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Breaking the Glyco-Code of HIV Persistence and Immunopathogenesis

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Abstract

Purpose of review Glycoimmunology is an emerging field focused on understanding how immune responses are mediated by glycans (carbohydrates) and their interaction with glycan-binding proteins called lectins. How glycans influence immunological functions is increasingly well understood. In a parallel way, in the HIV field, it is increasingly understood how the host immune system controls HIV persistence and immunopathogenesis. However, what has mostly been overlooked, despite its potential for therapeutic applications, is the role that the host glycosylation machinery plays in modulating the persistence and immunopathogenesis of HIV. Here, we will survey four areas in which the links between glycan-lectin interactions and immunology and between immunology and HIV are well described. For each area, we will describe these links and then delineate the opportunities for the HIV field in investigating potential interactions between glycoimmunology and HIV persistence/immunopathogenesis.
Recent findings Recent studies show that the human glycome (the repertoire of human glycan structures) plays critical roles in driving or modulating several cellular processes and immunological functions that are central to maintaining HIV infection.
Summary Understanding the links between glycoimmunology and HIV infection may create a new paradigm for discovering novel glycan-based therapies that can lead to eradication, functional cure, or improved tolerance of lifelong infection.

Keywords HIV persistence · Glycosylation · Galactosylation · Sialylation · Fucosylation · Galectins

Introduction

The main barrier to HIV eradication is the ability of HIV to establish latent infection in long-lived CD4+ T cells, which persist in the blood and tissues [1]. These latently infected cells are the source of viral rebound after interruption of antiretroviral therapy (ART), and their continual reactivation in vivo probably contributes, among other drivers, to the immune activation, chronic inflammation, and organ damage

that persist despite long-term suppressive therapy [2, 3]. These realities have prompted a renewed interest in developing new effective and accessible therapies that can lead to eradication, functional cure, or improved tolerance of lifelong infection.

Many studies have described the important role the immune system plays in regulating HIV infection during suppressive ART [4, 5, 6•, 7]. These studies suggest that a comprehensive understanding of the host immune determinants

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shaping the persistence and immunopathogenesis of HIV is a critical step in developing new strategies to cure HIV and/or prevent or delay the development of inflammation-associated co-morbidities, which are more prevalent in HIV+ individuals compared with those in the general population, despite long-term suppressive ART [8–16].

After the initial success of the genome-wide association approach, it became evident that genetic information was only one of the layers of biologic complexity and that knowledge about several additional layers would be needed to understand life at the molecular level. A particularly important layer in this respect is glycomics. Glycobiology is an emerging field focused on defining the structures and functional roles of complex carbohydrate structures, called glycans, in biological systems. These glycan structures, composed of branched chains of monosaccharides, are added to a wide variety of biological molecules (such as proteins and lipids) through a biological process called glycosylation. Glycosylation alters not only protein/lipid structure but also their function. The specific structure of a glycan allows it to bind to a specific type of glycan-binding proteins called lectins, leading to activation of downstream signaling pathways. Glycans integrate genetic and environmental factors, contribute significantly to variability in protein structure, and function as a bridge between cells and their complex environments; thus, aberrations of glycan structures closely associate with complex diseases [17–19]. Evolutionary conservation is in the order of: genetic code "genome" > RNA sequences "transcriptome" > primary protein sequence "proteome" > metabolic pathways "metabolome" > cellular lipid composition "lipidome" > glycan structures "glycome." The reverse order generates structural diversity and richness of biological information. In other words, the genome is the most evolutionarily conserved and the least diverse, and the glycome is the least evolutionarily conserved and the most diverse, rich with biological and chemical information [20].

Recent advances in glycobiology show that the glycome (the repertoire of glycan structures of an organism) is not just a biomarker of biological functions but actually plays critical roles in modulating immune responses [21] and in cell-cell [22] and cell-pathogen interactions [23]. Since glycans affect protein structure and function, it is not surprising that they play an important role in regulating both physiological and pathophysiological processes. The recent consensus report of the National Research Council concluded that "glycans are directly involved in the pathophysiology of every major disease" … "additional knowledge from glycoscience will be needed to realize the goals of personalized medicine and to take advantage of the substantial investments in human genome and proteome research and its impact on human health" [24].

At the intersection of immunology and glycobiology is "glycoimmunology," an emerging field focused on understanding how immune responses are mediated by glycans and glycan-lectin interactions. How glycans influence immunological functions is increasingly well understood. In a parallel way, in the HIV field, it is increasingly understood how the host immune system controls HIV infectivity, persistence, and immunopathogenesis. However, how the host glycosylation machinery may modulate the persistence and immunopathogenesis of HIV has been mostly overlooked. An association between glycomic alterations and HIV infection was suggested over two decades ago [25–27], but the precise role of the host glycome in HIV infection was never characterized due to the lack of glycobiological technologies that can analyze clinical samples at a large scale. Now, a wide range of advanced glycomic technologies are emerging, and we are becoming able to tackle the complexity of the host glycome. Using these new tools to understand the role of glycoimmunology in the maintenance of HIV latency, and the development of the aging- and inflammation-associated co-morbidities, may allow us to develop novel therapies that can lead to eradication, functional cure, or improved tolerance of lifelong infection.

