# Sex steroidal modulation of collagen metabolism in uterine leiomyomas

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**Summary**

Uterine leiomyoma is a fibrotic disease that contains abundant extracellular matrix (ECM) components, particularly collagen fibrils. Aberrant ECM metabolism has been thought to contribute to the pathogenesis of uterine leiomyomas. However, it remains poorly understood whether ovarian sex steroid hormones modulate collagen metabolism in uterine leiomyomas. More recently, a few articles have demonstrated the differential effects of ovarian sex steroids, selective estrogen receptor modulators (SERMs), and selective progesterone receptor modulators (SPRMs) on the induction of the ECM-remodeling enzymes and collagen synthesis in uterine leiomyoma cells. Sex steroids may act to up-regulate collagen synthesis, whereas SERMs and SPRMs down-regulate collagen synthesis. Further study will be needed to clarify the precise mechanism underlying steroidal regulation of collagen synthesis in uterine leiomyomas.

*Key words:* Collagen; Leiomyoma; Estrogen; Progesterone; Estrogen receptor modulator; Progesterone receptor modulator.

## Introduction

Uterine leiomyomas are characterized by aberrant metabolism of the extracellular matrix (ECM) components, including collagen and glycosaminoglycans [1-3]. Compared with the myometrium, types I and III collagen mRNAs were shown to be elevated in uterine leiomyomas in the proliferative phase of the menstrual cycle [1], and pro-alpha1 (III) and pro-alpha1 (I) collagen mRNAs were up-regulated in uterine leiomyomas [4]. Uterine leiomyomas contain an abnormal collagen fibril structure and orientation [5]. The aberrant metabolism of the ECM has been thought to contribute to the pathogenesis of uterine leiomyomas.

Collagens are the major elements of the ECM and play a vital role in the maintenance of the structural integrity of the tissues [6]. Collagen molecules that are secreted into the extracellular space self-assemble into fibrils in the ECM [7]. The turnover and homeostasis of the ECM is controlled by the action of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) [8, 9]. MMPs degrade the ECM, whereas TIMPs inhibit the activity of MMPs [9]. Extracellular matrix metalloproteinase inducer (EMMPRIN) is known to regulate the levels of MMPs [10].

The possibility of sex hormonal regulation of MMPs and TIMPs has been speculated in uterine leiomyomas [11]. However, little is known about the direct action of sex steroid hormones on the ECM metabolism in uterine leiomyomas. This article provides recent evidence showing the regulatory activity of ovarian sex steroids and their steroid receptor modulators on collagen metabolism in uterine leiomyomas.

We have recently demonstrated that cultured human uterine leiomyoma cells have significantly lower EMMPRIN, MMP-1, and membrane type 1-MMP (MT1-MMP) protein contents, but significantly higher TIMP-1, TIMP-2, and types I and III collagen protein contents compared with cultured myometrial cells [12]. Treatment with selective progesterone receptor modulators (SPRMs) significantly increased EMMPRIN, MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MT1-MMP at mRNA/protein levels and the enzymatic activities of MMP-1, MMP-2, MMP-3 and MMP-9 in the culture medium [12, 13]. In contrast, SPRMs significantly decreased TIMP-1, TIMP-2, and types I and III collagen protein levels in cultured leiomyoma cells compared with untreated control cultures. Moreover, RNA interference of EMMPRIN abrogated SPRM-mediated induction of MMPs and SPRM-mediated reduction of TIMPs and collagens in cultured leiomyoma cells. Thus, SPRMs disrupt the MMPs/TIMPs balance and reduce collagen synthesis in uterine leiomyoma cells, possibly resulting in the reduced deposition of collagens in the extracellular spaces. Thus, it is tempting to speculate that the antifibrotic action of SPRMs would cause the loss of tissue integrity and the reduced expansive activity of uterine leiomyomas *in vivo*. The shrinkage of uterine leiomyomas observed in patients treated with SPRMs [14, 15] may be partly attributed to the SPRM-induced inhibitory action on collagen synthesis.

Estrogen has recently been shown to modulate collagen metabolism in culture uterine leiomyoma cells. Collagen biosynthesis was demonstrated to be stimulated by low doses of estradiol (5 nM) in uterine leiomyoma cells, but high doses of estradiol concentration (10 nM) inhibited the process, while selective estrogen receptor modulator (SERM), raloxi-

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fene and tamoxifen, inhibited collagen biosynthesis in uterine leiomyoma cells [16]. In addition, estrogen and SERMs inhibited MMP-2 levels in uterine leiomyoma cells. The authors suggested that estrogen may contribute to the accumulation of collagen in the ECM of uterine leiomyomas.

Estrogen metabolite 2-methoxyestradiol was shown to induce apoptosis and inhibit cell proliferation and collagen production in human uterine leiomyoma cells [17]. The authors demonstrated that 2-methoxyestradiol inhibited [$^3$H]-proline incorporation in uterine leiomyoma cells, suggesting that collagen synthesis-inhibiting action of 2-methoxyestradiol decreases the leiomyoma size.

Collectively, it seems likely that both estrogen and progesterone act to up-regulate collagen synthesis in uterine leiomyomas, thereby increasing collagen accumulation in the ECM and promoting the expansion of leiomyoma tissues. By contrast, SERMs and SPRMs down-regulate collagen synthesis in uterine leiomyomas and may cause the suppression of tumor growth. The antifibrotic potential of SERMs and SPRMs may be promising for the treatment of uterine leiomyomas. Further study will be needed to clarify the precise mechanism underlying ovarian steroidal regulation of collagen synthesis in uterine leiomyomas.

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