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.

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