Although the glycosylation of the HIV envelope (Env) protein and the potential for exploiting this glycan shield to elicit antibodies with broad neutralizing activity have been a key area of interest in the HIV vaccine field, here, we will not discuss this area as excellent reviews have already been published [28, 29]. We rather will focus on the potential role of the host glycosylation machinery, including the binding of virus glycans to host lectins, in regulating HIV persistence and immunopathogenesis, as this area remains completely understudied, despite its potential for therapeutic applications. We will survey four areas in which the links between glycan-lectin interactions and immunology and between immunology and HIV are well described. For each area, we will describe these links and then delineate the opportunities for the HIV field in investigating potential links between glycoimmunology and HIV persistence/immunopathogenesis.

The Potential Role of the Circulating Human Glycome in Modulating Immunological Responses During HIV Infection

Glycomic analyses of circulating biofluids such as serum/plasma, cerebrospinal fluid (CSF), and urine have provided many biomarkers of human diseases and biological states, such as cancer progression [30–38]. These studies have suggested that the circulating glycome plays an important role in regulating the immunological responses to disease. Within the human circulating glycome, glycans on circulating immunoglobulins (Igs) are known to play an important role in regulating several immunological functions [39]. Igs are glycoproteins produced

by plasma cells that contain two domains separated by a hinge region. The Fab (Fragment, antigen binding) domain determines specificity towards antigens and the Fc (Fragment, crystallizable) domain is involved in binding to Fc receptors on the surface of immune cells. The most abundant Ig in humans is immunoglobulin G (IgG), with many non-neutralizing effector functions, such as antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and several pro- and anti-inflammatory activities [40–42]. The ability of IgG to function in these capacities is conferred and modulated by its glycosylation at an evolutionarily conserved *N*-glycosylation site at Asn-297 of the Fc domain and by variable glycosylation sites resulting from somatic hypermutation [43] in the Fab domain (15–20 % of IgG molecules) [44]. Glycans of the Fc domain are positioned in a hydrophobic pocket and quite rigid; these enable binding to the Fcγ receptors, likely by keeping the Fc domain in an open conformation [45]. On the other hand, glycans on the Fab domain are more flexible, contain more sialylated glycans and more glycans with a bisecting *N*-acetylglucosamine (GlcNAc) [44] and can modulate antigen binding [45]. The next two sections will discuss the potential role of the IgG glycome in regulating both inflammatory responses and plasma-mediated innate immune effector activities during HIV infection. Note that although the glycosylation of other circulating glycoproteins in biofluids likely also plays an important role in regulating immune functions, these influences are much less well understood and will not be reviewed here.

Chronic Inflammation Has Been Associated with Aberrant IgG Glycosylation Patterns and Is Prevalent in HIV+ Individuals, Despite ART

Even after long-term suppressive ART, HIV+ individuals suffer from a high incidence of diseases that are commonly associated with aging and that are caused, at least in part, by low-grade, systemic, chronic inflammation, observed typically in elderly individuals, and termed inflammaging [46–49]. Examples include cardiovascular disease, cancers, neurocognitive disorders, and osteoporosis. It is hypothesized that inflammaging occurs in HIV+ individuals at younger ages than in HIV counterparts [50]. Although considerable gaps remain in our understanding of the pathophysiological mechanisms driving the development of aging-associated co-morbidities in HIV+ individuals, the chronic inflammatory state caused by HIV infection is likely a key. Indeed, in HIV+ individuals, systemic inflammation, as measured by serum markers, can predict the incidence of mortality, cardiovascular disease, lymphoma, type 2 diabetes, cognitive dysfunction, and frailty [51–56]. Chronic inflammation likely involves multifactorial mechanisms, not all of which are well characterized. Sources of chronic inflammation in HIV+ individuals

include on-going HIV production, cytomegalovirus infection, loss of regulatory T cells, and microbial translocation [57–64]. Comprehensively understanding the causes of HIV-associated chronic inflammation can lead to the development of tools to prevent it, and thereby prevent or delay the development of aging-associated co-morbidities in HIV+ individuals.

Since immunological functions are shaped by the host glycome, it is not surprising that inflammation is associated with aberrant glycosylation. A number of studies have linked altered IgG glycosylation, in particular, lowered levels of sialic acid, to systemic inflammatory responses [65–67]. A reduction in IgG sialylation, termed hypo-sialylation, increases the pro-inflammatory function of IgGs [65–68]. The exact mechanism of this action is not clear. One suggestion is that sialylation switches the antibody's binding from classical to non-classical Fc receptors [69]; however, other studies suggest that this switching is minimal [70, 71]. Another suggestion is that binding of sialic acid–containing glycans to the sialic acid–binding immunoglobulin-like lectins (siglecs) on the surface of monocytes/macrophages initiates an inhibitory signal that leads to an anti-inflammatory response, through inhibition of TLR4 signal transduction. Such TLR4 inhibition reduces the production of pro-inflammatory cytokines such as TNFα and induces the production of anti-inflammatory cytokines [72, 73, 74•]. This anti-inflammatory effect of sialic acid is supported by studies showing that the anti-inflammatory effect of intravenous immunoglobulin (IVIg), used to treat rheumatoid arthritis and other inflammatory conditions, is driven by sialic acid–containing *N*-linked glycans [66, 75, 76].

IgG glycosylation also has been closely linked to both chronological and biological age, in several large glycomic studies in the general population. Intriguingly, certain glycomic traits were found to predict chronological and biological age better than typical markers such as telomere length [77, 78]. Altered glycosylation also has been shown to associate with age-related illness: large patient cohorts showed that IgG glycosylation is significantly altered in patients with inflammatory bowel disease, systemic lupus erythematosus, cardiovascular disease (CVD), cancer, and diabetes [17, 79–85]. Whether IgG glycosylation is a driver or simply a biomarker of aging and aging-associated co-morbidities is still a matter of debate. However, evidence that altered glycosylation actually drives disease comes from recent studies indicating that IgG glycosylation changes years before the onset of disease [86, 87].

