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Commentary

Glycosylation tips the scales: Novel insights into the dual role of type-I interferons in treated HIV infection

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It is well known that the release of type-I interferons, IFNα and IFNβ in response to infection is a "tightrope walk" since they may act as either friend or foe. On one hand, type-I IFNs induce an antiviral state in host cells during early infection, preventing viral spread. On the other hand, their pro-inflammatory activity can have detrimental effects, particularly during chronic infections [1-3]. Owing to their antiviral and immune-modulatory properties, type-I IFNs may hold therapeutic potential for viral infections, such as human immunodeficiency virus (HIV). Clinical studies in which antiretroviral therapy (ART) was combined with an application of pegylated (Peg)-IFNα2a produced promising results, evidenced by suppressed HIV viremia and reduction in levels of genome-integrated HIV DNA [4]. However, to effectively exploit this antiviral potential of type-I IFNs, while avoiding undesirable side effects including immune pathology, it is essential to understand the timing and conditions that mediate these opposing effects of type-I IFNs from beneficial to damaging during the course of viral infections [5]. Besides, there is a gap in our knowledge of how type-I IFNs act on the host glycosylation machinery to induce inflammatory processes.

In an article in *EBioMedicine*, Giron and colleagues address the dual role of type-I IFNs by investigating the impact of Peg-IFNα2a treatment on host glycosylation during ART-suppressed chronic HIV infection [6]. To this end, the authors profiled IgG glycome as well as cell surface glycomic signatures of CD8$^+$ *T* cells and NK cells in peripheral blood mononuclear cells (PBMCs) from 18 HIV-infected individuals treated with a combination of ART and Peg-IFNα2a. To correlate IFNα-mediated changes in the glycomic signatures with inflammatory response, the authors measured pro- and anti-inflammatory cytokines and soluble markers in plasma as well as activation markers expressed by CD8$^+$ *T* cells and NK cells. Interestingly, significant changes occurred in the glycan traits after five weeks of starting the Peg-IFNα2a treatment. Particularly striking was the IFNα-induced increase in the portion of bisecting GlcNAc glycans within the IgG glycome (Fig. 1). Higher levels of bisecting GlcNAc glycans on IgG molecules may enhance binding to Fcγ receptors and may contribute to inflammation as shown in previous studies [7]. Consistently, IFNα treatment (in combination with ART) induced pro-inflammatory cytokine IL-18 and led to increased levels of soluble monocyte and macrophage activation markers, sCD14, and sCD163. Whereas, the production of anti-inflammatory cytokine IL-10 was reduced. The authors observed a positive correlation between IFNα-mediated fold change of bisecting GlcNAc glycans and an increased expression of sCD14 and sCD163, suggesting that IFNα treatment causes a pro-inflammatory phenotype. This inflammatory profile was associated with constrained CD8$^+$ *T* cell functions, such as perforin secretion, and reduction in IFNα-mediated downregulation of integrated HIV DNA (Fig. 1). A specific bisecting glycan trait (A2FB) strongly correlated with poor IFNα-mediated fold reduction in integrated HIV DNA, thus rendering this glycan trait a potential biomarker to predict undesirable side effects of IFNα therapy.

The analysis of cell surface glycome after five weeks of Peg-IFNα2a treatment showed lower levels of immunosuppressive sialic acid-containing glycans on CD8$^+$ *T* cells, albeit an increase of immunosuppressive GalNAc-containing glycans, such as T/Tn antigen, was observed. These immune-modulatory antagonistic traits of glycans underline the counteractive effects of IFNα on the host glycosylation machinery. Further studies are needed to investigate whether these glycan signatures can be selectively influenced by different IFNα therapy regimens. In contrast, surface glycome of NK cells was associated with enhanced NK cell functions upon IFNα treatment; increased levels of fucosylated glycans, and reduced levels of immunosuppressive GalNAc-containing glycans. Consistently, these glycan traits positively correlated with NK cell functional markers, including transcription factors, T-bet and Eomes, indicative of enhanced NK cell effector functions. However, as seen for CD8$^+$ *T* cells, IFNα may have counteractive effects on NK cell functions as it was shown to promote increased production of immunosuppressive sialic acid-containing glycans (Fig. 1).

The present study is first of its kind comprehensive analysis of how IFNα may affect host glycosylation and downstream immune functions in vivo. The authors provide evidence that the host glycosylation machinery may be a "missing link" contributing to the dual role of IFNα during HIV infection. By demonstrating that IFNα

