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Editorial

Moving towards Developing Stable Medical Treatments for Uterine Leiomyomas that can be Used for Long on the Bases of Molecular Mechanisms Like MED 12 Mutation Status

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Uterine leiomyoma is the most common benign estrogen (E) dependent tumor in women of reproductive age. Roughly 25% of women are affected and the cumulative incidence is 70% of women by the age of 50 years. Additionally, it is more common at younger age and is more prevalent in African-American women (73%) compared to White women (45%). Uterine leiomyoma is made up of smooth muscle cells and an extracellular matrix rich in collagen, fibronectin and proteoglycans. Because of these properties tumor expansion occurs and result in a well-defined fascicular capsule within the myometrium. Most women with Uterine leiomyomas are asymptomatic, however 15 - 30% present with symptoms like metrorrhagia, pelvic pain or pressure, urinary incontinence, infertility, miscarriage, and preterm birth.

Inspite of distressing symptoms and its prevalence little is known about the etiology of Uterine leiomyoma. Because of which there is scarcity of effective medical treatments, which use hormonal treatment as a therapy. Currently commonly used therapies include Selective Progesterone Receptor Modulators (SPRM's) like mifepristone, ulipristal acetate and right now vilaprisan is undergoing randomized phase 2 asteroid 1 study [1,2]. Though that is used for a short term in view of the presence of side effects like progesterone receptor modulator associated endometrial changes. Moreover, once treatment is stopped, Uterine leiomyomas enlarge again, generally recovering their initial size within 6 months. Developing new therapies makes it necessary to study the detailed molecular mechanisms implicated in growth and development of Uterine leiomyoma for defining its etiology. Earlier we had reviewed how in animal studies interaction of REI silencing transcriptor factor (REST) and mediator subunit 12 (MED 12) interacts in etiopathogenesis of uterine leiomyomas (Figure 1) [1,3-5]. Recent research has revealed recurrent and mutually exclusive mutations in leiomyomas like 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 [6]. This genetic heterogeneity suggests the involvement molecularly distinct pathways underlying Uterine leiomyoma development and thus highlighting the requirement of molecular stratification in research into these tumours and possibly in clinical practice. Among these mutations HMGA1, HMGA2) rearrangements and MED12 mutations are considered the major cytogenetic abnormalities specific for Uterine leiomyomas because of their high prevalence in patients with this pathology. A total of 20% of leiomyomas present with HMGA rearrangements and 70% with MED12 mutations. Thus, most studies try to clarify the molecular role of these mutations in the pathogenesis of uterine leiomyomas.

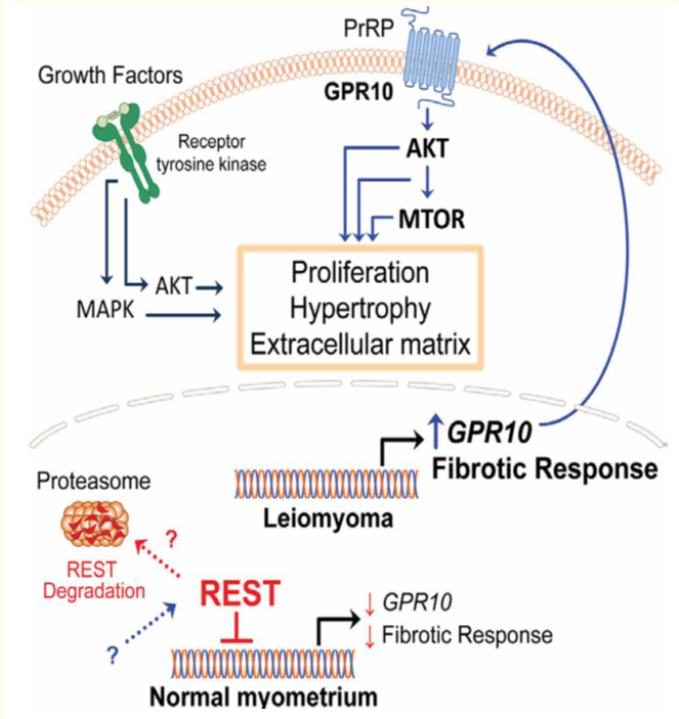

Figure 1: *Courtesy ref no 4 - Loss of REI silencing transcription factor (REST) in patient leiomyoma cells resulted in the expression of the G protein coupled receptor 10 (GPR10) and Akt/MTOR/signaling pathway. Transgenic overexpression of GPR10 in mouse myometrial smooth muscle cells resulted in a phenotype characteristic of human.*

