Non-coding RNAs: an important regulatory mechanism in pathogenesis of uterine fibroids

Uterine fibroids (UFs; also known as leiomyomas) are the most common benign neoplastic threat to women's health in U.S. and worldwide, with annual health care costs estimated in the hundreds of billions of dollars. UF-caused morbidities negatively impacts women of all ethnicities, but disproportionately affect African-American women, who have a 3- to 4-fold higher incidence rate and relative risk of UFs than Caucasian women. These tumors can grow and cause severe adverse health outcomes such as excessive vaginal bleeding, pelvic pain, as well as urinary and bowel compression with a major negative effects on women's quality of life (1). Although the cause of UFs is largely unknown, several risk factors are linked to the pathogenesis of UFs, which include race and ethnicity, age, family history, vitamin D deficiency, early life environmental exposure to toxins, body mass index, etc.

An increasing body of literature demonstrates that UFs are monoclonal tumors that arise from the uterine smooth muscle tissue. Accordingly, myometrial stem cells and tumor-initiating cells (TICs) from myometrial tissues and UFs, respectively, are successfully identified. TICs represent a subgroup of cells within a tumor cell population that retain the ability to reconstitute tumors. Moreover, TICs derived from UFs, but not myometrium, carry transcriptional mediator subunit MED12 mutations, which have been accounted in ~70% of UFs, suggesting that at least one genetic hit may convert a myometrial stem cell into TIC.

Epigenetics refers to changes in phenotype with altered gene expression and these changes do not occur because of the alteration in DNA sequencing. The mechanisms underlying epigenetic regulation include DNA methylation, histone modification, and non-coding RNAs (ncRNAs) (2). The latter one is a functional RNA molecule that is transcribed from DNA, but not translated into proteins. The ncRNAs contain two main groups: short ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). The three major classes of sncRNAs related to epigenetic process are microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). In addition, the small nucleolar RNAs (snoRNAs) perform sequence-specific 2′-O-methylation and pseudouridylation of ribosomal RNA which takes place in the nucleolus after forming the small nucleolar ribonucleoprotein complex.

Although mutations have been found in several genes in UFs, high throughput RNA sequencing in combination with epigenetic approach such as global DNA methylation analysis indicate that epigenetic processes play an important role in altered gene expression in UFs. In addition, experimental animal studies have also shown that early life exposure to endocrine disrupting chemicals reprograms the myometrium epigenome towards a pro-fibroid epigenome landscape, leading to increased risk for UFs development later in life (3).

Although the epigenetics including ncRNAs play a critical role in pathogenesis of many diseases, little is known about the role of ncRNAs in UFs. In this issue of *Fertility and Sterility*, Chuang et al. (4) provide extensive evidence that snoRNAs are involved in the pathogenesis of UFs based on their previous findings (5). In their previous studies, they determined the expression profiling of lncRNAs, miRNAs, and messenger RNAs (mRNA) and their expression in UFs using next generation RNA sequencing approach. Their study showed that 5,941 lncRNA (2,813 upregulated, 3,128 downregulated), 148 miRNA (56 upregulated, 92 downregulated), 3,855 mRNA (2,030 upregulated, 1,825 downregulated) exhibited differential expression between UFs and myometrium tissues.

In this issue, they extend their previous study using the existing sequencing data set and demonstrate that the differential expression of other sncRNAs occurs in UFs as compared with matched myometrium tissues. Among the 594 sncRNAs analyzed, they identify 15 small nucleolar RNAs and 24 piRNAs, which are shown differentially expressed between UFs and matched myometrium tissues. In addition, they also find that 7 transfer RNAs and 6 ribosomal RNAs exhibit differential expression between myometrium and UFs. Some of the snoRNSa, piRNAs, etc., are further confirmed for their differentially expression in 20 pair tissues from both phases of the menstrual cycle. Moreover, the pattern of these sncRNAs is similar to RNA sequencing analysis. Although further functional analysis of these identified sncRNAs in pathogenesis of UFs needs to be investigated, the altered expression of these sncRNAs are first reported in UFs.

Argonaute proteins are the active part of RNA-induced silencing complex for mRNA regulation and sncRNAs mediated gene silencing. In this context, an additional study by Chuang et al. (4) in this issue is done to compare the expression level of Argonaute 2 between UFs and paired myometrium tissues by Western blot analysis. Their data show that UFs exhibit higher levels of Argonaute 2 expression as compared to paired myometrium tissues further suggesting the potential role of sncRNAs in pathogenesis of UFs. This work (4) combined with their previous study (5) provide more comprehensive information about sncRNA expression profiling which is involved in the UFs development.

Although these sncRNAs are first identified in UFs, as described in the Chang et al. (4) article, the data was generated in a relative small population (N=20): 15 from white-Hispanics and 5 from African-Americans. Thus, further studies are required to expand this work in a larger and diversified population to characterize the epigenetic mechanism by which African-American women exhibit higher incidence rate and increased risk of UFs. Moreover, UFs come from monoclonal stem cells. Comparative analysis of ncRNA expression profile in stem cells from both myometrium and MED12-mutant UFs is needed to determine the ncRNA network, and therefore, characterize the regulatory mechanism underlying the functional role of ncRNA in pathogenesis of UFs. Understanding the abnormal signaling, genetic instability including MED12 mutation and corresponding epigenetic regulating and complex network of genetic and epigenetic interaction in UFs will provide new opportunities

to develop an efficient therapeutic approach, capable of effectively reducing the severity of UFs while avoiding side effects.

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