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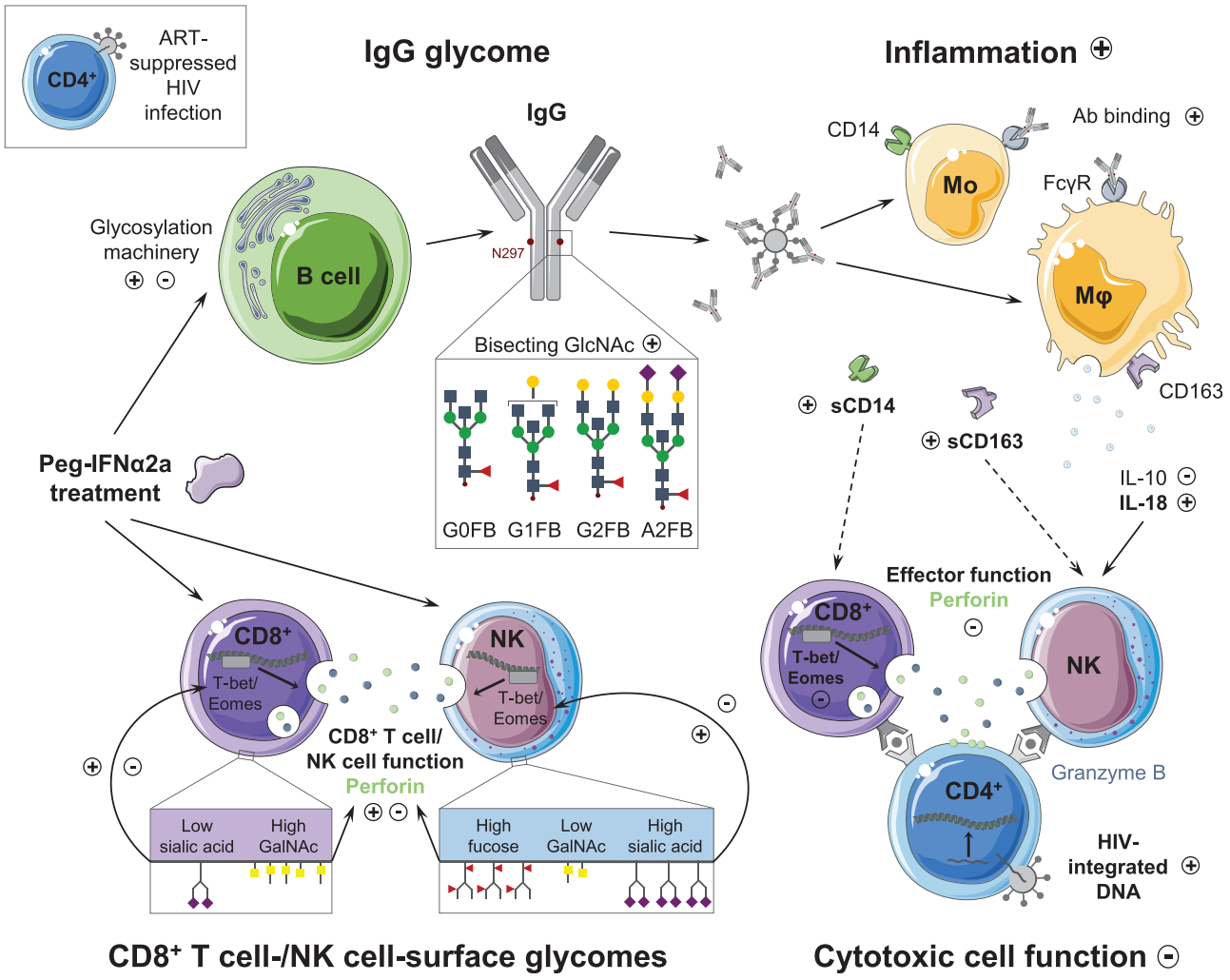

Fig. 1. Giron and colleagues show that differential glycosylation of IgG and immune cell surface glycome in INFα-treated HIV patients correlate with altered immune functions[6]. Pegylated (Peg)-IFNα2a treatment of ART-suppressed HIV infection affects host glycosylation machinery leading to enrichment of bisecting GlcNAc glycans on IgG and differential surface glycosylation of $CD8^+$ *T* cells and NK cells. Higher levels of bisecting GlcNAc glycans on IgG molecules may enhance binding to Fcγ receptors (FcγR) and lead to a higher abundance of the soluble monocyte/macrophage activation markers sCD14 and sCD163. Exacerbated inflammation is associated with suppressed $CD8^+$ *T* cell and NK cell effector functions. Consistently, IFNα-mediated reduction of genome-integrated HIV DNA is decreased. Altered surface glycosylation of $CD8^+$ *T* cells has counteractive effects on $CD8^+$ *T* cell functions. While higher levels of immunosuppressive GalNAc-containing glycans in $CD8^+$ *T* cell surface glycome may negatively impact the transcription factors T-bet and Eomes and perforin secretion, low sialic acid glycans are positively associated with these functions. Similarly, changes in NK cell surface glycome have counteractive effects on NK cell functions.

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differentially affects the IgG glycome leading to beneficial as well as detrimental effects, this study emphasizes the importance of fine-tuning IFNα-mediated effects for a successful treatment. It will be crucial to reproduce and extend the findings of this study in a larger cohort of treated HIV patients and assess IFNα-mediated effects on the IgG glycome and cell surface glycosylation of immune cell subsets under different therapeutic regimens. These insights could open up possibilities for glycan-based strategies to interfere with the host glycosylation machinery or lectin/glycan interactions during inflammation [8]. The present study may also provide a basis for the identification of glycan-based biomarkers to evaluate the success of IFNα therapy during chronic viral infections, as shown here for a combination of ART and Peg-IFNα2a treatment for HIV latency.

The article by Giron and colleagues raises questions that can now be addressed in further studies, for instance, how IFNα acts on the host glycosylation machinery and which roles interferon-stimulated genes (ISGs) and IFNα-induced cytokines play in this process. Future studies need to investigate the involvement of host lectin receptors in the recognition of different glycan traits, e.g. engagement of Siglecs by sialylated glycans or C-type lectin receptors by GalNAc-containing glycans [9]. In recent years, it is becoming increasingly clear that glycomic and glycoproteomic techniques are highly useful tools for studying protein glycosylation in immunity [10]. The study by Giron and colleagues highlights how glycomic analyses can help to address clinically relevant questions and suggests that interference of the host glycomic machinery may be a promising therapeutic strategy during chronic viral infections.

Author contributions

Both authors contributed to writing of the commentary and production of the figure.

Declaration of Competing Interests

M.-K.R. and B.L. have nothing to disclose.

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