Patients having MED12 mutations tend to develop multiple and smaller sized tumors. A recent study showed that leiomyomas without MED12 mutations were comparatively larger in size than those having MED12 mutations [7]. Possibly this finding can explain why some uterine leiomyomas present with an accelerated growth rate which often provokes patients to undergo medical intervention, while others might grow slowly or remain unchanged indefinitely.

At the molecular level Asano., *et al.* [7] demonstrated that erythropoietin (EPO) is sometimes detected at greater levels in uterine leiomyomas compared with the surrounding myometrium and EPO mRNA levels appear to correlate with tumor progression and size. EPO is an important hormone involved in haematopoietic activity. But also in cell differentiation, control of angiogenesis, and/or vasculogenesis, EPO expression might affect the growth patterns of uterine leiomyomas. In this study, among uterine leiomyomas with higher levels of EPO mRNA expression those without MED12 mutations had higher EPO expression than those with MED12 mutations under estrogenic influence, independent of hypoxia. These findings suggest that uterine leiomyomas lacking MED12 mutations are more susceptible to more tumor growth, possibly due to increased EPO expression levels in response to E. Reversely the attenuated EPO expression in response to E in MED12 mutated leiomyomas might be the reason why these tumors generally tend to be smaller than uterine leiomyomas without MED12 mutation. Thus, studying the molecular mechanism by which MED12 mutation regulates EPO expression levels could give us a better understanding of uterine leiomyomas pathophysiology and hence a personalized therapy as per the 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 [8]. Mutations in MED12 result in the disruption of mediator kinase activities and consequently the CDK8 function. In uterine leiomyomas context MED12 linked mutations disrupt its direct interaction with components of the CDK8 and results in suppression of E-induced transcription, as seen by Asano., *et al*'s [7] study in MED12 response to E. Thus, new treatments inhibiting EPO expression might be considered as a therapy to prevent the growth in uterine leiomyomas lacking MED12 mutations.

Still, MED12 mutation is highly prevalent in uterine leiomyomas and is implicated in tumorigenesis. Hence defining the mechanism by which MED12 mutations promotes uterine leiomyomas development would clarify the pathogenesis of uterine leiomyomas with the most common mutation. Al-Hendy [9] have reported that MED 12 plays an important role in the regulation of uterine leiomyomas cell proliferation through the Wnt/β-catenin signaling pathway, cell cycle, and fibrosis-associated protein expression. MED 12 is associated with the WNT (Wnt family member 4) and activation of β-catenin signaling, promoting the expression of down-stream proteins involved in cell proliferation (CCDK1 and CDK2), as well as extracellular matrix proteins (collagen type1, 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 mutations.

Recently, vitamin D has been widely studied for its antitumorigenic and antiproliferative roles in certain cancers, including signaling uterine leiomyomas. A recent study which is an in-depth study of the molecular mechanism through which vitamin D acts in uterine leiomyomas [10]. Corachan's study [10] showed that Vitamin D exerts an antiproliferative action through the cell growth arrest and inhibition of Wnt/β-catenin pathway. This suggests that vitamin D treatment is a possible therapy to treat leiomyomas with the Wnt/β-catenin pathway deregulated.

Observing 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 MED1were observed in uterine leiomyomas lacking the MED12 mutation could be explained by the E-induced expression of EPO. Hence the personalized therapy applied according to MED12 mutation status could be a viable approach for treating mutation uterine leiomyomas.

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