Evolving role of microRNAs in uterine fibroid pathogenesis: filling the gap!

Uterine fibroids (leiomyoma) are benign monoclonal neoplasms of the myometrium and represent the most common tumors in women worldwide. Tumors occur in ~77% of women overall and are clinically manifest in ~25% by age 45 years. Although benign, these tumors are nonetheless associated with significant morbidity; they are the primary indication for hysterectomy, and a major source of gynecologic and reproductive dysfunction, ranging from profuse menstrual bleeding and pelvic pain to infertility, recurrent miscarriage, and preterm labor. Accordingly, the annual U.S. healthcare costs associated with uterine fibroids have been estimated at ~$34 billion. Uterine fibroids thus represent a significant public health and financial burden. Mechanisms underlying uterine fibroid pathogenesis are largely unknown. However, the prevailing model invokes the genetic transformation of a single myometrial stem cell into a tumor-initiating cell that seeds and sustains clonal tumor growth, characterized by cell proliferation and abundant extracellular matrix (ECM) production, under the influence of endocrine, autocrine, and paracrine growth factor and hormone receptor signaling (1).

MicroRNAs (miRNAs) are small, noncoding, single-strand RNAs ~22 base pairs in length that control a wide range of biological processes, including tumorogenesis. miRNAs expression has been discovered to be profoundly dysregulated in cancer cells and could be applied for tumor diagnosis, classification, and prognosis. Studies have revealed that several mechanisms include amplification or deletion of miRNA genes, epigenetic changes, transcriptional control changes, and errors in the miRNA biogenesis machinery lead to this dysregulation. Under certain conditions, and depending on target genes, miRNA could function as either tumor suppressor or oncogene (2).

Several genomic studies have shown that miRNAs play a crucial role in cellular circumstances and epigenetic control of gene expression resulting in uterine fibroid development. Chuang and Khorram (2) have shown that expression of three important miRNAs (miR-29 family, miR-93, and miR-200c) are decreased in uterine fibroid as compared with matched myometrium, with an associated increase in their targets expression and thus uterine fibroid phenotype. The miR-29 family consists of miR-29a, miR-29b, and miR-29c and regulates essential ECM genes, including collagen subtypes and elastin. Thus, overexpression of miRNA-29a diminished the production of ECM composites, while knockdown of mir-29c enhanced ECM production. Furthermore, another study illustrated that the recovery of miR-29b could repress the enormous ECM accumulation and uterine fibroid growth. Recently, cyclin-dependent kinase 2 (CDK2), which is a cell cycle regulatory protein and required for the shift from the G1 phase to the S phase of the cell cycle, was revealed to be a target of *miR-29c*. The same group concluded that tissue factor 3 (F3), interleukin-8, plasminogen activator inhibitor−1 (PAI-1), and connective tissue growth factor (CTGF), which are connected to inflammation and tissue turnover, are regulated directly and/or indirectly by miR-93/106b function and may be of importance in uterine fibroid growth and symptoms. Moreover, it has been shown that E2F transcription factor 1 (E2F1) and cyclin D1 (CCND1) are the direct targets of miR-93 in primary uterine fibroid cells (2). Finally, data suggest that the miR-200 family may act as tumor suppressors by inhibiting epithelial to mesenchymal transformation (EMT) (3). This family also regulates the activation of nuclear factor−κB as a key regulator of many pro-inflammatory mediators, including interleukin-8, by phosphorylating its inhibitor (3). One study showed that reactive oxygen species could induce these miRNAs and launch uterine fibroids into the senescence pathway. Moreover, they may also control several functional genes in the Akt pathway. Similarly to miR-29c, miR-200c may also target CDK2, which is a key regulator of G1/S transition (2). miR-150 was found to influence the repression of uterine fibroid growth. The authors revealed that following cell transfection, the expression level of Akt was reduced, whereas p27 was significantly increased. Therefore, these findings suggest that miR-150 may influence cell cycle control in uterine fibroids by interaction with the Akt-signaling pathway.

