Editorial Article

Action of progesterone receptor modulators on uterine leiomyomas

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Summary

Novel progesterone receptor modulators (PRMs) have recently been demonstrated to be effective in the treatment of patients with symptomatic uterine leiomyomata. PRMs are shown to reduce leiomyoma size and improve leiomyoma-associated symptoms. However, the precise mechanisms underlying the action of PRMs remain to be elucidated. My co-workers and I have investigated *in vitro* action of PRMs in cultured leiomyoma cells and revealed that PRMs inhibit cell proliferation and induce apoptosis of leiomyoma cells. Moreover, our recent studies show that PRMs can modulate the metabolism of extracellular matrix proteins in cultured leiomyoma cells toward the collagenolysis. The update about an action of PRMs in uterine leiomyoma cells *in vitro* is described in this article.

Key words: Progesterone receptor modulator; Leiomyoma; Proliferation; Apoptosis; Angiogenesis; Extracellular matrix.

Traditionally, it has been thought that estrogen mainly acts to promote the growth of uterine leiomyomas. However, recent investigations have accumulated the evidence that progesterone also promotes the growth of uterine leiomyoma cells through a cross-talk with growth factors [1]. In this context, attention has been paid to the application of progesterone receptor modulators (PRMs) in the treatment of uterine leiomyomas.

Two recent studies have demonstrated that novel PRMs, asoprisnil and CDB-2914, are effective in the treatment of symptomatic uterine leiomyomas [2, 3]. Asoprisnil was shown to suppress uterine bleeding in patients with leiomyomas, and reduces leiomyoma and uterus volume [2]. The median percentage changes in leiomyoma size and uterine volume from baseline were reported to be 36% and 17% at week 12 in patients receiving a 25-mg dose of asoprisnil [2]. Similarly, three-month treatment with 10 mg and 20 mg dosages of CDB-2914 has been reported to result in a respective 36% and 21% reduction in leiomyoma volume [3]. PRMs did not cause hypoestrogenism, suggesting minimal adverse effects on bone mineral density. The safety of these drugs was confirmed in clinical trials, but a single case of endometrial cystic hyperplasia developed in a patient receiving CDB-2914 [3]. The optimal treatment regimen for PRMs remains undetermined, and the effects of long-term use of PRMs on safety and efficacy outcomes should be assessed [2].

However, the precise mechanisms underlying the action of PRMs remain to be elucidated. To explore the mechanisms by which PRMs reduce the size of uterine leiomyomas, we have investigated the effects of PRMs, asoprisnil and CDB-2914, on the growth, apoptosis, growth factor expression, and metabolism of the extracellular matrix proteins in cultured leiomyoma cells. The diverse actions of PRMs on cultured leiomyoma cells can be summarized as follows:

1) PRMs inhibit cell proliferation of cultured leiomyoma cells [4, 5].

2) PRM suppresses the protein contents of growth factors in cultured leiomyoma cells, including epidermal growth factor, insulin-like growth factor-I, and transforming growth factor ß3, and their receptors [6]. PRM antagonizes the growth stimulatory action of growth factors in cultured leiomyoma cells.

3) PRM suppresses the protein contents of angiogenic factors and their receptors in cultured leiomyoma cells, including vascular endothelial growth factor and adrenomedullin [7].

4) PRMs induce apoptosis of cultured leiomyoma cells through activation of the mitochondrial pathway and tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptotic pathway [4, 5, 8]. PRM increases the protein contents of proapoptotic proteins such as Bax and Bak, but decreases the protein content of antiapoptotic protein such as Bcl-2 [4, 5, 9].

5) PRM elicits endoplasmic reticulum stress in cultured leiomyoma cells, leading to the induction of apoptosis [9]. PRM augments the expression of the proapoptotic proteins such as growth-arrest- and DNA-damage-inducible gene 153 (Gadd153) and tribbles-related protein 3 in cultured leiomyoma cells. RNA interference of Gadd153 confirmed the close association of Gadd153 in the induction of apoptosis in cultured leiomyoma cells.

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6) PRMs promote collagen degradation in cultured leiomyoma cells by modulating the expression of several extracellular matrix proteins [10, 11]. PRMs augmented the expression of extracellular matrix metalloproteinase inducer (EMMPRIN) and matrix metalloproteinases (MMPs), but attenuated the expression of tissue inhibitors of MMP (TIMPs) and type I and III collagen protein levels in cultured leiomyoma cells. RNA interference of EMMPRIN abrogates both PRM-mediated induction of MMPs and reduction of TIMPs and collagens in cultured leiomyoma cells.

In these serial studies, it is noteworthy that PRMs did not affect the growth, apoptosis, growth factor expression, and extracellular matrix metabolism in cultured myometrial cells. This suggests that PRMs may not inversely affect the growth of myometrial cells.

PRMs were shown to inhibit the growth of cultured leiomyoma cells, suggesting that PRMs exhibit progesterone antagonist activity on cultured leiomyoma cells. Although increasing data indicate the promoting activity of progesterone on leiomyoma growth [1], there is little information regarding progesterone-regulated genes in uterine leiomyomas. It is speculated that the unknown mechanisms by which PRMs induce growth suppression of leiomyoma cells are involved. Microarray studies will reveal the genes regulated by PRMs in cultured leiomyoma cells. This elucidation would contribute to the understanding of more detailed mechanisms responsible for PRM-regulated inhibition of leiomyoma growth.

In conclusion, recent clinical data demonstrate that PRMs are effective even in the short-term treatment of patients with symptomatic uterine leiomyomas. Our *in vitro* data corroborated the growth inhibitory action of PRMs in cultured leiomyoma cells in the absence of comparable effects on myometrial cells. The elucidation of the precise mechanisms by which PRMs regulate the growth of uterine leiomyomas will shed new light on the clinical application of these novel drugs in the treatment of uterine leiomyomas.

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