HIV infection causes certain IgG glycomic alterations including hypo-sialylation and agalactosylation (lack of galactose) [88•]. Lower levels of galactosylation in HIV+ individuals compared with healthy controls are most pronounced in the IgG1 subclass [89]. Interestingly, agalactosylation has also been associated with pro-inflammatory functions of IgGs [90]. The pro-inflammatory action of IgG agalactosylation is thought to be conferred both indirectly, because galactose is

a prerequisite for terminal sialylation, and directly, by activating the complement system through either the alternative pathway [91] or the mannose-binding lectin-dependent pathway [92]. Intriguingly, HIV-associated agalactosylation is reversible by ART, whereas hypo-sialylation is not [88•]. These glycomic alterations may reflect a chronic inflammatory state as they are also observed in other inflammatory conditions [89] such as inflammatory bowel disease [79], rheumatoid arthritis [93], systemic lupus erythematosus [94], and with aging [39, 77].

Although it is becoming increasingly established that there is a link between the circulating glycome and the development of several pro- and anti-inflammatory responses (Fig. 1), whether the HIV-induced changes in the circulating glycome are linked to inflammaging and HIV-associated co-morbidities (during both viremic and ART-suppressed HIV infection) is less clear. Recently, plasma glycomic biomarkers were identified (using lectins) to predict HIV-associated cardiovascular events [95]. However, more work is needed in this direction. Understanding the link between circulating glycomic alterations and inflammation, during HIV infection, may provide clues about the mechanistic underpinnings of age- and inflammation-associated diseases in HIV+ individuals. This line of research might allow for discovering novel glycomic-based biomarkers of inflammaging during HIV infection or novel glycan-based interventions to prevent inflammation- and aging-associated diseases in HIV+ individuals.

Antibody-Mediated Effector Functions Are Significantly Affected by Changes in IgG Glycosylation and Are Important for Preventing and Controlling HIV Infection

The importance of the non-neutralizing Fc-mediated effector functions of antibodies (including ADCC) in preventing and controlling HIV infection has been highlighted by several studies [96–103]. In addition, the recently discovered broadly neutralizing antibodies (bNAbs) are being investigated within HIV curative strategies, especially in combination with latency reversal agents that may provoke antigen presentation [103, 104]. ADCC is one of the potential mechanisms by which bNAbs may target the latent HIV reservoirs [103, 104]. However, the molecular determinants of ADCC and other Fc-mediated effector functions (such as ADCP and CDC), especially during ART-suppressed HIV infection, are not fully characterized.

Effector- and antigen-binding functions of IgG are significantly affected by changes in glycosylation. The absence of core fucose results in a stronger binding to Fcγ receptor IIIA and leads to enhanced ADCC activity, while the presence of core fucose reduces ADCC [105]. Although core fucose has the greatest impact on ADCC activity, terminal galactose also has been shown to increase ADCC [106], as well as CDC [107] and ADCP [108] (Fig. 2). Despite these results, the role of galactosylation in ADCC activity is somewhat controversial, likely because the effects of terminal galactosylation are

