesis of SLE, characterised by loss of tolerance to autoantigens. In healthy T cells, the lipid rafts form when they contact the earliest antigen signal (58, 59), and important signal components are recruited into the TCR-CD3 complex, in which the CD3ζchain is phosphorylated by Lck kinase. Then the downstream signals are transmitted by phosphorylated ZAP-70 (60). In SLE patients, CD3ζchain is found to significantly decrease and replaced by the FcR γ chain (61-64) which alter T cell signalling phenotype and lead to excessive activation of T cells (63, 65). The activation signal is transferred from the normal ZAP-70 pathway to tyrosine kinase (Syk) (64), causing a high level of intracellular calcium (Ca^{2+}) (60, 66). On the other hand, activated Syk pathway attenuates the level of IL-2, produced by JNK-c-Jun-AP-1 pathway, and resists gal-1-mediated apoptosis (67). The abnormal level of Ca^{2+} promotes the overexpression of CD40 ligand (CD40L) and activates B cells proliferation (68). As intracellular Ca^{2+} concentration increased, the high mitochondrial membrane potential drives mTOR complex 1 and 2 appear opposite content. And T cells differentiate into T_h1 or T_h17 lineage (69, 70). Moreover, high mitochondrial membrane potential accelerates the consumption of ATPs, which leads to cells necrosis and self-antigens exposure causing a vicious circle(71-73) (Fig. 2).

We observed that the activity of T cells was much higher in both SLE patients and mouse lupus models, especially the activity of phosphokinase 2a (PP2A) in T cells (56, 74). Increased activation of PP2A promotes the reconnection of TCR and decreases the activation threshold. At the same time, the costimulatory molecules on T cells are elevated due to the interaction with other cells (75). In this state, the level of cell metabolism, especially the function of mitochondria, increased rapidly, which leads to more productions of reactive oxygen species (ROS) and oxidative stress (76, 77). The ROS strengthens the level of intracellular AKT-mTOR signal and promotes the differentiation of $CD4^+$ T regulatory cells (Tregs) into T effector cells (Teffs) (78, 79). Also, the expression of DNA methyltransferase (DNMT1) in T cells is inhibited by ROS together with PP2A. The low-level of methylation in $CD4^+$ T cells is beneficial to the proliferation and functional stability of Tregs. In contrast, increased cytotoxicity and up-regulated expression of inflammatory cytokines are shown in $CD8^+$ T cells due to the inhibition of methylation (80). T-cell glycosylation is gradually attracting considerable attention in TCR recognition of antigens and regulation of downstream signals. Despite we have known that glycosylation is a key step after translation modification, there remains a paucity of evidence on a comprehensive understanding of glycosylation. With the improvement of detection and analysis technology in recent years, such as the high-performance liquid chromatography (HPLC) and lectin chip, we have discovered the modification sites of glycosylation in different cells. This helps us explore the pathogenesis in autoimmune diseases from the perspective of glycosylation. In the following paragraphs, we will focus on the current study of glycosylation on T cells in patients with SLE.

Table I. The biological similarities and differences between N-glycosylation and O-glycosylation.

N-glycosylation		O-glycosylation	References
Synthetic position	endoplasmic reticulum and golgi	endoplasmic reticulum and golgi	(30)
Synthetic modified site	β-1N of asparagine residue	serine/threonine residue	(31, 36)
Enzymes involved in synthesis	α-mannosidases, N-acetyl-glucosaminyltransferases, β1,4 galactosytltransferases (β4Gal-Ts), β1,3N-acetylglucosainyltransferases (βGNTs)	polypeptide GalNAc transferases (ppGalNAc-Ts) core 1 α1,3 galactosyltransferase (T-synthase or C1GalT1)	(31, 35)
The distribution position of the mature glycan chains	mainly on the cell surface	on the cell surface and some secreted proteins, such as IgA, IgG	(30)
Ligands	lectins in the environment and some cell surface	lectins in the environment	(31, 33, 34) (35, 37-39)
Related physiological processes	immune homeostasis, thymocyte development, glucose metabolism, fat metabolism, early postnatal development, cell signal transduction, cell differentiation	immune homeostasis, neuromuscular system function, kidney podocyte function, hyperphosphatemia, cell differentiation, serve as functional enzymes	(38-46) (47, 49)

The role of glycosylation in T cells in SLE – The regulation of N-glycans on T cells in SLE

