Author's reply to: Comment on: Fibronectin in tissue regeneration: timely disassembly of the scaffold is necessary to complete the build

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Author's reply

We read with much interest the comment of Dr. Moroz on our review, in which we describe how persistence of fibronectin structural variants contributes to failure of tissue regeneration. We agree with Dr. Moroz that, like fibronectin and in line with our main conclusion, matrix metalloproteinases (MMPs) also display both beneficial and detrimental effects in tissue regeneration. Some beneficial effects of MMPs are highlighted by Dr. Moroz, such as their function in extracellular matrix remodeling and absorption important for complete regeneration. In addition, as Dr. Moroz acknowledges, we review at multiple places how adverse changes in MMP levels provide one of several mechanisms for the detrimental effects of persistent fibronectin variants [1]. Fibronectin fragments adversely upregulate MMP levels in osteoarthritis [2, 3]. Similarly, fibronectin aggregates may harmfully alter MMP activity in multiple sclerosis, which is normally tightly regulated on demyelination [4] and important for remyelination [5]. Adverse MMP activity would possibly also require an imbalance in tissue inhibitor of metalloproteinase (TIMP) expression (reviewed, for example, in [6]). In turn, persistent MMP activity mediates structural remodeling of fibronectin, such as fibronectin

fragmentation in osteoarthritis [7], resulting in a bidirectional 'loop' of unfavorable MMP activity.

In short, our main conclusions can certainly be extended to other extracellular matrix molecules, such as MMPs and collagen fragments, tenascin-C, and high molecular weight hyaluronan that are specifically mentioned in our review [1]. We encourage any attempt to do so, because this may accelerate the development of therapeutic strategies to enhance tissue regeneration.

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