1. ABSTRACT

Decorin (Dcn) is a small leonine-rich proteoglycan with a single chondroitin/dermatan sulfate (CS/DS) chain, which, in skin, is mainly composed of DS. CS and DS are linear polysaccharides, modified by different sulfate groups. The CS/DS microheterogeneity is important for the function, determining the GAG binding affinity to biological active proteins, such as fibroblast growth factors (Fgfs). In humans, mutations in DS biosynthetic enzymes cause an Ehlers-Danlos syndrome, with skin fragility and delayed wound healing. Mice with disruption of decorin (*Dcn*$^{-/-}$) exhibit a similar phenotype. In vitro, DS-decorin can save the *Dcn*$^{-/-}$ phenotype more efficiently in contrast to the protein without the DS chain.

Therefore, the impact of *Dcn*$^{-/-}$ DS in mouse skin was analyzed. The loss of decorin affected the GAG composition and sulfation, specifically 2-O sulfation of CS/DS due to a reduced expression of uronyl 2-O sulfotransferase (Ust). Functionally, the alterations in 2-O sulfation of CS/DS in *Dcn*$^{-/-}$ samples reduced their binding to Fgf7 and -2. CS/DS act as low affinity receptors for Fgfs presenting them to the Fgf receptors (FgfR), therefore inducing activation of different signaling pathways. The role of 2-O sulfated CS/DS in this process has not been determined yet. To analyze this, CHO-K1 cells as established proteoglycans study model were used to manipulate Ust and CS/DS 2-O sulfation. The CS/DS chains with increased or decreased 2-O sulfation showed enhanced or reduced Fgf7 and -2 binding, accordingly. As a functional consequence of 2-O sulfated CS/DS and Fgf2 interaction, cell migration was induced. This was supported by activation of ERK1/2, PKCα and -μ, FAK and paxillin. Inhibition of sulfation or knock-down of *Ust* displayed reduced migration as well as blocking of FgfR or PKCα by specific inhibitors. Downregulation of Ust expression, led to reduced migration rate in 3T3 fibroblasts as well. Melanoma cells, as highly migrating cells, express high amount of CS/DS and Ust. Downregulation of Ust expression in B16 cells reduced their migration rate as previously observed for CHO cells and fibroblasts, however in Fgf2 independent mechanism. The invasiveness of B16 melanoma cells was supported by 2-O sulfated CS/DS, but blocked by CS/DS lacking 2-O sulfation.

The results, point to a modulatory effect of 2-O sulfated CS/DS, which can tune the cells, towards migration depending on the signaling cascade induced. Therefore, the application of CS/DS structures which can modulate these processes might be used as targeted pharmacological treatment in wound healing and cancer.