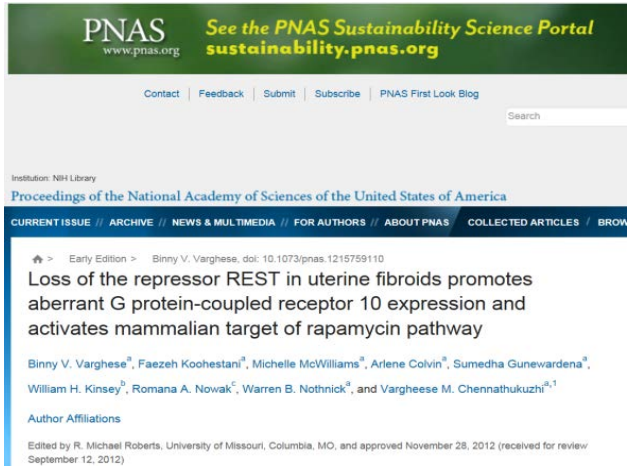
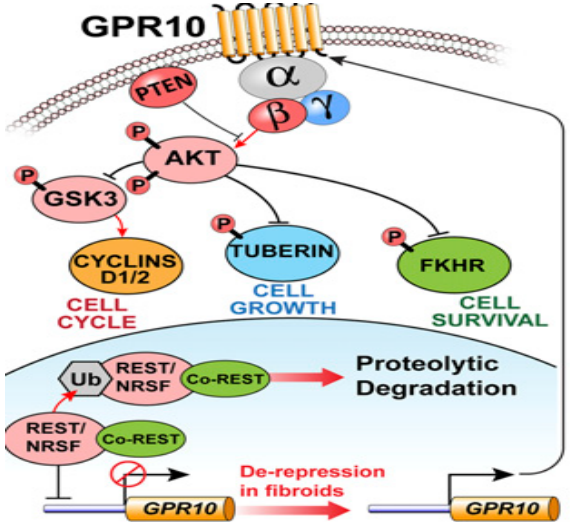
Loss of the Repressor REST in Uterine Fibroids Promotes Aberrant G Protein-coupled Receptor 10 Expression and Activates Mammalian Target of Rapamycin Pathway

- 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.





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

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