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Commentary

Role of Glycans in Immune Modulation and Inflammation: Implications for Therapeutic Strategies

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DESCRIPTION

Glycosylation, the addition of carbohydrate moieties to proteins, lipids, and other biomolecules, is an essential post-translational modification that governs many cellular processes, including immune cell communication, adhesion, signaling, and migration. Glycans, the sugar molecules attached to these biomolecules, play an important role in regulating the immune response, modulating inflammation, and maintaining immune homeostasis. Aberrant glycosylation can result in dysregulated immune responses, leading to chronic inflammation, autoimmune diseases, and impaired immune function. Understanding the role of glycans in immune modulation and inflammation is thus key to developing novel therapeutic strategies aimed at treating a wide range of immune-related diseases.

Glycans and immune cell interactions

The immune system relies on a complex network of interactions between immune cells and other tissue types to detect and respond to pathogens, damage, and abnormal cells. Glycans, particularly those present on the surface of immune cells, are essential for mediating these interactions. The interaction between selectins, integrins, and their glycan ligands, for example, is important for immune cell trafficking and adhesion to endothelial cells during inflammation. The selectin-glycan interactions are important for the rolling and tethering of leukocytes, while integrin-glycan interactions are necessary for firm adhesion and transmigration into tissues. Alterations in these glycan-mediated interactions can affect immune cell recruitment and function, contributing to both acute and chronic inflammation.

Leukocyte trafficking and adhesion: Glycans on the surface of leukocytes (white blood cells) play a key role in immune cell trafficking to sites of infection or injury. These glycans interact with selectins (e.g., E-selectin, P-selectin) expressed on endothelial cells lining blood vessels, facilitating the rolling and migration of immune cells into inflamed tissues. In chronic inflammatory diseases like rheumatoid arthritis, abnormal glycosylation of selectin ligands may lead to sustained or dysregulated leukocyte trafficking, perpetuating inflammation.

Antigen recognition and immune activation: Glycans also mediate immune cell recognition of pathogens or tumor cells. Pattern Recognition Receptors (PRRs) on immune cells, such as C-type Lectin Receptors (CLRs), recognize specific carbohydrate patterns on the surface of pathogens, triggering immune responses. For instance, mannose and fucose residues on bacterial or fungal pathogens can bind to CLRs on dendritic cells and macrophages, initiating innate immune responses. These interactions are pivotal for recognizing infectious agents and activating downstream inflammatory pathways.

Glycosylation and inflammation

Inflammation is a tightly regulated response to infection, injury, or harmful stimuli. However, when inflammation becomes chronic or uncontrolled, it can lead to tissue damage and contribute to various diseases, including autoimmune disorders, cardiovascular disease, neurodegeneration, and cancer. The role of glycosylation in inflammation is multifaceted, influencing the activation of inflammatory mediators, the trafficking of immune cells, and the resolution of inflammation.

Inflammatory cytokine production: Glycans play a key role in regulating the production of pro-inflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF-α), interleukins, and interferons. These cytokines are critical for orchestrating the immune response, but their overproduction can lead to chronic inflammation. Abnormal glycosylation of cytokine receptors or signaling molecules can lead to enhanced cytokine production, contributing to chronic inflammatory conditions. For example, sialylation (the addition of sialic acid residues to glycans) is known to suppress the activity of certain inflammatory cytokines by affecting the binding affinity of their receptors, thus modulating immune responses.

Chronic inflammation in autoimmunity: In autoimmune diseases, the immune system mistakenly targets self-antigens,

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resulting in chronic inflammation and tissue damage. Changes in glycosylation on autoantibodies or immune cell receptors can promote the inappropriate activation of immune cells. For instance, altered glycosylation of Immunoglobulin G (IgG) antibodies can affect their interaction with immune cells, such as macrophages or neutrophils, and lead to the persistence of autoimmune responses. Additionally, the glycosylation of Major Histocompatibility Complex (MHC) molecules and T-cell receptors can influence immune cell activation, potentially leading to autoimmune diseases such as Systemic Lupus Erythematosus (SLE) or rheumatoid arthritis.

Resolution of inflammation: In addition to promoting inflammation, glycans are also involved in the resolution phase of inflammation. This phase is important for restoring tissue homeostasis after an immune response. Anti-inflammatory cytokines, such as Interleukin-10 (IL-10), and resolving mediators, such as lipid mediators derived from omega-3 fatty acids, help to switch off inflammatory signaling pathways.

Therapeutic implications of targeting glycosylation in immune modulation

The central role of glycosylation in immune modulation and inflammation, therapeutic strategies aimed at targeting glycan structures offer promising avenues for treating a variety of immune-related diseases. These therapies can either modulate glycosylation directly or exploit glycans as biomarkers or therapeutic targets.

Glycosylation inhibitors: One approach is to use glycosylation inhibitors to modulate the immune response. Inhibitors of glycosyltransferases, enzymes responsible for the addition of sugar molecules, can be used to alter the glycosylation patterns on immune cells or inflammatory mediators. For example, fucosyltransferase inhibitors can block the formation of selectin ligands, reducing leukocyte trafficking to sites of inflammation and potentially alleviating symptoms of chronic inflammatory diseases like rheumatoid arthritis or inflammatory bowel disease.

Lectin inhibitors: Lectins are proteins that specifically bind to carbohydrate structures on glycoproteins or glycolipids. Inhibiting the interaction between lectins and glycan ligands can disrupt critical immune cell signaling pathways. For example, CLR inhibitors have been proposed as a therapeutic strategy for modulating immune responses in autoimmune diseases or preventing infection by blocking pathogen recognition by immune cells.

CONCLUSION

Glycans are key regulators of immune function and inflammation, influencing everything from immune cell trafficking to cytokine production and the resolution of inflammation. Aberrant glycosylation is implicated in a range of immune-related diseases, including autoimmune disorders, chronic inflammatory conditions, and cancer. Understanding the role of glycans in these processes offers exciting therapeutic possibilities, from glycosylation inhibitors and lectin-based therapies to glycan-based vaccines. Targeting glycosylation to modulate the immune system presents a promising approach for treating a variety of diseases, advancing personalized medicine, and improving patient outcomes in immune-mediated diseases.