Growth disparities in uterine leiomyomas associated with *MED12* mutation

Uterine leiomyoma is the most common benign estrogen (E)-dependent tumor in women of reproductive age. Approximately 25% of women are affected and the cumulative incidence is 70% of women by the age of 50 years. In addition, this tumor is more prevalent at younger ages, and is more common in African-American women (73%) compared to White women (45%). Uterine leiomyoma comprises smooth muscle cells derived from the myometrium and an extracellular matrix rich in collagen, fibronectin, and proteoglycans. These features contribute to tumor expansion and result in a well-defined fascicular capsule within the myometrium. Most women with uterine leiomyomas are asymptomatic; however, 15%–30% present with symptoms such as metrorrhagia, pelvic pain or pressure, urinary incontinence, infertility, miscarriage, and preterm birth.

Despite the distressing symptoms and the prevalence of uterine leiomyoma, little is known about the etiology of this tumor. This lack of understanding contributes to the scarcity of effective medical treatments. Several studies have identified an important role of sex steroid hormones in the pathogenesis of uterine leiomyoma, leading to the use of hormonal treatment as a therapy. However, hormonal treatments are used only for short term due to the presence of side effects. In addition, once treatment is stopped, leiomyomas enlarge again, generally recovering their initial size within 6 months. An efficient, nonsurgical treatment to reduce these tumors with lasting impact and minimal side effects remains elusive. Developing new treatments necessitates a detailed study of the molecular mechanisms implicated in growth and development of uterine leiomyoma to define its etiology.

Recent research has revealed recurrent and mutually exclusive mutations in leiomyoma, such as High Mobility Group AT-hook 1 and 2 (*HMGA1, HMGA2*) rearrangements, mediator complex subunit 12 (*MED12*) mutations, biallelic inactivation of fumarate hydratase, and collagen type IV alpha 5 and collagen type IV alpha 6 (*COL4A5-COL4A6*) deletions (1). This genetic heterogeneity suggests the involvement of molecularly distinct pathways underlying uterine leiomyoma development, thereby highlighting the need for molecular stratification in research into these tumors, and possibly in clinical practice. Among these mutations, *HMGA1-HMGA2* rearrangements and *MED12* mutations are considered the major cytogenetic abnormalities specific for uterine leiomyoma due to their high prevalence in patients with these pathology. A total of 20% of leiomyomas present with *HMGA* rearrangement and 70% *MED12* mutation. Accordingly, most ongoing studies seek to clarify the molecular role of these mutations in the pathogenesis of uterine leiomyoma.

Patients with *MED12* mutations reportedly tend to develop multiple and smaller-sized tumors. In line with this, a recent study (2) demonstrated that leiomyomas without *MED12* mutation were comparatively larger in size than those with *MED12* mutation. This finding could explain why some uterine leiomyomas present an accelerated growth rate that often provokes patients to undergo medical intervention, whereas others might grow slowly or remain unchanged indefinitely. Thus, *MED12* mutation may explain some of the growth disparities observed in uterine leiomyoma.

At the molecular level, one study (2) reported that erythropoietin (EPO) is sometimes detected at higher levels in uterine leiomyoma compared with the surrounding myometrium, and EPO messenger RNA levels appear to correlate with tumor progression and size. Considering that EPO is an important hormone involved not only in hematopoietic activity, but also in cell differentiation, control of apoptosis, angiogenesis, and/or vasculogenesis, EPO expression may affect the growth patterns of leiomyoma. Interestingly, this study (2) demonstrated that among leiomyomas with higher levels of EPO messenger RNA expression, those without *MED12* mutation had higher EPO expression than those with *MED12* mutation under estrogenic influence, independent of hypoxia. These findings suggest that leiomyomas lacking *MED12* mutation are more susceptible to more tumor growth, possibly due to increased EPO expression levels in response to E. Conversely, the attenuated EPO expression in response to E in *MED12*-mutated leiomyomas may be the reason why these tumors tend to be generally smaller than leiomyomas without *MED12* mutation. Therefore, studying the molecular mechanism through which *MED12* mutation regulates EPO expression levels could provide us with a better understanding of uterine leiomyoma pathology and lead to a personalized therapy according to *MED12* mutation status.

MED12 is one of the RNA polymerase II transcriptional mediator complex subunits that links cyclin C-CDK8 and stimulates cyclin C-dependent CDK8 kinase activity. Mutations in *MED12* result in the disruption of mediator kinase activity and consequently alter CDK8 function. In the context of uterine leiomyoma, *MED12*-linked mutations disrupt its direct interaction with components of the CDK8 and results in suppression of E-induced transcription and diminished cell growth (3). Considering that EPO production is regulated by E, the suppression of E-induced transcription, as observed in the study by Asano et al. (2) in response to E. These findings provide clarity for why the lack of *MED12* mutation is correlated with accelerated growth in certain leiomyomas, in that elevated transcription of EPO is induced by E. Thus, new treatments inhibiting EPO expression might be considered as a therapy to prevent the growth in uterine leiomyomas lacking *MED12* mutation.

However, *MED12* mutation is highly prevalent in uterine leiomyoma and is implicated in their tumorigenesis. Therefore, defining the mechanism by which *MED12* mutation promotes uterine leiomyoma development would clarify the pathogenesis of leiomyomas with the most common mutation. Studies (4) have reported that *MED12* plays an important role in the regulation of leiomyoma cell proliferation

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through the Wnt/β-catenin signaling pathway, cell cycle, and fibrosis-associated protein expression. *MED12* is associated with the induction of WNT4 (Wnt family member 4) and activation of β-catenin signaling, promoting the expression of downstream proteins involved in cell proliferation (CCD1, CDK1, and CDK2), as well as extracellular matrix proteins (collagen type I, fibronectin, and plasminogen activator inhibitor type I [PAI-1]). These findings suggest that new treatments based on the inhibition of Wnt/β-catenin signaling pathway could be considered as a therapy to prevent the growth in uterine leiomyomas with *MED12* mutation.

Recently, vitamin D has been widely studied for its antitumorigenic and antiproliferative roles in certain cancers, including uterine leiomyoma. In this regard, a recent in-depth study (5) of the molecular mechanisms through which vitamin D acts in human uterine leiomyomas. That study (5) demonstrated that vitamin D exerts an antiproliferative action through cell growth arrest and the inhibition of Wnt/β-catenin pathway. This suggests that vitamin D treatment is a possible therapy to treat those leiomyomas with the Wnt/β-catenin pathway deregulated.

In light of these findings, although low EPO levels could explain the smaller size observed in leiomyomas with *MED12* mutations, the Wnt/β-catenin signaling pathway activation could explain the tendency of *MED12*-mutated cells to lead to the development of multiple uterine leiomyomas. However, the larger size observed in leiomyoma lacking the *MED12* mutation could be explained by the E-induced expression of EPO. Therefore, a personalized therapy applied according to *MED12* mutation status could be a viable approach to treat uterine leiomyomas.

Hortensia Ferrero, Ph.D.
Fundación IVI/INCLIVA, Valencia, Spain

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