Galectin 1 (gal-1) is a member of the mammalian lectin family bound by β-galactoside, which can specifically recognise the N-acetyllactosamine terminal motif on the cell surface and has immunomodulatory effects (81). The mainly regulatory mechanism of gal-1 in T cells is to promote the apoptosis of T_h1 and T_h17 but maintain the function of T_h2 and Tregs (82, 83). The mechanism of T cells apoptosis induced by gal-1 may be that the extracellular gal-1 binds to a receptor on T cells and triggers the recombination of lipid rafts that is a key element in regulating signal transduction. Then it induces tyrosine phosphorylation which requires functional p56Lck and ZAP70 to release ceramide (84). The ceramide lowers the expression of Bcl-2 and accelerates mitochondrial depolarisation which initiates caspase independent mitochondrial apoptotic pathway. Also, this process activates initiator caspase-9 and effector caspase-3, resulting in the breakdown of protein and nuclear DNA in low concentration gal-1 (Fig. 3) (85, 86).

Researches have observed that the gal-1 level is reduced in SLE and results in diminished function of Tregs (87-89). Multiple phenomena and hypotheses explain the effects of gal-1 on T cells in SLE. Among them, the overactivation of Teffs leads to insufficient production of gal-1 and reduces the sensitivity of cells to gal-1, which may be related to the changes of glycosylation on the T-cell surface. And, the deletion of CD3ζ chain leads to the decrease of Lck and ZAP70 activation, which is the key component of gal-1-mediated apoptosis (89-91).

Another theory said that gal-1 changes the T cells activation threshold by reducing the interaction between glycoprotein lattices and TCR (92). In the Golgi apparatus, TCR, together with other glycoproteins, loads mature N-sugar chains under the action of mannosidases, N-acetyl-glucosaminyltransferases (Mgat5) which produced by *MGAT5* gene. Post-modulated TCR binds to gal-1 to form a lattice on the cell surface, and T cells need more activation signals for further activation (93). This regulatory function has been verified in *Mgat5*-knockout mice, a model of spontaneous glomerulonephritis and autoimmune encephalomyelitis (94).

Toscano *et al*. proved that different glycosylation on cell surface can control the T-cell activation signalling and delete particular effector T cells. The expression of glycosyltransferases will determine the sensitivity of T cells to lectins (27). Indeed, abnormal glycosyltransferase was found to associate with T cell activation in patients with SLE. Szabó *et al*. detected the expression of the glycosylation and the glycosylases in T cells with SLE and compared them with healthy control T cells (95). They found that the binding amount of activated SLE T cells to gal-1 was significantly lower than that of the control group, while other lectins were no differences. Interestingly, levels of ST3 beta-galactoside alpha-2,3-sialyltransferase 6 (ST3GAL6) mRNA in activated T cells of SLE patients were increased. The ST3GAL6 is involved in the process of capping the sialic acid to the poly-N-acetyllactosamine chain, which can cleave by the neuraminidase. The opposite effects of sialytransferases and neuraminidases determine the form of sialylation on the cell surface. Therefore, a hypothesis can be concluded that the resistance to gal-1-mediated apoptosis of T cells in SLE is caused by excessive sialylation on the cell surface (95). One pilot study analysed that the B-cell sialytransferase/neuraminidase3 ratio was positively correlated with SLE activity, and the ratio of these two enzymes on T cells was related to the levels of complement and antibody in serum (96). This study suggests that the abnormality of glycosylation on T cells may originate from the unbalanced enzyme activity. Similarly, mice with α-mannosidase II gene knockout developed an SLE-like disease. This enzyme removes mannose from maturing glycoconjugates and is essential for the final formation of complex N-glycan chains on the surface of mammalian cells. The α-mannosidase deficiency increases the number of immature mannose-rich glycoconjugates, while mannose-rich glycoconjugates are more common