Fig. 1 Circulating IgG glycans mediate pro- or anti-inflammatory responses. Sialylated and galactosylated glycans have been associated with anti-inflammatory responses while bisected *N*-acetylglucosamine (GlcNAc) has been associated with pro-inflammatory responses. HIV infection causes pro-inflammatory changes, e.g., ART-irreversible loss of sialic acid and ART-reversible loss of galactose. Whether the HIV-induced changes in the circulating glycome are linked to inflammaging and HIV-associated co-morbidities (such as cardiovascular diseases and neurological impairments) is not clear. Asn, asparagine
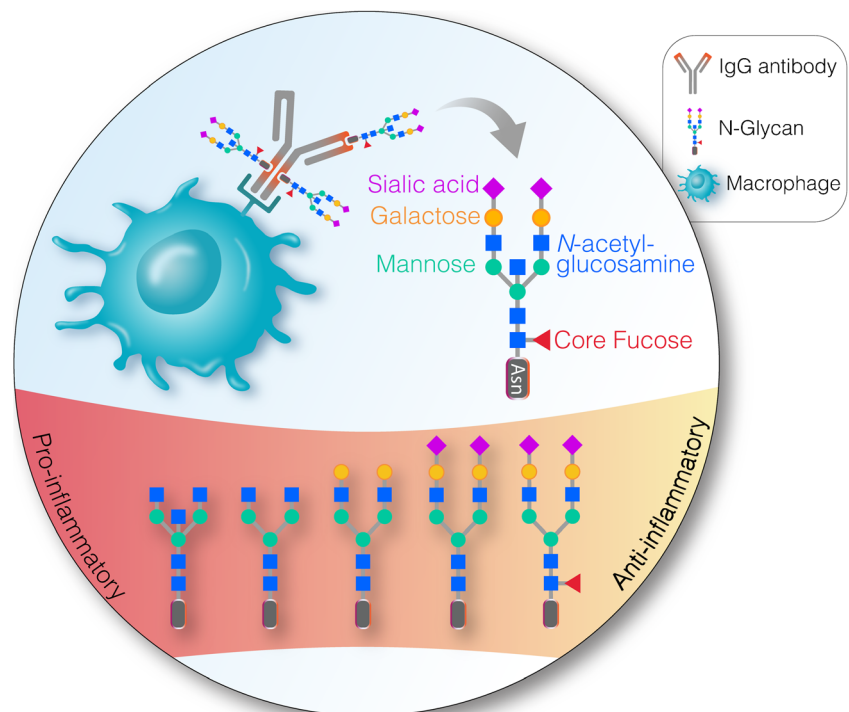
Fig. 2 Antibody-mediated effector functions ADCC, ADCP, and CDC are significantly affected by changes in IgG glycosylation. The presence of core fucose reduces ADCC, and the presence of galactose induces ADCC, ADCP, and CDC. The size of the HIV reservoir, measured using nucleic acid–based methods (CD4+ T cell–associated HIV DNA and RNA), negatively associates with the levels of non-fucosylated galactosylated glycans, during suppressive ART. However, it is not clear if the documented roles of non-fucosylated galactosylated glycans in promoting ADCC and ADCP impact viral control during ART. C1q, complement component 1q
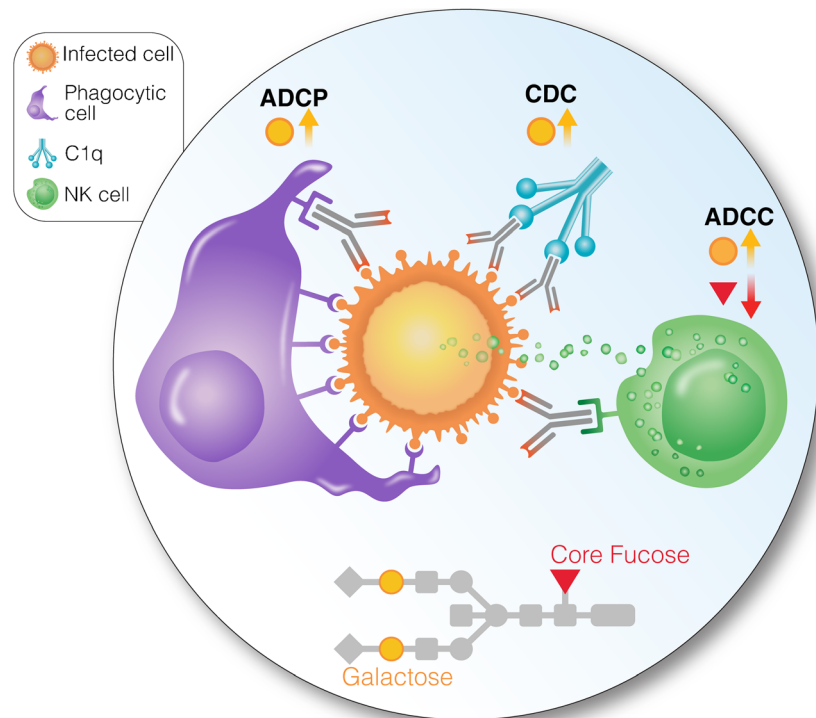
not singular [106, 109]. For example, recent research shows that the effect on ADCC activity differs between galactose bound to antenna of the α1-3-mannose of IgG Fc-glycan (inversely correlated with ADCC activity) and galactose bound to antenna of the α1-6-mannose (directly correlated with ADCC activity) [108].

The HIV field has started to investigate whether IgG glycosylation is important for HIV infection. Changes in global and antigen-specific antibody glycosylation have been associated with a differential ability of anti-HIV antibodies to control HIV infection [110]. Lower abundance of Fc glycans with core fucose (afucosylation) has been observed in antigen-specific anti-HIV antibodies, suggesting that there is active tuning of glycosylation by B cells to increase antiviral control during HIV infection [110]. This afucosylation, in addition to agalactosylation, was also linked to enhanced natural killer (NK) cell activity in spontaneous controllers of HIV [110]. During suppressive ART, certain plasma and antibody glycomic traits, in particular levels of non-fucosylated galactosylated glycans, are negatively associated with levels of nucleic acid–based measures of HIV reservoir (CD4+ T cell–associated HIV DNA and RNA) [88•]. These findings, during suppressive ART, are intriguing as these particular glycomic features imply higher antibody-mediated effector functions, as described above. However, it is not clear if the documented roles of non-fucosylated galactosylated glycans in promoting ADCC and ADCP activities translate into an impact on viral control during ART, because ADCC and ADCP require antigen presentation (viral production) on the

cell surface, which is debatable during ART [111, 112]. Continuing this work to understand the role of antibody glycosylation in regulating HIV persistence may reveal new mechanistic underpinnings of HIV persistence, which can serve as a foundation of novel, glycomic-based HIV curative strategies. In addition, this understanding may lay the groundwork to engineer bNAbs and improve their ADCC/ADCP activities for HIV curative purposes.

Complex Interactions Between HIV Glycans and Host Lectins Modulate Viral Attachment, Entry, and Spreading

The glycosylation of HIV virions has been well described [113]. HIV gp120 is heavily *N*-glycosylated, with a majority of high-mannose *N*-glycan structures and a lower proportion of complex *N*-glycans carrying lactosamine residues and terminal sialic acid. HIV particles themselves contain cell-derived glycolipids, including the sialic acid–containing GM3 ganglioside [114].

