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Heparan sulfate proteoglycans fine-tune macrophage inflammation via IFN-β

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ABSTRACT

Macrophages are important mediators of diseases associated with metabolic inflammation such as obesity and atherosclerosis. In this Stimulus we discuss recent findings showing that heparan sulfate proteoglycans on macrophages serve as an important inflammatory rheostat. This observation has significant implications as the degree of macrophage proteoglycan sulfation can determine and possibly predict disease outcomes of metabolic inflammatory disorders.

Macrophages play a central role in both acute and chronic inflammation and have remarkable plasticity when it comes to their inflammatory phenotype. Naïve macrophages are directed to distinct phenotypic programs designated as classically activated pro-inflammatory macrophages (M1) or alternatively activated resolving macrophages (M2). The transition of a naïve macrophage to an M1 phenotype is mediated by lipopolysaccharides as well as cytokines produced by Th1 lymphocytes, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α [1]. M1 macrophages produce several other inflammatory cytokines including Type I IFNs. Several of these cytokines interact with heparan sulfate (HS), which are linear sulfated glycosaminoglycans covalently linked to a specific subset of proteoglycan core proteins [2]. Heparan sulfate (HSPGs) are expressed by virtually all animal cells and are a major constituent of the glycocalyx and extracellular matrix [2]. Their role in cytokine presentation and their abundance in the extracellular environment place HSPGs in a unique position to modulate macrophage phenotypes.

In a current study published in Cell Metabolism, we investigated the importance of macrophage HSPGs in atherosclerosis and diet-induced obesity [3]. Atherosclerosis and obesity are very distinct conditions, but both are characterized by low-grade chronic inflammation and accumulation of M1-like macrophages [4]. We examined the role of HSPGs in these processes using mice bearing a conditional "floxed" allele of *N*-acetylglucosamine *N*-deacetylase-*N*-sulfotransferase 1 (*Ndst1*$^{f/f}$) and the bacterial Cre

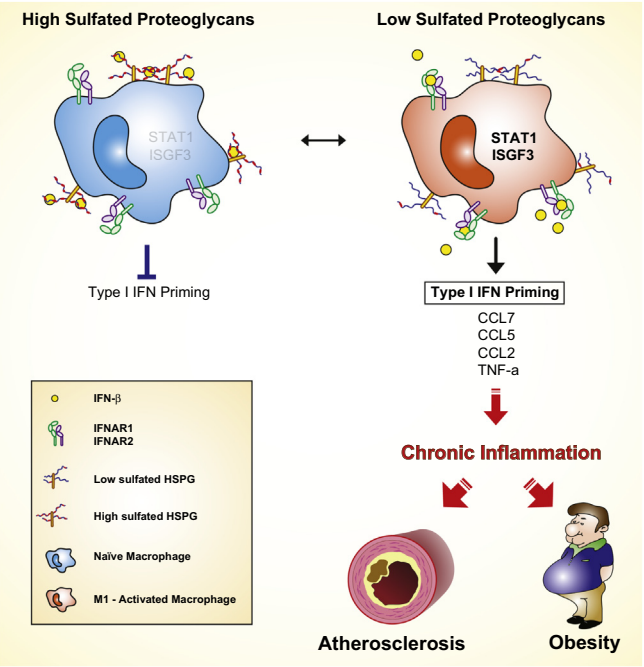

Fig. 1. Highly sulfated HS produced by macrophages (left) maintain cells in a quiescent state through sequestration of IFN-β. Genetic or enzymatic reduction of cell-associated HSPGs (right) increases the bioavailability of IFN-β resulting in activation of macrophages. This shift in tonic Type I IFN signaling boosts activation of macrophages and sensitizes mice and possibly human subjects to diseases with chronic inflammation such as atherosclerosis and obesity.

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recombinase under control of the lysozyme 2 promoter (*LysMCre*) to drive inactivation of the gene in myeloid cells. *Ndst1* inactivation reduced the overall sulfation of HSPG in macrophages by ~15%. In spite of this modest change in HS composition, *Ndst1*$^{f/f}$*LysMCre*$^{+}$ mice on a high fat diet exhibited excessive body weight gain compared to control mice, became profoundly type-2 diabetic and developed exacerbated atherosclerosis on an *Ldlr*$^{-/-}$ background. The increased fat content in adipose tissue and the more advanced atherosclerotic lesions seen in *Ndst1*$^{f/f}$*LysMCre*$^{+}$ mice were associated with hallmarks of metabolic inflammation such as increased macrophage infiltration and expression of chemoattractant chemokines *Ccl5*, *Ccl7*, *Ccl8* and *Tnf-α*. Gene expression analysis of naïve bone marrow derived macrophages from *Ndst1*$^{f/f}$*LysMCre*$^{+}$ mice confirmed that in fact the macrophages were responsible for this increased expression of inflammatory genes. Motif analysis of promoters of up-regulated genes revealed increased Type-I IFN signaling in mutant macrophages. Also STAT1 phosphorylation induced by IFN-β was elevated in *Ndst1*$^{f/f}$*LysMCre*$^{+}$ macrophages.

It is well established that macrophages constitutively express very low levels of IFN-β [5]. Based on our results we propose a model wherein HSPGs determine the bioavailability of IFN-β for its receptors IFNAR1 and IFNAR2 on macrophages under naïve conditions (Fig. 1). Thus, highly sulfated macrophage HS maintains type I IFN reception in a quiescent state through sequestration of IFN-β. Reduction of cell-associated HSPG or alteration of HS composition either genetically or enzymatically increases the bioavailability of IFN-β resulting in macrophage activation. Further support for this hypothesis derived from the observation that IFN-β interacts in a sulfation dependent manner with macrophage HS. Importantly, the data imply that natural variation in macrophage heparan sulfate [6–9] or conditions that result in proteolytic shedding of cell surface HSPGs [10], or desulfation [11] and cleavage of the chains [12] might render some individuals more prone to atherosclerosis, obesity and Type-2 diabetes.

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