A putative role of versican in uterine leiomyomas

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Summary

The extracellular matrix (ECM) has been thought to contribute to the pathogenesis of uterine leiomyomas. Uterine leiomyomas have abundant ECM components, including collagen, fibronectin, and glycosaminoglycans. Recent studies have demonstrated the overexpression of versican in uterine leiomyomas. Versican is a chondroitin sulfate proteoglycan that constitutes the main component of the ECM. However, the role of versican in the growth of uterine leiomyomas remains unknown. In this article a putative role of versican in uterine leiomyomas is discussed in association with cell proliferation and apoptosis..

Key words: Versican; Leiomyoma; Extracellular matrix.

Uterine leiomyoma is a fibrotic disease characterized by the accumulation of the abundant extracellular matrix (ECM) components such as collagen, fibronectin, and glycosaminoglycans. The deregulated ECM metabolism has been thought to play a pivotal role in the pathogenesis of uterine leiomyomas [1]. Versican is one of the main ECM components and is widely distributed in various tissues and cancers.

Versican belongs to the family of hyaluronan-binding proteoglycans that include aggrecan, neurocan, and brevican [2]. Versican modulates cell adhesion, proliferation, migration, and ECM assembly, and hence plays a central role in tissue morphogenesis and maintenance [2, 3]. An alternative splicing yields four isoforms, V0, V1, V2, and V3 [2]. Versican V0 isoform possesses two chondroitin sulfate carrying segments, GAG-α and GAG-ß, whereas V1 and V2 isoforms lack the GAG-α or GAG-ß domain, respectively, and the smallest versican V3 isoform has no GAG carrying modules [3].

Versican interacts with several ECM molecules. All versican isoforms interact with hyaluronan and form different sized versican-hyarulonan aggregates, thereby determining the tissue volume [2]. Versican also binds to the other ECM components such as collagen, tenascin-R, fibulin, fibrillin, fibronectin, P- and L-selectin, and cell surface proteins such as CD44, integrin ß1, and epidermal growth factor receptor (EGFR) [2, 3]. The diverse interaction of versican with its partners regulates cell tissue behavior [3].

A recent study has demonstrated that the versican gene is up-regulated in primary cell cultures of uterine leiomyomas compared with the myometrium [4]. Furthermore, versican V0, V1, and V3 isoform mRNAs are shown to be elevated in cultured leiomyoma cells as compared to myometrial cells [5]. However, the biological significance of versican in uterine leiomyomas remains unknown. Nevertheless, it is speculated that versican may act to promote cell proliferation and inhibit apoptosis of uterine leiomyoma cells. Because the biology of versican in uterine leiomyomas has never been explored so far, a putative role of versican in leiomyoma growth is discussed here based on the known actions of versican examined in various cells.

In addition to the role of versican in the ECM assembly, versican has recently been reported to regulate cell proliferation and apoptosis. Platelet-derived growth factor (PDGF) was shown to increase versican expression at mRNA and protein levels in arterial smooth muscle cells, leading to ECM expansion [6]. PDGF was demonstrated to be up-regulated in leiomyoma tissue compared with myometrial tissue [7]. This suggests that the PDGF-induced stimulation of versican may cause the expansion of the ECM in uterine leiomyomas.

Versican isoforms have different roles in the regulation of cell proliferation and apoptosis. Wu *et al*. [8] reported that versican V1 induced neuronal differentiation and promoted neurite outgrowth by enhancing EGFR and integrin activities in PC12 cells. Furthermore, they reported that stable expression of versican or its C-terminal domain protected astrocytoma cells from oxidative stress-induced apoptosis and enhanced cell attachment and the expression of integrin ß1 and fibronectin, suggesting that versican may promotes cell survival and cell adhesion [9]. Moreover, versican V1 isoform was shown to enhance cell proliferation and inhibit apoptosis of NIH3T3 fibroblasts [10]. It was demonstrated that V1 isoform activated EGFR expression, induced p27 degradation, and enhanced cyclin-dependent kinase 2 activity as well as down-regulated the expression of proapoptotic protein Bad, whereas V2 isoform inhibited cell proliferation and down-regulated EGFR and cyclin A expression [10]. A recent study has demonstrated that overexpression of versican V1 isoform in cultured fibroblasts increased proliferation and apoptotic resistance by down-regulating Fas

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expression [11]. By contrast, V3 isoform was shown to inhibit migration and reduce proliferation of arterial smooth muscle cells [12]. Thus, V1, V2, and V3 isoforms act differently on cell proliferation and apoptosis. The alternation of the balance among versican isoforms may determine the proliferative potential of the cells. Although versican V1 isoform mRNA was reported to be up-regulated in uterine leiomyomas [5], the expression of V2 isoform in uterine leiomyomas remains to be explored. The biology of each versican isoform in the growth of uterine leiomyomas remains to be clarified. However, it is tempting to speculate that the balance of versican isoform activities may be in favor of the promotion of cell proliferation and inhibition of apoptosis in uterine leiomyoma cells. Further study will be necessary to elucidate the effects of V1, V2, and V3 isoforms on the proliferation and apoptosis of uterine leiomyoma cells. The elucidation of versican action on leiomyoma growth would contribute to a better understanding of the novel role of the ECM in leiomyoma growth.

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