These various glycan structures on HIV gp120 and HIV particles interact with a wide range of host lectins during HIV infection, promoting viral spreading or immunological responses. The dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a member of the C-type lectin family and an HIV receptor [115]. DC-SIGN recognition of HIV high mannose glycans mediates HIV capture by dendritic cells (DC), which can subsequently

lead to CD4+ T cell trans-infection. B cells also express DC-SIGN, and a similar role of HIV capture and presentation to CD4+ T cells has been described [116]. Langerin is another C-type lectin, which is expressed on Langerans cells (LCs) and binds to high-mannose HIV glycans [117]. In contrast, to capture by DC-SIGN, HIV capture by langerin was associated with viral clearance, as LCs are mostly resistant to HIV infection and rapidly degrade the virus [118]. However, the role of langerin in HIV clearance or spreading remains controversial [119, 120]. A third C-type lectin that can bind gp120 HIV high-mannose structures is the mannose-binding lectin (MBL) [121]. This soluble lectin has been shown to compete in vitro with DC-SIGN for HIV binding, thereby inhibiting DC-mediated CD4+ trans-infection [122]. However, in vivo, the association between HIV progression and MBL level/genotype remains elusive [123–125]. Recently, the C-type lectin L-selectin has also been described as an HIV adhesion receptor that facilitates infection of CD4+ T cells [126]. Three additional C-type lectins can bind to HIV gp120 high mannose structures: the DC immunoreceptor (DCIR) [127], the DC-SIGN-related protein (DC-SIGNR) [128], and the surfactant protein D (SFTPD) [129]. DCIR has been shown to play a role similar to DC-SIGN. In addition, DCIR is expressed on the surface of CD4+ T cells of HIV-infected patients, enhancing HIV attachment, entry, and transfer [130]. The DC-SIGN homolog DC-SIGNR is expressed mostly on endothelial cells, including in lymph nodes, and can promote viral trans-infection [128]. SFTPD is a soluble protein present in mucosal secretions [131]. The role of SFTPD-HIV binding remains unclear [129, 131].

A second layer of complexity in the interaction between HIV glycans and host lectins is conferred by sialic acid—siglec binding. Sialic acid present on gp120 complex N-glycans or HIV gangliosides is recognized by different members of the family of sialic acid–binding immunoglobulin-type lectins called siglecs. On macrophages and dendritic cells, it is siglec-1 that binds to sialic acid on HIV and mediates particle-capture and trans-infection of CD4+ T cells [132, 133]. Interestingly, the macrophage siglec-1 is described to recognize HIV ganglioside, mostly GM3, whereas the DC siglec-1 is thought to interact with gp120. Despite these interactions, a loss-of-function mutation in siglec-1 in vivo did not significantly impact HIV prevalence and progression [134]. On monocyte/macrophage and NK cells, it is siglec-7 that interacts with HIV to facilitate CD4+ T cell infection [135]. Finally, soluble galectin-1 has been described to directly bind to HIV particles and increase HIV infectivity, apparently by interacting with CD4 glycans and gp120 lactosamine containing complex N-glycans [136].

It is unclear to what degree these complex interactions between HIV glycans and host lectins influence viral attachment, entry, and spreading in vivo, and whether they play any role during suppressive therapy, especially in tissues, where ART penetration might be suboptimal and ongoing HIV replication is debatable [111, 112]. Understanding the forces that lead to HIV acquisition, pathogenesis, and persistence, especially in tissues, will be needed to develop effective therapeutic strategies to clear the infection. These glycomic interactions could be a key for this understanding and may also play a role in improving antigen presentation, which can be critical for developing effective vaccination strategies.

Cell-Surface Glycan-Lectin Interactions Mediate Signals that Define Cellular Processes and Immunological Functions; Many of Which Are Central to HIV Infection

During HIV infection, the host immune system experiences several dysfunctions that are not fully recovered by ART. Several of these dysfunctions can be linked to glycan-lectin interactions. The specific structure of a glycan allows it to bind to specific lectins, leading to the activation of downstream signaling pathways. These pathways are critical for a variety of cellular processes and, importantly here, immunological functions. For example, galectins (lectins that bind β-galactoside) promote immune evasion by inducing T cell exhaustion and apoptosis, expanding regulatory T cells, and inhibiting NK cells [137–140, 141••]. Siglecs (lectins that bind sialic acid) play an essential role in inflammation, cell death, and immune suppression [66, 75, 138, 142–147]. Selectins (lectins that bind fucosylated and sialylated glycans) regulate leukocyte recruitment and migration to the sites of inflammation [148–150]. Figure 3 summarizes some of the glycan-lectin interactions that regulate important cellular and immunological functions and that can be critical for HIV persistence and immunopathogenesis. After first summarizing the roles of various immune cell types in HIV infection, we will describe some of the glycan-lectin interactions that modulate function in these different cell populations.

