Complex networks of multiple factors in the pathogenesis of uterine leiomyoma

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Objective: To summarize the information regarding pathogenetic factors of leiomyoma formation and growth, and to make a simple integrated pathogenetic view of this tumor for further thinking to establish new therapeutic options.
Design: PubMed and Google Scholar searches were conducted to identify the relevant studies on pathogenesis of uterine leiomyoma, which are hereby reviewed and discussed.
Setting: Academic medical center.
Patient(s): Not applicable.
Intervention(s): Not applicable.
Main Outcome Measure(s): Not applicable.
Result(s): To date, the pathogenesis of uterine leiomyomas is not well understood. However, genetic alterations (especially *MED12* and *HMGA2*) and involvement of epigenetic mechanisms (DNA methylation, histone modifications, and microRNA) in leiomyoma provide the clue of initiator of this tumor. Estrogens and P are considered as promoters of leiomyoma growth, and growth factors, cytokines, and chemokines are thought to be as potential effectors of estrogens and P. Extracellular matrix components are a major structural part of leiomyoma tissue that are abnormally orientated and can modify mechanical stress on cells, which leads to activation of internal mechanical signaling and may contribute to leiomyoma growth.
Conclusion(s): Besides many genetics and epigenetic factors, the important link among the sex steroids, growth factors, cytokines, chemokines, and extracellular matrix and their involvement in cell proliferation, fibrotic processes, apoptosis, and angiogenesis are implicating a complex network in leiomyoma formation and growth. Those findings could provide information to establish future therapeutic options for the management of this tumor. (Fertil Steril® 2013;100:178–93. ©2013 by American Society for Reproductive Medicine.)
Key Words: Uterine leiomyoma, fibroid, pathogenesis, genetic, epigenetic factors

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Uterine leiomyomas (fibroids or myomas), benign tumors of the uterus, are the single most common indication for hysterectomy (1). The lifetime incidence of this tumor is approximately 70% and 80% in white and black women, respectively (2). They are clinically apparent in up to 25% of reproductive-age women and cause significant morbidity, including prolonged or heavy menstrual bleeding, pelvic pressure or pain, and reproductive dysfunction (1, 3). Surgery is definitive treatment for fibroid management, and various minimally invasive procedures have been developed. However, no long-term medical treatments are available for fibroid management. New research into the basic biology of these tumors may offer new treatment options.

Although the initiator or initiators of fibroids are not recognized, estrogens (Es) and P are considered as promoters of fibroid growth (Fig. 1). However, growth factors, cytokines,

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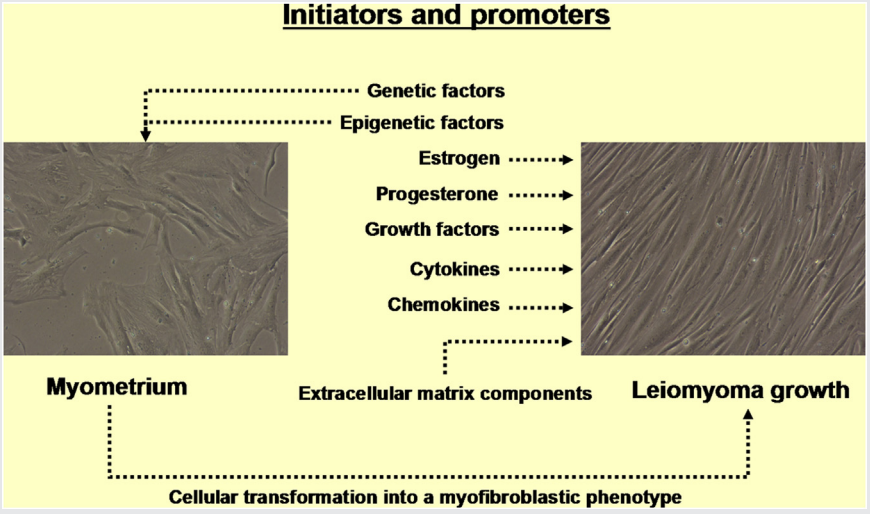
FIGURE 1



Fundamental factors involved in the pathogenesis of uterine leiomyoma (the cells in the photographs are primary cells cultured in our laboratory).

Islam. Pathogenesis of uterine leiomyoma. Fertil Steril 2013.

and chemokines are considered as potential effectors of Es and P. In addition, genetic alterations, epigenetic mechanisms, and extracellular matrix (ECM) components are thought to be important on the initiation and development of this tumor. In the present review, we aimed to give a simple integrated pathogenetic view of this tumor based on the updated informations of pathogenetic factors that have been implicated in myometrial and leiomyoma biology.

METHODS

To generate this review, multiple strategies were used to identify relevant studies regarding the pathogenesis and medical treatment of uterine leiomyoma. We conducted extensive PubMed and Google Scholar searches using the following search terms: pathogenetic factors, genetic factors, epigenetic factors, estrogens, progesterone, growth factors, cytokines, chemokines, ECM components, and medical therapies of uterine leiomyoma/fibroid. Each of these key words was paired with several related terms. After reading the titles and abstracts, the articles were then selected according to relevance of the topic. Bibliographies were cross-referenced to identify additional studies. Review articles were retrieved as a useful source of references. The final number of studies referenced in this review was 254. We downloaded all references identified into EndNote software (version 9.0).

RACIAL DISPARITIES AND UTERINE FIBROIDS

The prevalence of uterine leiomyoma is more than threefold higher in black women than in white women (4). In addition to ethnicity, some other factors, such as early menarche, age (late reproductive years), heredity, nulliparity, obesity, polycystic ovary syndrome, diabetes, hypertension, and alcohol intake, have been proposed to increase the risk of developing uterine leiomyomas (5–9).

The molecular mechanism underlying ethnic disparity is not fully understood. However, polymorphism of E-related genes has been reported to be associated with increased leiomyoma risk in different ethnic groups. It is known that a series of enzymes is involved in E synthesis and metabolism. Although *CYP1A1* and *CYP*1B1 polymorphisms are associated with increased risk of uterine leiomyoma in Chinese women (10), Barão et al. (11) found no relation between *CYP1A1* polymorphism and the risk of leiomyoma in Brazilian women. In addition, polymorphisms of *HSD*17B1 and *HSD*17B2 genes are also associated with increased risk of uterine leiomyoma in Chinese women (12).

Ishikawa et al. (13) showed that aromatase messenger RNA (mRNA) levels are strikingly higher in leiomyoma than adjacent myometrium in African American (83-fold), Caucasian American (38-fold), and Japanese women (33-fold). However, a later study did not confirm this finding (14).

Studies have shown a differential ethnic distribution of specific functional genetic variants in E receptor-α (ER-α) and catechol-O-methyltransferase (*COMT*) and their association with uterine fibroid susceptibility (15–18). The ER-α PP variant has a higher prevalence among black women and has been associated with an increased risk of fibroids (15). The wild-type *COMT* val/val variant has significant enzymatic activity, which is more prevalent in African American compared with white or Hispanic women (16). On the other hand, the *COMT* val/met polymorphism has intermediate activity and has no associations between fibroids and Val158-Met polymorphism of *COMT* among African American or white women (19). The above findings might be an explanatory factor for the higher risk of uterine leiomyomata in black women and others as well. Therefore, E synthesis and metabolic inhibitors might be a potential medical intervention for leiomyomata.