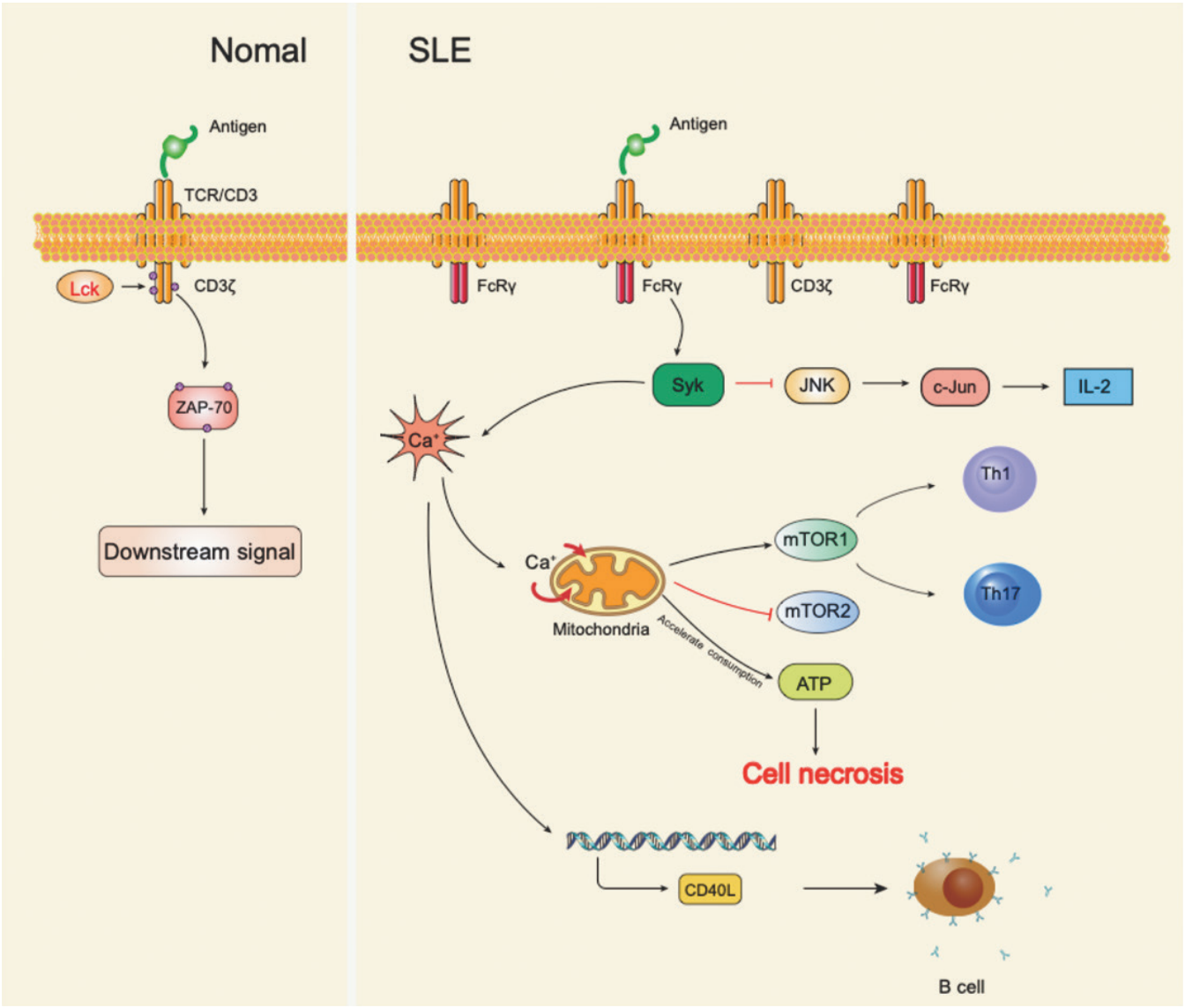

Fig. 2. Signal pathway alterations in T cells of SLE patients and healthy controls.
In healthy T cells, the CD3ζchain of TCR-CD3 complex is phosphorylated by Lck when they contact the earliest antigen signal. Then the downstream signals are transmitted by phosphorylated ZAP-70. In SLE patients, CD3ζchain is decreased and replaced by the FcR γ chain. The activation signal is transferred from the normal ZAP-70 pathway to Syk, causing a high level of intracellular Ca^{2+}. The increased level of Ca^{2+} promotes the overexpression of CD40L and activates B cells proliferation. At the same time, the high mitochondrial membrane potential which elevated by increased Ca^{2+} level drives mTOR complex 1 and 2 appear opposite content. And T cells differentiate into T_h1 or T_h17 lineage. High mitochondrial membrane potential also accelerates the consumption of ATPs, which leads to cell necrosis and self-antigens exposure causing a vicious circle.
T-cell receptor; SLE: systemic lupus erythematosus; Lck: lymphocyte-specific protein tyrosine kinase; ZAP-70: Zeta-chain-associated protein kinase 70; FcR: Fc Receptor; Syk: spleen tyrosine kinase; Ca^{2+}: calcium; CD40L: CD40 ligand; mTOR: mammalian target of rapamycin; T_h17: T helper 17 cells; T_h1: T helper 1 cells; ATP: adenosine triphosphate.