T Cells T cell activation, CD8+ T cell dysfunction, T cell proliferation, and bystander CD4+ cell death are all critical components of HIV infection, persistence, and disease progression [151–157]. Glycan-lectin interactions are known to regulate several of these functions. One class of glycan-binding proteins that have been described to play critical roles in T cell function activation and apoptosis are the galectins, a family of β-galactoside-binding soluble lectins. Galectin-1, galectin-3, and galectin-9 induce T cell apoptosis, and increased expression, a classical galectin receptor, lactosamine chains, has been associated with HIV infection [25]. This upregulation of galectin ligands has been proposed as a possible mechanism for the bystander T cell death during HIV infection. A rapid secretion of galectin-9 has been described after HIV
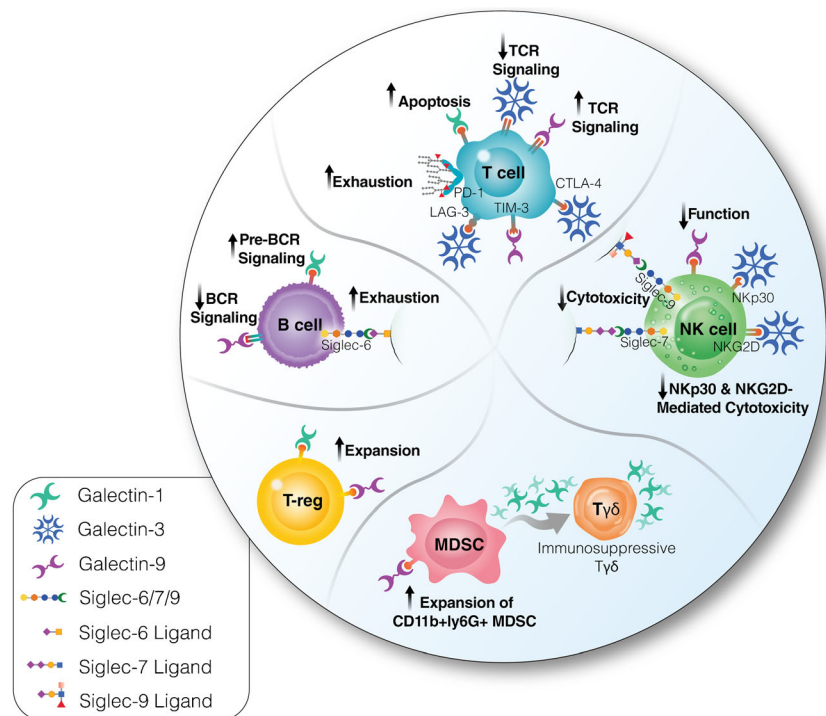
Fig. 3 Cell-surface glycan-lectin interactions mediate signals that define several cellular processes and immunological functions central to HIV infection. The specific structure of a glycan allows it to bind to specific lectins, leading to the activation of downstream signaling pathways. These pathways are critical for a variety of cellular processes and immunological functions. T cells. Galectin-1 induces T cell apoptosis. Galectin-9 induces TCR signaling, while galectin-3 reduces it. Galectin-3 alters T cell function through interaction with LAG3 and other immune negative checkpoints. Last, the fucosylation of PD-1 impacts its function. NK cells. Siglec-7 and siglec-9 inhibit NK activity. Galectin-9 impairs NK function/cytotoxicity and cytokine production through a Tim-3 independent mechanism. Galectin-3 antagonizes NK cell–mediated antitumor immunity by diminishing the affinity of MHC I–related chain A (MICA) for the NKG2D receptor or by acting as an inhibitory ligand of the NKp30 receptor. B cells. Siglec-6 induces B cell exhaustion. Galectin-1 is a pre–B cell receptor ligand that induces receptor clustering, leading to efficient B cell differentiation. Galectin-9 suppresses BCR signaling. T-regs. Galectin-1 and galectin-9 can expand T-regs. Myeloid-derived suppressive cells (MDSC). The galectin-9/Tim-3 interaction drives the expansion of CD11b+ly6G+ MDSC. Granulocytic MDSCs induce γδ–T cells to produce galectin-1, thus transforming them into immunosuppressive cells. These glycan-lectin interactions represent potential novel targets to enhance immune functionality during HIV infection to either cure HIV or prevent HIV-associated immune dysfunction and the subsequent development of immune dysfunction-associated diseases

infection, and the increased serum concentration of galectin-9 does not return to normal after ART suppression [158]. Galectin-9 has several effects on T cells in addition to inducing apoptosis; it activates cells through T cell receptor (TCR) signaling [159], reactivates latent HIV [6•], renders CD4+ T cells less susceptible to HIV infection via induction of host restriction factors [160], and increases the cell-surface concentration of protein disulfide isomerase (PDI) that alters redox state and increases HIV entry [161]. Galectin-9 also has the ability to increase the function of regulatory T cells (T-regs) through interaction with CD44 [162]. Conversely, galectin-3 reduces T cell activation through direct interaction with the TCR and alters TCR functional state through interaction with LAG3 and other immune negative checkpoints [163]. Intriguingly, the glycosylation of T cell immune negative checkpoints (including PD-1) significantly impacts their functions and response to cancer immunotherapy [164•, 165, 166•]. How glycan-lectin interactions impact these important T cell functions during HIV infection is yet not clear. Clarifying the role

these interactions play during HIV infection can provide insights that may lead to the development of novel therapies.

NK Cells NK cells are important innate effector immune cells during HIV infection [167, 168] whose functions can be influenced by glycan-lectin interactions. Altered NK function has been described for two families of lectins, the siglecs and the galectins. A decreased level of the lectin siglec-7 has been described to be a marker for a dysfunctional NK subset (CD56dim) in HIV viremic individuals [169]. Siglec-9, which is also expressed on the NK cell surface and known to play an important role in anti-tumor NK activity [170, 171•], is yet to be studied in the context of HIV infection. Galectins interfere with NK cell–mediated antitumor immunity by modulating NK cell recruitment, lytic activity, and cytokine production. Galectin-9 impairs NK cytotoxicity and cytokine production through a Tim-3 independent mechanism [172]. Galectin-3 also antagonizes NK cell–mediated antitumor immunity by diminishing the affinity of MHC I–related chain A (MICA)

for the NKG2D receptor [173] or by acting as an inhibitory ligand of the NKp30 receptor [174]. These glycan-lectin interactions represent potential novel targets to enhance NK functionality during HIV infection to either cure HIV or prevent immune dysfunction and the subsequent development of immune dysfunction–associated diseases such as AIDS-defining and AIDS-non-defining cancers.

