WNT4 Balances Development vs Disease in Gynecologic Tissues and Women's Health

Lauren M Pitzer[1], Marisa R Moroney[2], Natalie J Nokoff[3], Matthew J Sikora[1]

[1]Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045, USA.
[2]Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045, USA.
[3]Department of Pediatrics, Section of Endocrinology, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045, USA.

University of Colorado Anschutz Medical Campus

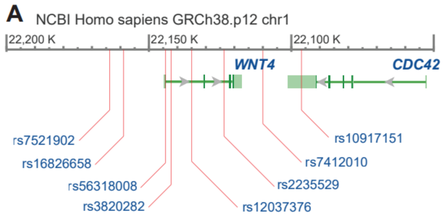
Background

- Wnt ligands are paracrine signaling molecules that regulate the proliferation and self-renewal of cells
- WNT4 loss-of-function is lethal in utero or immediately postnatal because of multiorgan dysgenesis
- Sex reversal syndromes have been described as a result of homozygous WNT4 mutations
- Biason-Lauber syndrome results from a WNT4 mutation and presents with uterine agenesis
- Single-nucleotide polymorphisms (SNPs) encompassing the WNT4 gene, have been associated with increased risk of a range of gynecologic pathologies
- In ILC cells, WNT4 expression is directly controlled by Erα, contrasting progesterone-regulation of WNT4 in the mammary gland

Methods

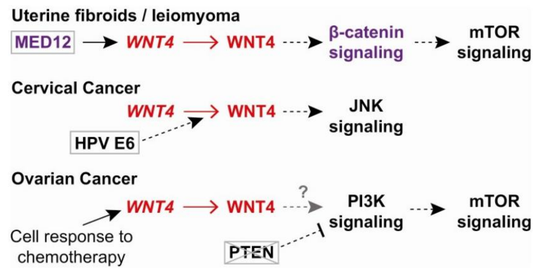
- NCBI PubMed, Google Scholar, and Web of Knowledge were used to search for the terms "WNT4" or "WNT-4," alone or in conjunction with "müllerian," "sex differentiation," "fertility," "cancer," "endometriosis," "leiomy- oma," "GWAS," or "cancer." Searches were primarily conducted from March 2020 to December 2020.
- We use human vs murine or other species' nomenclature throughout this review based on the context of immediately referenced work, and default to human nomenclature (WNT4/WNT4) for broader discussion

Results

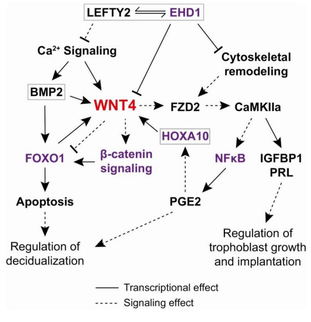


B 1p36 index SNPs associated with gynecologic pathologies

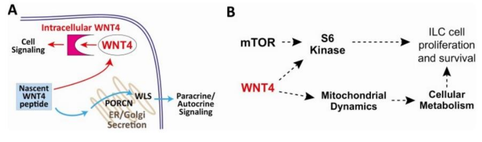
Endometriosis	rs7521902 (Painter, 2011; Nyholt, 2012; Pagliardini, 2013; Rahmioglu, 2014, 2015; Matalliotakis, 2017) rs16826658 (Uno, 2010; Lee, 2014; Méar, 2019); rs3820282 (Powell, 2013); rs12037376 (Sapkota, 2017); rs2235529 (Albertsen, 2013; Wu, 2015); rs7412010 (Masuda, 2020)
Endometriosis with infertility	rs16826658 and rs3820282 (Mafra, 2015)
Uterine fibroids / leiomyoma	rs2235529 (Välimäki, 2018); rs7412010 (Gallagher, 2019); rs10917151 (Rafnar, 2018; Edwards, 2019)
Pelvic organ prolapse	rs3820282 (Olafsdottir, 2020)
Epithelial ovarian cancer	rs56318008 (Zhang, 2018); rs3820282 (Kuchenbaecker, 2015)
Gestational duration	rs56318008, rs12037376, rs3820282* (Zhang, 2017) **functional study*



WNT4 signaling pathways in gynecologic pathologies. Details are described in the text. Transcription factors shown in purple text. Boxes denote key upstream factors that are critical in pathogenesis. Solid vs dashed lines represent transcriptional vs signaling effects, as in Fig. 2. The mechanisms by which WNT4 controls PI3K signaling in ovarian cancer are unknown, denoted by "?".



WNT4 signaling pathways in uterine development and pregnancy. Details described in text. Transcription factors shown in purple text. Boxes denote key upstream regulatory factors that are "entry points" into the pathway.



Intracellular WNT4 signaling. A, Wnt peptides are typically secreted via PORCN/Wntless (WLS) activity, but WNT4 can signal independent of secretion as a soluble, intracellular protein via receptor proteins to be identified. B, In invasive lobular carcinoma (ILC) cells, intracellular WNT4 signaling regulates mammalian target of rapamycin (mTOR) signaling via downstream S6 kinase, and also regulates cellular metabolism via control of mitochondrial dynamics.

Conclusions

- WNT4 has distinct, separable signaling functions in organogenesis vs gynecologic and reproductive health
- WNT4 is critical for embryonic organogenesis, as well as the continued development and maintenance of müllerian and reproductive tissues
- Dysregulation of WNT4 expression primarily manifests as gynecologic and reproductive pathologies
- WNT4 functions via atypical pathways, including PORCN-independent signaling and novel intracellular signaling roles in ILC and other cancer cells

Implications

- Defining WNT4 signaling and the underpinning of WNT4 tissue-specific functions can improve the understanding of endocrine organogenesis and reproduction, and will identify new treatment approaches for a broad range of WNT4-related gynecologic pathologies
- WNT4 dysregulation is associated with a spectrum of sex development and women's health issues that should be a major consideration in research when looking at sex as a biological variable

Disclosures

No disclosures

Citation

Pitzer LM, Moroney MR, Nokoff NJ, Sikora MJ. WNT4 Balances Development vs Disease in Gynecologic Tissues and Women's Health. Endocrinology. 2021 Jul 1;162(7):bqab093. doi: 10.1210/endocr/bqab093. PMID: 33963381; PMCID: PMC8197283.