

# Loss of the Repressor REST in Uterine Fibroids Promotes Aberrant G Protein-coupled Receptor 10 Expression and Activates Mammalian Target of Rapamycin Pathway

- Uterine fibroids (leiomyomas) are the most common tumors of the female reproductive tract, occurring in up to 77% of reproductive-aged women, yet molecular pathogenesis remains poorly understood.
- Research identified that G protein-coupled receptor 10 [GPR10, a putative signaling protein upstream of the phosphoinositide 3-kinase–protein kinase B/AKT–mammalian target of rapamycin (PI3K/AKT–mTOR) pathway, earlier suspected in uterine fibroid pathogenesis] is aberrantly expressed in uterine fibroids.
- The activation of GPR10 by its cognate ligand, prolactin releasing peptide, promotes PI3K–AKT–mTOR pathways and cell proliferation specifically in cultured primary leiomyoma cells.
- Additionally, RE1 suppressing transcription factor/neuron-restrictive silencing factor (REST/NRSF), a known tumor suppressor, transcriptionally represses GPR10 in the normal myometrium, and that the loss of REST in fibroids permits GPR10 expression.
- Importantly, mice overexpressing human GPR10 in the myometrium develop myometrial hyperplasia with excessive extracellular matrix deposition, a hallmark of uterine fibroids.
- This study demonstrated previously unrecognized roles for GPR10 and its upstream regulator REST in the pathogenesis of uterine fibroids.

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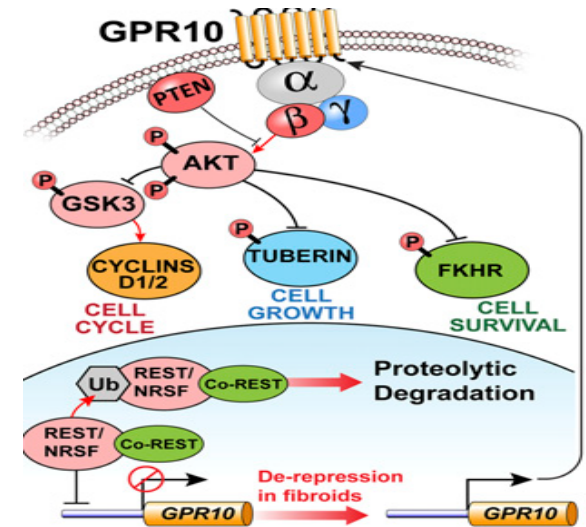
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Loss of the repressor REST in uterine fibroids promotes aberrant G protein-coupled receptor 10 expression and activates mammalian target of rapamycin pathway

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Working model depicting the link between loss of REST and the overexpression of GPR10 in myometrium.