Neurotrimin: a novel neural cell adhesion molecule correlating with uterine fibroid phenotype

Uterine fibroids (UFs), also known as leiomyomas, are benign pelvic tumors that occur in nearly 70% of all reproductive-aged women (1, 2). Some of these women will develop severe symptoms associated with the presence of these tumors. Annually, UFs account for over 200,000 hysterectomies in the U.S. This is due to the lack of long-term effective medical therapies (3). Tumor growth is characterized by slow proliferation with increased deposition of extracellular matrix (proteoglycans and collagens), which participates in the fibrotic phenotype of UFs (3). This process is usually in a steroid-hormone dependent manner (2). Besides steroid hormones, growth and maintenance of UFs are strongly related to growth factors, stem cells, and genetic and epigenetic abnormalities and other risk factors (1, 2).

The myometrial smooth muscles are supplied by nerves (sympathetic, parasympathetic, sensory), which run in neurovascular bundles between myometrial cells (2). Distortion of the nerves by masses of UFs leads to pelvic pain and dysmenorrhea symptoms (2). Axonal degeneration could be pathological or physiological. The latter occurs in adults as a part of autonomic (sympathetic, parasympathetic) axon remodeling in the reproductive tract. Previous innervation remodeling animal studies in female reproductive tract provided insight into mechanisms underlying neuroplasticity associated with hormonal changes driven by changes in reproductive status. Sympathetic nerves are found to be the most susceptible uterine nerves to the cyclical variations in ovarian sex hormones; estrogen-induced uterine sympathetic axon degeneration (axon pruning), which regenerate rapidly during the low estrogen stages. The process is similar to what occurs during pregnancy, where uterine sympathetic innervation undergoes widespread degeneration, followed by reinnervation after delivery. Explanation of these findings is that estrogen acts directly on the myometrium to render it inhospitable to sympathetic axons, thus preventing the normally robust direct innervation to the myometrium to render it inhospitable to sympathetic innervation of UFs (2, 4). However, the link between NTM and UF phenotype has not yet been explored.

Surgical intervention with hysterectomy is the main cure for UFs that results in tremendous health expenses; In the U.S., the yearly cost of UFs related management expenses is up to US$34.4 billion (1). Despite the recent shift of focus in the etiology of UFs from hormones to genetic aberrations and UF stem cells, to date, treatment with hormonal medications remains the mainstay therapy for UFs (2). Currently, several medications are available for UFs but have varying degrees of success to help reduce the bulk symptoms of UFs (3). Success in the medical management of steroid-dependent disease processes such as symptomatic UFs is often due to the use of hormone modulators (2). Ulipristal acetate (UPA) is a recent hormonal medication that could be considered as the first long-term treatment for UFs. UPA is a selective progesterone (P) receptor modulator. UPA can have both antagonist and partial agonist activity, depending on the levels of serum P (3). The promising action of UPA on suppression of UF phenotype was demonstrated by experimental as well as clinical studies. Several mechanisms underlying the potential decrease in size of UFs have been determined with the use of UPA. UPA affects the water content of the UFs, concomitantly with alterations in apoptosis and proliferation of UF cells. In addition, UPA has been shown to affect several markers related to fibrosis, inflammation, and angiogenesis of UFs (3, 5). UPA treatment exhibits an inhibitory effect on UFs phenotype, concomitantly with an improvement of quality-of-life (3). Although the success of clinical findings of UPA that conducted in both Europe and the United States, detailed mechanism underlying the UPA treatment and related clinical information is largely unknown.

In this issue of Fertility and Sterility, Parikh et al. (2) have demonstrated a novel finding that NTM, a neural cell adhesion molecule, is linking to UF phenotype. First, they showed differential expression of NTM in human UFs and myometrial tissue specimens by applying different methods. RNA-sequencing analysis revealed increased expression of NTM transcripts in placebo patient UFs tissue relative to placebo patient myometrium, which confirmed by qRT-PCR. Additionally, the authors supplemented this confirmation by measuring NTM protein, which revealed a statistically significant increase in NTM protein levels in UFs as compared to matched myometrium of the placebo group patients. Furthermore, immunohistochemistry analysis demonstrated a qualitatively increase in cytoplasmatic NTM staining in UFs as compared to myometrium in the placebo patients (2). These studies suggest that abnormal increase in NTM expression correlates to UF phenotype.

Since steroid hormone contributes to the UF phenotype, Parikh et al. (2) determined the impact of steroid hormone (17 β-estradiol, medroxyprogesterone acetate) and hormone antagonists (fulvestrant and UPA) on NTM expression in both tissues and cell lines. Parikh et al.’s (2) in vitro studies demonstrated that treatment of UF cell lines with 17 β-estradiol resulted in an increase in NTM protein expression; however, treatment with fulvestrant (an Anti-estrogen
and treatment response (2). To date, despite the use of several medications for UFs, serum biomarkers for assessing the response to medications are not available in clinical practices. In this regard, NTM might potentially provide a novel biomarker that may have an accurate prediction of treatment responses that would help to guide medical therapies in UFs, especially, with the recent data showing that UPA may provide a promising option for long-term relief from UFs.

Lastly, UFs are monoclonal tumors arising from the myometrium, often as multiple distinct tumors. Increasing evidence supports the hypothesis that these benign tumors originate from a stem cell population resident in the uterus. Notably, myometrial stem cells and UF stem cells have now been identified (1). In this regard, it will be interesting to compare the expression patterns of NTM and other neural cell adhesion molecules between and UF stem cells and myometrial stem cells and investigate how they respond to treatments of anti-UF drugs.

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