in many fungal strains which are easily identified as non-self-substances to produce autoimmune responses (97). The levels/ratios of transferases are related to disease activity and serological performance, which is likely to provide a new marker of SLE to evaluate disease activity. Nevertheless, we still need more cohort studies and mouse experiments to support this mechanism. In conclusion, genetic defects and aberrant expression of enzymes activity can explain the abnormal N-glycans on T cells which caused the decreased sensitivity to lectins and changed the downstream signalling. Understandings in this field of glycobiology in SLE will enable the development of a variety of glycan-based therapeutics.

– *Effect of core fucosylation on T cells in SLE*

Core fucosylation locates on the cell surface of T and B cells and plays a crucial role in the conformation of TCR (98, 99). It is related to the severity of SLE and increased on the surface of $CD4^+$ T cells (100). There are two models to explain how core fucose enhances T cell activity (101). The first is that the increased binding time of TCR to pMHC (peptide major histocompatibility complex) on B cells or antigen-presenting cells (APCs) improves the excitability of T cells. The alternative is that pMHC induces changes in the

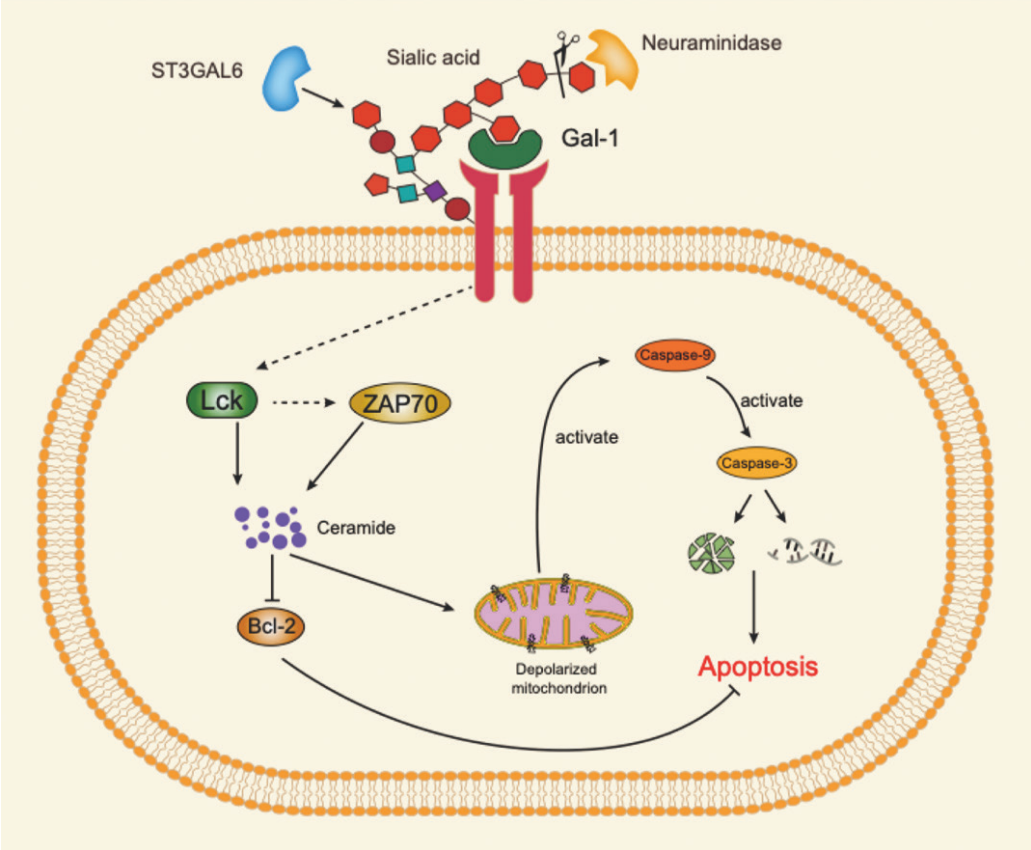

Fig. 3. The regulatory mechanism of gal-1 in T cells.
The extracellular gal-1 binds to the sialic acid of N-glycoprotein on T cells receptor and induces tyrosine phosphorylation which requires functional p56Lck and ZAP70, followed by the release of ceramide. The ceramide lowers the expression of Bcl-2 and accelerates mitochondrial depolarisation. Mitochondrial depolarisation initiates caspase-9 and effector caspase-3, resulting in the breakdown of protein and nuclear DNA.
gal-1: galectin-1; p56Lck: lymphocyte-specific protein tyrosine kinase; ZAP-70: Zeta-chain-associated protein kinase 70; Bcl-2: B-cell lymphoma 2.

