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Hormones and pathogenesis of uterine fibroids

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The role of ovarian steroid hormones in the pathogenesis of uterine fibroids is supported by epidemiological, clinical, and experimental evidence. Estradiol and progesterone induce mature leiomyoma cells to release mitogenic stimuli to adjacent immature cells, thereby providing uterine leiomyoma with undifferentiated cells that are likely to support tumor growth. Progesterone action is required for the complete development and proliferation of leiomyoma cells, while estradiol predominantly increases tissue sensitivity to progesterone by increasing the availability of progesterone receptors (PRs). The selective estrogen receptor modulator (SERM) raloxifene and the selective PR modulators (SPRMs) mifepristone, asoprisnil, and ulipristal acetate have been shown in clinical trials to inhibit fibroid growth. The role of sex steroids is critical for leiomyoma development and maintenance, but a number of autocrine and paracrine messengers are involved in this process; hence, numerous pathways remain to be explored in therapeutic innovations for treating this common disease.

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Introduction

Uterine fibroids (leiomyomas) are benign tumors arising from the myometrium and largely prevalent in the woman's reproductive years. This epidemiologic profile suggests that uterine fibroids are initiated and/or maintained by stimuli that last for the duration of ovarian activity. Although gonadotropins [1], adipokines [2], and ovarian peptides [3] may be postulated to have some influence on fibroid onset and growth, estradiol and progesterone are the strongest candidates to play such roles [4].

The pivotal role of ovarian steroid hormones in the pathogenesis of uterine fibroids is supported by epidemiological, clinical, and experimental evidence. The effects of estradiol and progesterone are interrelated and involve the mediation of receptors, transcription factors, kinase proteins, growth factors, and numerous autocrine and paracrine factors. Uterine stem cells are critical for the development of leiomyomas (Fig. 1). However, these pluripotent cells in the leiomyoma express very low levels of estrogen receptor (ER) and progesterone receptor (PR); therefore, to maintain the growth ratio, these cells require paracrine factors released from the mature cells expressing abundantly ER and PR [5]. Furthermore, an intricate network of post-receptor signaling can also be activated by alternative pathways that bypass the hormone–receptor complex (Fig. 2), thus allowing hormone-like effects of chemical disruptors on the one hand [6] and refined strategies for drug design on the other [7].

Clinical evidence for the role of estradiol and progesterone

Absence of fibroids before puberty and low prevalence after menopause

Uterine fibroids are typically found in the reproductive years, with peak incidence around 40 and involution after menopause. There are exceptions where the tumors continue to grow after menopause, but no case has been reported of uterine fibroid before puberty. This profile has led to the assumption that estrogen is the main feeder of uterine leiomyomas [8]. The high prevalence of the disease in the last premenopausal years, when anovulatory cycles are more frequent and progesterone levels may decrease [9], also implies a greater role of estradiol than progesterone in fibroid pathogenesis. A more accurate analysis of clinical and translational evidence, however, has revealed that progesterone action is required for the full development and proliferation of leiomyoma cells and that

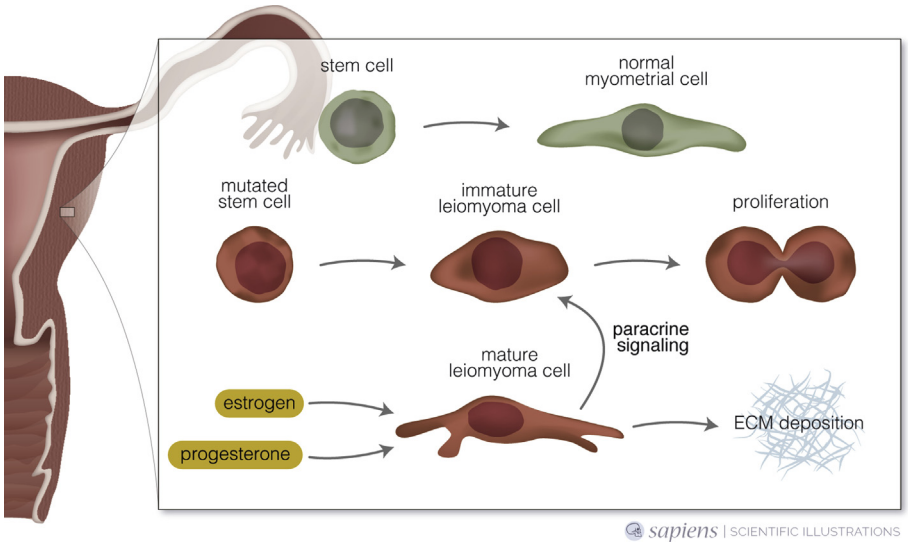

Fig. 1. Diagrammatic representation of the roles of estrogen and progesterone in the pathogenesis of uterine fibroids. ECM: extracellular matrix.