Best Practice & Research Clinical Obstetrics and Gynaecology 34 (2016) 25–36

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Growth factors and pathogenesis

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Keywords:
uterine leiomyoma
uterine fibroid
growth factors
activin-A
TGF-β
VEGF

Growth factors are relatively small and stable, secreted or membrane-bound polypeptide ligands, which play an important role in proliferation, differentiation, angiogenesis, survival, inflammation, and tissue repair, or fibrosis. They exert multiple effects through the activation of signal transduction pathways by binding to their receptors on the surface of target cells. A number of studies have demonstrated the central role of growth factors and their signaling pathways in the pathogenesis of uterine leiomyomas. Numerous differentially expressed growth factors have been identified in leiomyoma and myometrial cells. These growth factors can activate multiple signaling pathways (Smad 2/3, ERK 1/2, PI3K, and β-catenin) and regulate major cellular processes, including inflammation, proliferation, angiogenesis, and fibrosis which are linked to uterine leiomyoma development and growth. In this chapter, we discuss the role of growth factors and their signaling pathways in the pathogenesis of uterine leiomyomas.

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http://dx.doi.org/10.1016/j.bpobgyn.2015.08.018
1521-6934/

Uterine fibroids and growth factors

Uterine leiomyomas are benign (noncancerous) tumors originating from the smooth muscle of the uterus (myometrium) and are the most common indication for hysterectomy in the world [1]. They affect about 77% of women of reproductive age, but approximately only 25% bear clinically apparent tumors [2,3]. Heavy or abnormal uterine bleeding, pelvic pain or pressure, infertility, and recurrent pregnancy loss are associated with leiomyoma. Despite the high prevalence, significant health problems, and huge economical impact on the health-care system, relatively little is understood about the pathogenesis of uterine leiomyoma. Consequently, medical treatments are still limited. Growth of leiomyoma is believed to be dependent on ovarian hormone activity through intermediate elements such as growth factors [4,5].

Growth factors are polypeptides or proteins that are secreted by a number of cell types. They are important for regulating a variety of cellular processes, such as proliferation, differentiation, angiogenesis, survival, inflammation, and tissue repair, or fibrosis. Growth factors exert their effects on leiomyoma growth through activating multiple signal transduction pathways, including Smad 2/3, ERK 1/2, PI3K, and β-catenin by binding to their receptors [6–9] (Fig. 1). A number of studies reported that multiple growth factors, including activin-A [10], acidic fibroblast growth factor (aFGF) [11], basic fibroblast growth factor (bFGF) [12], epidermal growth factor (EGF) [13], heparin-binding EGF (HB-EGF) [12], insulin-like growth factor (IGF) [14], myostatin [10], platelet-derived growth factor (PDGF) [15], transforming growth factor-β (TGF-β) [16,17], transforming growth factor- α (TGF-α) [13], and vascular endothelial growth factor (VEGF) [18,19], are differentially expressed in myometrium and leiomyoma.

Activin-A

Activin-A is a pleiotropic growth factor belonging to the TGF-β superfamily. It was originally isolated based on its activity in regulating follicle-stimulating hormone released from the anterior pituitary [20]. Later, its functions has been extended in cell proliferation, differentiation, apoptosis, immune response, wound repair, and fibrosis [21,22] Activin-A exerts multiple effects through the activation of Smad 2/3-dependent signaling pathway by binding to type II (ActRIIA or ActRIIB) and type I receptors (ActRIB, also known as activin receptor-like kinase 4 or ALK4). Activin A/Smad 2/3 signaling can be regulated by binding protein follistatin [23], follistatin-related gene (FLRG) [24], and Cripto [25] at extracellular and plasma membrane levels. In addition, Smad7 is known as an inhibitory downstream modulator of activin/TGF-β-like signaling, and its expression is induced by activin-A [26].

The role of activin-A in leiomyoma and myometrial cell functions has been studied [6,10,27]. The mRNA expression levels of activin-A [10,28] and FLRG [10] were found to be highly expressed in leiomyoma compared to myometrial tissues, whereas the receptors (ALK4, ActRIIA, and ActRIIB), follistatin, and Smad7 mRNAs remained unchanged [10]. Activin-A has been reported to downregulate primary myometrial cell proliferation [6] but not leiomyoma cells [6]. Interestingly, activin-A was reported to increase mRNA expressions of extracellular matrix (ECM) components (collagen1A1, fibronectin, and versican) in primary leiomyoma cells compared to untreated cells [6]. Furthermore, activin-A significantly increases phosphorylation of Smad signaling components, Smad2 and Smad3, in both leiomyoma and myometrial cells compared to untreated cells [6], suggesting that the fibrotic role of activin-A is mediated, at least in part, by the activation of Smad 2/3 signaling pathway.

Acidic fibroblast growth factor

aFGF (also known as FGF-1) is a member of the FGF family of growth factors and plays an important role in proliferation and angiogenesis. Immunohistochemical localization of aFGF was detected in human uterine leiomyomas with expression primarily localized to the smooth muscle cells [29]. Wolanska and Bankowski reported that leiomyomas contained several times more aFGFs compared to myometrium [11].