Other miRNAs have shown a role in uterine fibroid pathogenesis, such as miR-21, which promotes transforming growth factor−β (TGF-β) signaling by inhibiting Smad7, resulting in excessive ECM formation. Moreover, it also targets TGF-β receptor type II in uterine fibroids and may interfere with its biological activities. Cardozo et al. found that increased expression of miR-21 in an immortalized uterine fibroid via vector infection leads to enhanced TGF-β3 protein expression in uterine fibroids and myometrial cells. These data indicated numerous changes in several genes, including collagen and fibronectin, matrix metalloproteinase−2 and −9, and others. Eventually, upregulation of miR-21 resulted in increased proliferation and growth of uterine fibroid cells (4).

Current treatment options for uterine fibroids are primarily surgical or radiological. However, the deleterious impact of these procedures on reproductive function is clear and renders these options unsuitable for women who wish to retain future fertility. Likewise, hormonal therapies designed to blunt the growth-stimulatory effects of estrogen or progesterone on uterine fibroid growth are contraindicated in women actively pursuing a pregnancy and are otherwise approved only for short-term use because of long-term safety concerns. Accordingly, there is a critical current need to develop effective, safe, long-term, and fertility-compatible nonsurgical treatment options for uterine fibroid management.

In this issue, Chuang et al. (5) continued their work on the effect of Tranilast, a synthetic molecule with antiallergic/anti-inflammatory effects, on uterine fibroid cells. Previously, they have shown its growth inhibitory effect via down-regulation of cell cycle regulating genes CCND1 and CDk2 as

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well as reduction of ECM-related markers such as collagen and TGF-β3. These effects were mediated via downregulation of miR-29c promoter methylation status and subsequent induction of its expression/secretion. Following their previous findings of the miR-200c role in regulation of pro-inflammatory cytokine interleukin-8 in uterine fibroid cells via inhibitor of nuclear factor kappa B kinase subunit beta (IKBKB), in the current issue they explored the effect of the same drug on such pathway. Interestingly, Tranilast induced miR-200c expression in a dose-dependent manner. Moreover, it reduced p65 nuclear translocation as well as its binding to miR-200c promoter, resulting in miR-200c expression induction. This Tranilast-induced miR-200c regulatory function affected the expression of several genes that are involved in uterine fibroid phenotype including EMT, ECM, cell cycle and inflammation (5). Recently, inflammation has been presumed to have a key role in uterine fibroid pathogenesis as well as uterine fibroid–associated bleeding. Tranilast have been shown to inhibit cytokine-induced nuclear factor–κB activity and transcriptional ability on inflammatory-associated gene expression. It functions as tryptase inhibitor, which is stored in mast cells and promote angiogenesis. In vivo studies in an animal model to explore the effect of tranilast on uterine fibroid should be considered.

Micro-RNA research studies in uterine fibroid are expanding and might fill the current gap in understating its exact underlying molecular pathogenesis as well as explain the racial risk disparity in uterine fibroid incidence. African American women have a threefold higher incidence rate and relative risk of uterine fibroids than women of white ethnicity, and the basis for this risk disparity is not fully understood; previous studies have shown that the miR-200c expression level was lower in uterine fibroids from African American women as compared with white women. In addition, a recent study has shown positive associations of urine phthalates metabolite and several miRNAs in women with uterine fibroids undergoing surgery; mRNA gene targets of phthalate-associated miRNAs were significantly associated with multiple fibroid-related processes including angiogenesis, apoptosis, and proliferation of connective tissues. Exposure to endocrine disruptors such as diethylstilbestrol and phthalates have been linked to increased uterine fibroid risk. Finally, future studies might reveal miRNA to be used as a tool to noninvasively differentiate benign tumor such as uterine fibroids from more aggressive cancerous ones such as leiomyosarcoma.

In conclusion, uterine fibroids remain a significant health issue for many women. More miRNA studies are needed to understand complex mechanisms controlling uterine fibroid growth, as well as to explore new targets for possible therapeutics.

Mohamed Ali, B. Pharm., M.Sc.[a,b]
Sahar Esfandyari, D.V.M.[a]
Ayman Al-Hendy, M.D., Ph.D.[a]
[a] Department of Surgery, University of Illinois at Chicago, Chicago, Illinois; and [b] Clinical Pharmacy Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

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