Table II. The role of glycans in T cell biology in SLE.

Glycans	Ligands	Roles in T cell	Abnormal changes in SLE	References
N-glycans	Galectin-1	promote the apoptosis of Th1 and Th17	unbalanced enzyme activity leads to the abnormal sialic acid and mannose modification on	(77, 82-84)
		maintain the function of Th2 and Tregs	N-glycans lattices, the deletion of CD3ζchain	(78, 87, 88)
		change the T cells activation threshold by reducing the interaction between glycoprotein lattices and TCR	*MGAT5* mutation leads to low activation threshold	(87)
Core fucosylation	pMHC	increase binding time of TCR to pMHC on B cells or APCs induce changes in the specific conformation of the TCR complex and enhance the downstream cascade signal	overactivation of fucosyltransferase, overactivation of Mgat5	(95, 97, 98)
O-glycans	Amaranth lectin	alteration of T cells subsets and regulation of cell apoptosis	IL-6 and IL-4 inhibit the C1GalT1 and Cosmc activity	(26, 60, 87, 99, 100) (104-108)

specific conformation of the TCR complex, resulting in downstream cascade signal enhancement, such as increased tyrosine kinase (ZAP70) phosphorylation (102). Indeed, in the cells of Fut8$^{-/-}$OT-II (fucosyltransferase deficient) mice, the junction (TCR-pMHC) between T cells and B cells are decreased by a factor of 3.97, proved that core fucose is the key component of the connection between TCR and pMHC (100). In the EAE (experimental allergic encephalomyelitis) model, the Fut8$^{-/-}$mice have relatively mild symptoms and are resistant to inducing sensitive T cells, whereas Mgat5$^{-/-}$mice are highly sensitive. As mentioned above, Mgat5 is involved in the formation of fourth-order antennae of N-glycan on the cell surface, and its deficiency reduces the activation threshold of T lymphocytes which would lead to autoimmune responses *in vivo*. For example, one study showed that the Mgat5$^{-/-}$ mice had spontaneous leukocyte infiltration in their kidneys one year after birth, including monocyte infiltration and a large amount of fibrin accumulation, resulting in the disappearance of renal vesicle cavity, which was manifested as autoimmune-mediated glomerulonephritis (103). Thus, the glycosylation function regulated by Fut8 and Mgat5 is quite

opposite, which indicates the complexity of glycosylation pattern in patients with SLE. This information may lead to the creation of a specific enzyme inhibitor or agonist to correct the overactive T cell. However, further studies are needed to prove whether these series of glycosylation alterations confirmed on T cells are the initiating pathogenic factors in SLE.

– Role of O-glycans in T cells in SLE

Previous studies have found that O-glycans are involved in the alteration of T cell subsets and regulation of cell apoptosis in patients with SLE (27, 65, 92, 104). The affinity of galectin between CD43 or CD45 is determined by core 1 O-glycans and core 2 O-glycans which is associated with T cell activation and adhesion (105, 106). As explained above, Tn antigen binds galectin under the action of core 1 β 1 galactosyltransferase 3 (C1GalT1) and COSMC (C1GALT1 Specific Chaperone 1), a special molecular chaperone, to form galactose β 1-3GalNAc structure, which is called core 1 O-glycan. Ramos-Martínez *et al*. (107) detected the expression of mucin O-glycan chain on T helper cells in peripheral blood mononuclear cells (PBMCs) of 23 patients with SLE by flow cytometry. They found that the expression of O-glycosylation recognised by amaranth lectin (ALL) in active SLE patients was significantly lower than that in inactive SLE patients and healthy controls, which were consistent with the performance of the SLE-like mice (MLR-*lpr*) (108, 109). The decrease of core 1 may be caused by the low level of Tn contents, C1GalT1 or specific molecular chaperone COSMC (110, 111). However, a previous study reported that the contents of Tn were increased on T cells in patients with SLE, which proved that the decrease of enzymes or molecular chaperones was the reason for the reduced of core 1 O-glycan (111). The up-regulation cytokines such as IL-6 and IL-4 inhibited C1GalT1 or Cosmc activities in patients with active SLE (112-115). There was a direct evidence showed that the high expression of IL-4 reduced the later stage of C1GalT1 mRNA transcripts (111). In summary, this study suggested that abnormal O-glycosylation was also involved in the process of immune system disorders. However, limited to the number of patients included in this study, it remains to be verified whether there are differences in glycoproteins between SLE patients and healthy individuals. Table II summarises the role of glycans in T cell biology in SLE.