B Cells B cells are crucial for the humoral response during HIV infection. Subsets of B cells have been described to be altered in HIV chronic infection, including exhausted tissue-like memory B cells [175]. This exhausted phenotype has been associated with an increased expression of B cell–inhibitory glycan receptors, including siglec-2 and siglec-6 [175, 176]. Consistently, knock-down siglec-6 in tissue-like memory B cells restores normal function [176]. The ligands of siglec-6 in this context are not known, but the ligand is probably a sialylated glycan. In addition to siglecs, galectins can play an important role in B cell development and function. Galectin-1 is a pre–B cell receptor ligand that induces receptor clustering, leading to efficient B cell differentiation [177–179]. Recently, it was shown that galectin-9 suppresses B cell receptor signaling [180, 181]. Understating the impact of these interactions on B cell development and function, during HIV infection, could be crucial for the effective development of therapies and vaccines.

Myeloid-Derived Suppressive Cells Regulatory myeloid cells, including myeloid-derived suppressive cells (MDSC), expand during chronic infections and have several immunosuppressive activities [182]. Increased levels of MDSC have been associated with HIV disease progression [183]. This MDSC expansion during HIV infection has been shown to promote the differentiation of regulatory T cells and to impair T cell function [183]. One driver of CD11b+ly6G+ MDSC expansion is the galectin-9/Tim-3 interaction [184]. A second glycomic change that may augment immune suppression occurs as granulocytic MDSCs induce γδ–T cells to produce galectin-1, thus transforming them into immunosuppressive cells that abrogate protective antitumor immunity. These important roles of galectins in regulating immune responses could have a direct impact on immune functionality during HIV infection; however, they are yet to be studied.

The Potential Role of the Gut Glycome in Regulating the Homeostatic Relationship Between the Host and Its Gut Microbiota, During HIV Infection

The gastrointestinal (GI) tract plays key roles in HIV pathogenesis and persistence during suppressive ART [185]. HIV infection is associated with changes in the gut structure [186]

and in a breakdown of the epithelial barrier [187, 188], which may increase permeability to the gut microbial products [189]. This microbial translocation is thought to be a major cause of local and systemic immune activation and inflammation, which may further increase HIV replication (resulting in a positive feedback cycle [189–194]) and contribute to the development of non-AIDS co-morbidities [51, 52, 195–197]. In addition, the loss of cellular immune subpopulations such as Th17 and Th22 reduces mucosal immunity [198, 199]. These cells are crucial in responding to bacterial antigens and play an important role in maintaining gut epithelium integrity. Unfortunately, even with ART, the damage to the epithelial barrier caused by HIV infection is never fully repaired, allowing microbial translocation and inflammation to continue [200–202].

The gut cells are heavily glycosylated, and the intestinal epithelium is covered by a layer of mucus, which differs along the GI tract in composition, organization, and thickness. In addition, glycans expressed on the gut epithelial cells have physiological, immunological, and functional characteristics as they are in contact with multiple types of environmental antigens. Interestingly, the glycosylation on these cells can adapt in response to environmental stimuli including microbial stimulation [203–205]. The degree of glycosylation in the gut directly impacts the ability to maintain functional and healthy intestines. Furthermore, the availability of host- and diet-provided carbohydrates in the GI tract shapes the nature and function of the gut microbiome [206, 207]. Aberrant glycosylation patterns in the gut are strongly associated with chronic inflammation. For example, a unique, inflammation-associated glycome has been described on memory CD4+ T cells in the inflamed colon [208, 209]. In addition, impaired expression of intestinal *O*-glycans has been observed in patients with ulcerative colitis, and the deletion of intestinal core 1 *O*-glycans caused spontaneous colitis in mice [210].

The role of the gut glycome in regulating the homeostatic relationship between the host and its gut microbiota is complex and involves multiple glycan structures. Here, we will give one example by illustrating the role of gut fucosylation in the host-microbe interplay [211, 212]. Gut α1,2-fucosylation is induced by the presence of commensal and some pathogenic bacteria and acts as a food source for beneficial gut symbionts [213]. Fucosylated sugar chains are synthesized by fucosyltransferases (FUT) [214, 215]. Bacterial components, such as lipopolysaccharide (LPS), stimulate gut DCs via the TLR–Myd88 pathway [216]. IL-23 produced by gut DCs induces IL-22 production by type 3 innate lymphoid cells (ILC3s) [203, 217]. IL-22 produced by ILC3s provides activation signals to ECs via the IL-22R–STAT3 pathway, leading to the subsequent induction of FUT2 and α1,2-fucosylation [203]. Fucose is then liberated by microbial fucosidases and becomes available for consumption by the downstream microbiota. Recent reports showed that fucose
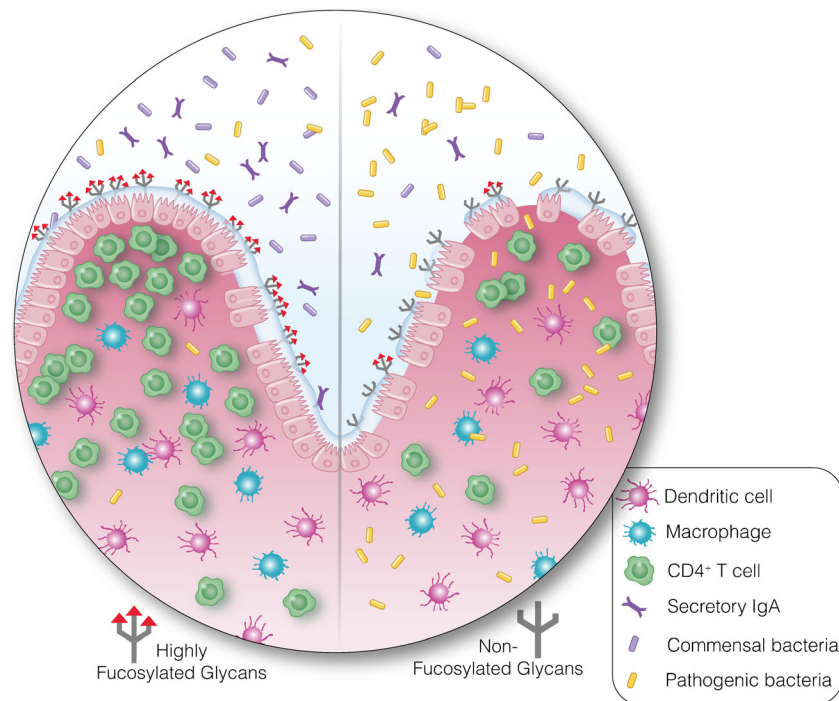
could enhance the beneficial activity of symbionts and improve colonization resistance against pathogens and pathobionts. In the absence of gut fucosylation, beneficial symbionts are weakened and decreased in abundance, and pathogenic bacteria increase, which leads to microbial translocation, inflammation, and breakdown of the epithelial barrier [211, 212] (Fig. 4). Some pathogenic microorganism can hijack epithelial fucosylation to colonize the host gastric and intestinal epithelial cells; these include *Helicobacter pylori*, norovirus, and rotavirus [211, 212]. Interestingly, ~ 20% of humans harbor homozygous loss-of-function mutations for FUT2 [218, 219]. FUT2 mutant humans are more susceptible to several inflammation-related diseases such as Crohn's disease, type I diabetes, and psoriasis [219–225]. They also are more susceptible to several infections, including *Candida albicans*, *Streptococcus pneumoniae*, and urinary tract infections [226–229]. On the other hand, these individuals are more resistant to *Helicobacter pylori*, norovirus, and rotavirus infections [230–235].

