Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Using the glycan toolbox for pathogenic interventions and glycan immunotherapy

RJ Eveline Li, Sandra J van Vliet and Y van Kooyk

Glycans play a crucial role to discern between self and foreign entities by providing key recognition elements for C-type lectin receptors (CLRs) and Siglec receptors expressed on immune cells. The glycan recognition of CLRs has illustrated a potent immune modulatory role affecting not only innate pathogen binding and immune signalling, but also Thelper differentiation, cytokine production and antigen presentation. This broad range of influence has implicated glycans in the pathogenesis of infectious diseases but also revealed their extraordinary properties in cancer. Glycan binding by CLRs and Siglecs can be exploited for immunotherapy and the design of glycan-based therapeutics and their multivalent requirements will aspire new biotechnological approaches to effectively interfere in immunological processes in cancer and infectious diseases.

Address
Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

Corresponding author: van Kooyk, Y (y.vankooyk@vumc.nl)

Current Opinion in Biotechnology 2018, **51**:24–31

This review comes from a themed issue on **Nanobiotechnology**

Edited by **Alfonso Jaramillo** and **Mark Howarth**

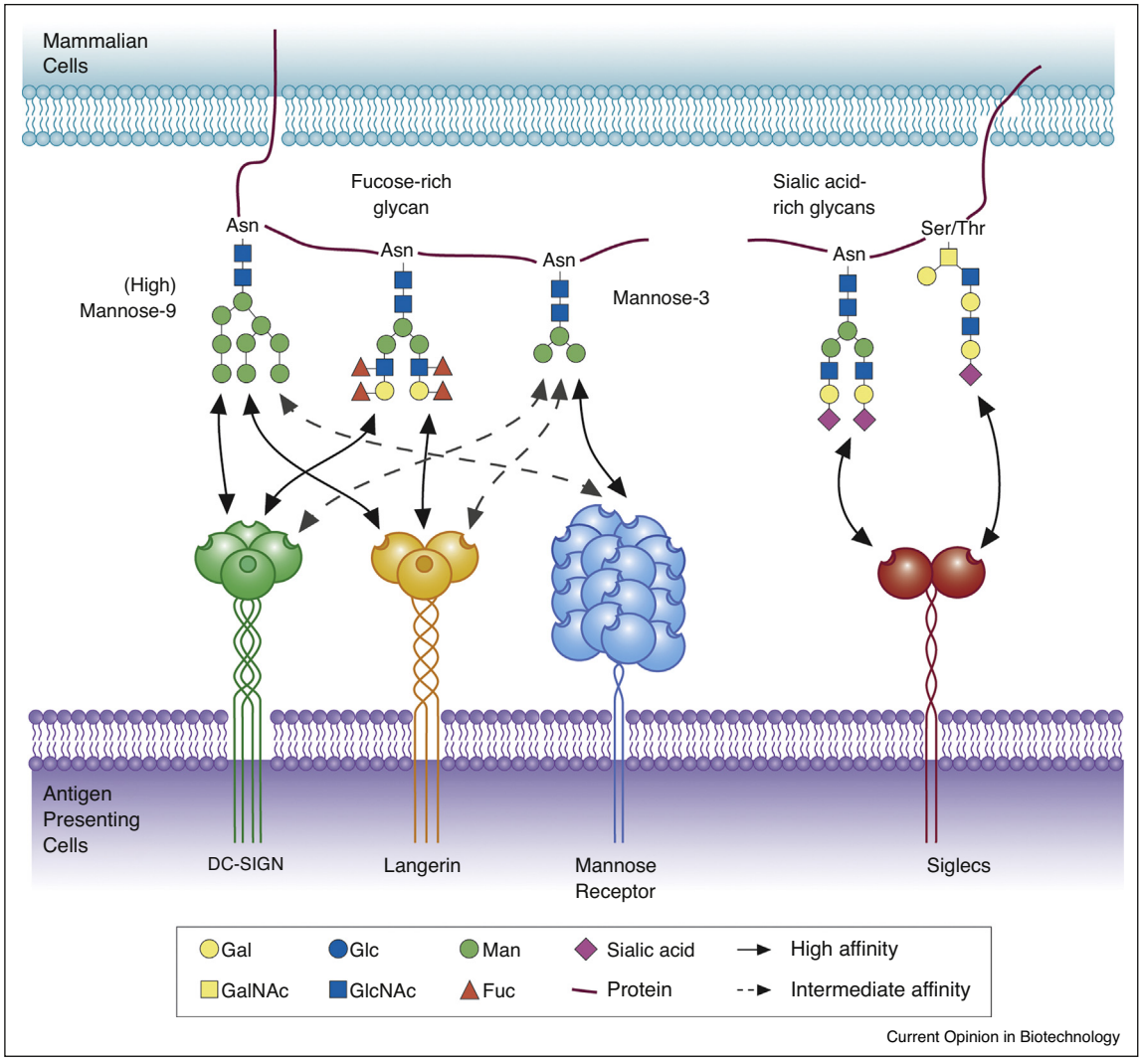
https://doi.org/10.1016/j.copbio.2017.11.003