T cell glycosylation as a potential therapeutic target for SLE

Some studies have aimed to inhibit specific glycosylation sites against overactive immune states. SLE-prone mice (NZB X NZW F1) treated with recombinant galectin-1 exhibited a lower production of anti-dsDNA IgG, a reduction of renal damage, and improved survival rate (116). Also, it was found that galectin-9 antibody inhibited the proliferation of T cells and reduced the release of inflammatory cytokines (IFN-γ, IL-2, IL-10, IL-6, IL-17) when antibody cultured with PBMCs from SLE patients *in vitro* (117). Therefore, the multiple biology functions of galectins suggest these proteins are valuable therapeutic targets in SLE; actually, many galectin antagonists are under development (118). Worth noting is that the level of sialylation on glycoprotein determines the pattern of immune response. Considering the excessive expression of sialylation on T cell surface in SLE patients, intervention on sialylation may help correct immune hyperactivity in SLE (95, 119).

Compared with tumour-related disease, the glycomedicine researches are far from enough in SLE. To date, a large number of glycosylation-targeted treatments have been applied in tumour researches, such as glycoprotein agonists or inhibitors, chemically modified receptors (CARs), antibodies or blockers and vaccine therapeutic (120-127). It is well established that SLE is a complicated and multiple factor-induced disease. Moreover, it is not often possible to analyse the specific glycan structure in a living cell from SLE patient, except for removing and purifying glycoprotein. Although studies pointed that glycosyltransferase would serve as another significant therapeutic target, these experiments were only performed in mice or *in vitro* cell culture (95, 128). Hence more efforts should be taken to explore T cell glycosylation pattern of different disease states, and the immune microenvironment component alterations during T cell migration and proliferation. Such efforts will further promote the development of novel therapeutic for SLE patients.

Conclusions

This review summarises the results of existing studies on glycosylation of T cells in patients with SLE and provides a more systematic understanding of the possible molecular regulatory mechanism which may provide direction for further research. Glycosylation is mainly divided into two categories, N-glycans and O-glycans, whose synthesis depend on the catalysis of different transferases and cleavage enzymes in substrates and gradually extend the sugar chain. Glycans on the cell surface or on secretory proteins are regulated by specific lectin ligands for cell-to-cell adhesion, recognition and immune homeostasis. N-glycans play a key role in undergoing positive and negative selection in the thymus. Mice with congenital glycosyltransferase deficiency may develop into serious autoimmune diseases or death after birth.

The glycosylation on the surface of T cells showed abnormal in SLE patients. It was found that the increased sialylation on the surface of activated T cells reduced the binding of gal-1 in the extracellular matrix and resisted the apoptosis of T_h1 and T_h17. Moreover, the expression of core fucosylation is increased in SLE patients correlated with disease activity. At present, most of the studies on glycosylation are mainly focused on N-glycan, which means that N-glycan has a more extensive and intimate relation with T cells. O-glycan is also considered to involve in the process of T-cell differentiation and apoptosis, while further researches need to address the specific regulatory mechanism.

Most galectins exist in the extracellular environment and they are convenient for detection; therefore, the glycosylation target therapy of T cells in SLE is

mainly concentrated on the galectin antibody. With the maturity of glycosylation research tools, glyco-engineering is gradually applied to the treatment of diseases (129). Glyco-engineering includes glycosylation-modified antibodies, glycan synthase or transferase inhibitors or agonists, glycosylation modified receptors, etc. Through glycan targeted therapy, a certain subset of abnormal T cells will be corrected, thus reducing the release of inflammatory cytokines in patients. Theoretically, it also reduces the side effects caused by non-specific treatment effects. However, this aspect is not now being exploited in T cells in SLE. It is hoped that glyco-engineering might be used to aid the development of T cell glycosylation therapeutic target in SLE.

Collectively, the researches of the abnormal glycosylation of T cells partly explain the breakdown of immune tolerance in SLE and provide us a new insight about the occurrence and development of autoimmune diseases.

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