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

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Uterine fibroids (UFs; AKA: leiomyomas) are the most common benign neoplastic threat to women's health in the United States and worldwide, with annual health care costs estimated in the hundreds of billions of dollars. UF caused-morbidities negatively impact women of all ethnicities, but disproportionately affect African American (AA) women, who have a 3–4 fold higher incidence rate and relative risk of UFs than Caucasian (CC) 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 effect 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 (BMI), etc.

An increasing body of literature demonstrates that UFs are monoclonal tumors that arise from the uterine smooth muscle tissue. Accordingly, myometrial stem cells (MSCs) 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, which retain the ability to reconstitute tumors. Moreover, TICs derived from UFs, but not myometrium, carry transcriptional Mediator subunit MED12 mutations, which have been accounted for ~70% of UFs, suggesting that at least one genetic hit may convert a MSC into TIC.

Epigenetics refers to changes in phenotype with altered gene expression and these changes do not occur as a result 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: the short ncRNAs and long ncRNAs. The three major classes of short ncRNAs related to the 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 rRNA which takes place in the nucleolus after forming the small nucleolar ribonucleoprotein complex.

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Although mutations have been found in several genes in UFs, high throughput RNA sequencing in combination with an 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 epigenetics including ncRNAs play a critical role in the pathogenesis of many diseases, little is known about the role of ncRNAs in UFs. In this issue of Fertility and Sterility (4), Chuang et al provide extensive evidence that sncRNAs 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 mRNA and their expression in UFs using next generation RNA sequencing approach. Their study showed that 5941 lncRNA (2813 up, 3128 downregulated), 148 miRNA (56 up, 92 downregulated), 3855 mRNA (2030 up, 1825 downregulated) exhibited differential expression between UFs and myometrium tissues.

In this current 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 594 sncRNAs analyzed, they identify 15 snoRNAs, 24 piRNAs, which are shown differentially expressed between UFs and matched myometrium tissues. In addition, they also find that 7 tRNAs and 6 rRNAs exhibit differential expression between myometrium and UFs. Some of the snoRNAs, piRNAs etc are further confirmed for their differential 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 the pathogenesis of UFs needs to be investigated, the altered expression of these sncRNAs is first reported in UFs.

Argonaute proteins are the active part of the RNA-induced silencing complex for mRNA regulation and sncRNAs mediated gene silencing. In this context, an additional study by Chuang et al 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 the pathogenesis of UFs. The work in this issue (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 paper, the data was generated in a relatively small population (N=20): 15 from white Hispanic, and 5 from AA, and thus further studies are required to expand these work in a larger and diversified population to characterize the epigenetic mechanism by which AA 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 cell 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 the 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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