Fucosylated glycans are only one group out of many glycan structures composing the gut glycome. These collective glycan structures are used as communication tools to shape the relationship between the gut and its microbiota. A change in the gut glycome, possibly induced by HIV infection and associated inflammation, may alter the distribution of microbial species. Therefore, it is possible that alterations in glycan metabolism may contribute to HIV-mediated intestinal damage, microbial translocation, and chronic inflammation. Given the importance of microbial translocation in shaping HIV disease progression, even after suppressive ART, understanding the functions of the large spectrum of glycan structures in the gut could be essential to understanding the forces that shape the microbiota during HIV infection and how to design strategies to manipulate these forces.

Conclusions

The human glycome might hold the key to better understand immunological functions that are central to HIV persistence and immunopathogenesis. More studies are needed at the intersection between glycobiology, immunology, and HIV research, to take advantage of the recent advances in the emerging field of glycoimmunology. Studies to comprehensively investigate the links between host glycomic alterations and

Fig. 4 The gut-associated glycome is critical for maintaining a homeostatic relationship between the host and its gut microbiota. The degree of glycosylation in the gut directly impacts the ability to maintain functional and healthy intestines. Here, we give one example, by illustrating the role of gut fucosylation in the host-microbe interplay. Fucosylated glycans in the gut (left) enhance the beneficial activity of symbionts and improve resistance against colonization by pathogens and pathobionts. In the absence of gut fucosylation (right), beneficial symbionts are weakened and decreased in abundance, and pathogenic bacteria increase, which leads to microbial translocation, inflammation, and breakdown of the epithelial barrier. Fucosylated glycans are only one group out of many glycan structures composing the gut glycome. A change in the gut glycome may alter the distribution of microbial species. Therefore, it is possible that alterations in glycan metabolism may contribute to HIV-mediated intestinal damage, microbial translocation, and chronic inflammation

inflammation, during HIV infection, may provide novel glycomic-based diagnostic or prognostic biomarkers of HIV-associated inflammaging. These studies may also allow for the development of novel glycan-based interventions to prevent/delay the development of inflammation- and aging-associated diseases during ART-suppressed HIV infection. For example, the information to be obtained from these studies could be used to develop novel strategies to manipulate the forces that shape the gut microbiota during HIV infection and reduce the degree of microbial translocation and associated inflammation. Additional studies will be also needed to investigate the extent to which cell-surface glycans, and their interactions with host lectins, interfere with the function of the immune system, during ART-suppressed HIV infection. These studies could lead to the design of novel immunotherapies to either cure HIV or prevent HIV-associated immune dysfunction. For example, targeting siglec interactions, on NK cells, and galectin interactions, on T cells, may induce the function of these immune cells, during HIV infection.

Importantly, recent advances in the cancer field focusing on glycobiology demonstrated that the aberrant glycosylation pattern of cancer cells alters their interaction with the immune system and allows them to evade immunosurveillance [236–238]. Such advances have promoted an increasing interest in developing tools that can target the tumor "glyco-code" [238]. Recently, a number of glycan-based strategies have been tested as novel cancer immunotherapy agents, e.g., anti-glycan vaccines, glycan-lectin interaction blockers, glycan-specific monoclonal antibodies, glycan-coated nanoparticles, and metabolic inhibitors for certain glycans [171•, 239–249]. These, and other tools, could be used in the HIV field to lay the groundwork for discovering novel glycan-based interactions that can be targeted for novel strategies to eradicate, functionally cure, or improve tolerance of lifelong HIV infection.

Compliance with Ethical Standards

Conflict of Interest GL declares he is a founder and owner of Genos Ltd, a biotech company, that specializes in glycan analysis and has several patents in the field. IT-A is an employee of Genos Ltd. Other authors have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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