Pathogenic glycans in infectious diseases

Glycans are polysaccharide molecules comprised of one or multiple monosaccharide units (Figure 1). In this review we will discuss how mannose, fucose and sialic acids influence the host immune response, and how glycans can be exploited to improve current cancer vaccination strategies. The host immune cells that are key in the innate recognition of pathogens are antigen presenting cells. Antigen presenting cells recognize glycans on pathogens using glycan binding receptors and communicate this information to the adaptive immune response which are the T cells. Antigen presenting cells have a specificity for interacting with various glycans. One of the most intensively studied monosaccharide units is mannose. **Mannose** is present on a vast range of pathogens, including *Mycobacterium tuberculosis*, HIV, and *Aspergillus fumigatus*. Depending on the position and abundance in a larger polysaccharide, mannose can interact with a multitude of glycan-binding C-type lectin receptors (CLRs) expressed on antigen presenting cells, amongst others DC-SIGN, Langerin, and the Mannose Receptor (MR), allowing rapid pathogen uptake to elicit naïve T cell polarization to mature effector T cells (T_H1 or T_H17) needed for recruitment and activation of macrophages and neutrophils at the place of infection (Figure 2). DC-SIGN and Langerin favour high mannose glycans, a polysaccharide comprised of unsubstituted terminal mannoses, with five to nine mannose monosaccharides build up from the N-glycosylation core (Figure 1). High mannose glycans are present on the envelope glycoproteins of HIV that mediates binding of antigen presenting cells via DC-SIGN [1–3] and thereby cause HIV spread and propagation of infection, while the virus is degraded by specific antigen presenting cells that express Langerin and subsequently process HIV for degradation [4]. In contrast, MR prefers glycans lower in mannose-content, including hybrid glycans with only a few terminal mannose residues. The localization, 3D orientation and quantity of this monosaccharide in a larger glycan is thus fundamental in CLR binding. However, through receptor dimerization, high mannose binding can be enhanced and additionally contribute to HIV infection [5].

Fucose differs from mannose only in a methyl group, yet it can still interact with some of the mannose-binding CLRs present on antigen presenting cells. The evoked immune response however is very dissimilar. Fucose-rich glycan antigens from for example *Helicobacter pylori* or *Schistosoma mansoni* are recognized by the immune system for their own benefit and survival, indicating that CLRs are also used for immune evasion by pathogens (Figure 2). DC-SIGN contributes to this dissimilarity in immune responses via the activation of different signalling cascades that are triggered in antigen presenting cells upon binding of fucose or mannose. The interaction of DC-SIGN with mannose-rich antigens recruits the Raf-1 kinase through the DC-SIGN signallosome, comprising of scaffold proteins LSP1, KSR1 and CNK, ultimately leading to the acetylation of the NF-κB subunit p65, an enhanced transcription rate and the production of pro-inflammatory cytokines, such as Interleukin-12p35 (IL-12p35), IL-12p40, and IL-6 to promote an effector T cell (T_H1 or T_H17) response [6]. In contrast, binding of fucose-containing ligands via DC-SIGN dissociates the signallosome in antigen presenting cells, which is

Figure 1



Glycan-binding receptors and their ligands. DC-SIGN, Langerin and Mannose Receptor on antigen presenting cells all have a binding preference for mannose-containing polysaccharides, albeit with different affinities (high mannose (mannose 5-mannose 9 versus mannose 3, strong binding indicated by the solid line, weak binding depicted as a dashed line)). DC-SIGN and Langerin are furthermore capable of binding fucose-rich glycans. Siglec receptors bind sialic acid moieties, often found at the termini of a N-glycan or O-glycan.

replaced for a fucose-specific signallosome, allowing nuclear translocation of the NF-κB complex regulator, BLC-3 [7]. Together with the p50-p50 dimer BLC-3 form a transcriptional complex suppressing IL-12p70 transcription in antigen presenting cells, while enhancing other subtypes of effector T cells, such as, T follicular helper (T_{FH}) and T_H2 through IL-27 and IL-10 cytokine secretion, respectively [6,8]. This indicates that binding of a differential glycan to DC-SIGN on antigen presenting cells modifies the adaptive immune response from an effector T cell response into an antibody generation T_{FH} cells that subsequently trigger B cell responses. The different glycan binding on antigen presenting cells modulates the TLR signalling cascade and the manner of NF-κB activation, which is associated with a tailored cytokine and chemokine production, that enables humoral (antibody) or adaptive (cellular) immunity.

The **neuraminic acid-derivative sialic acid** is clearly distinct from the above mentioned monosaccharides, as it is a negatively charged carbohydrate and is either alpha 2–3, alpha 2–6 or alpha 2–8 linked to the glycan chain [9]. Frequently found at the antenna termini of glycan structures, sialic acids interact with the Siglec receptor family, expressed on many immune cells, and are often associated with immune suppression and tolerance induction through negative signalling via Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs) present in the