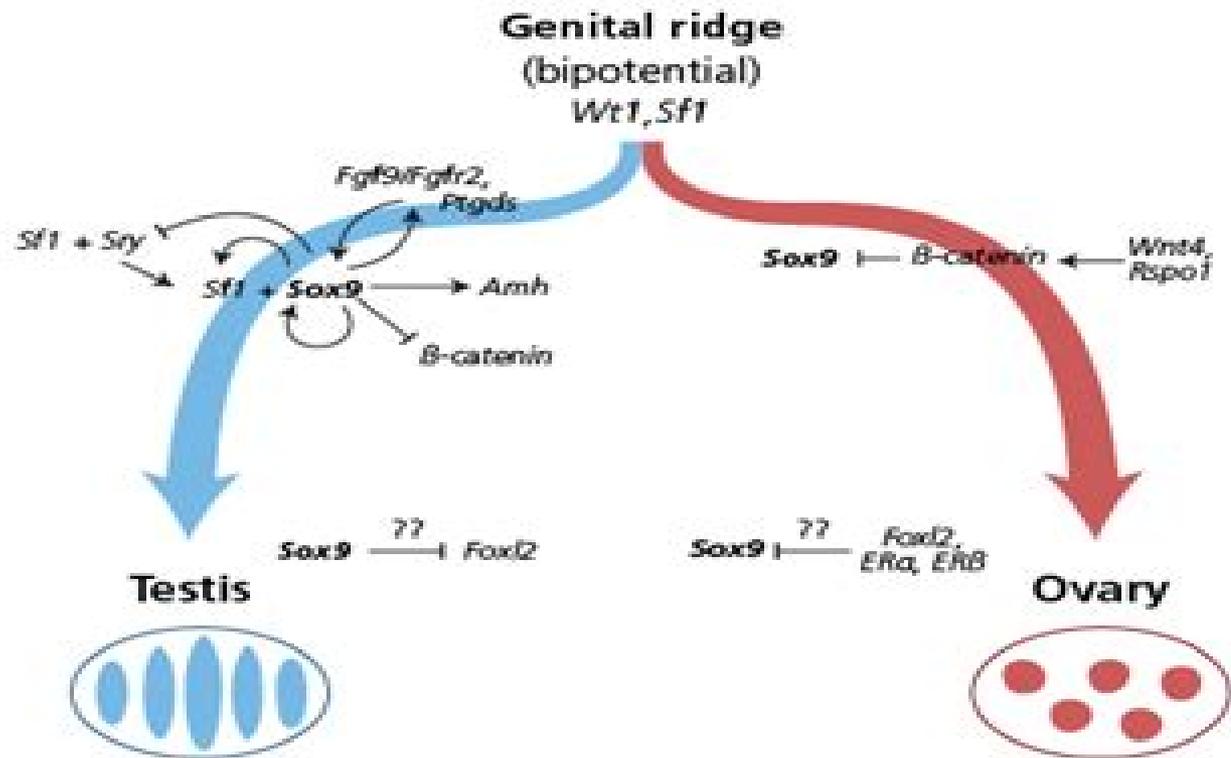


Molecular and Genetic Events in Mammalian Sex Determination

Genes in the female pathway repress *Sox9*; genes in the male pathway express it



"The bipotential genital ridge is established by genes including *Wt1* and *Sf1*, the early expression of which might also initiate that of *Sox9* in both sexes. *β-catenin* can begin to accumulate as a response to *Rspo1*-*Wnt4* signaling at this stage. In XX supporting cell precursors, *β-catenin* levels could accumulate sufficiently to repress *SOX9* activity, either through direct protein interactions leading to mutual destruction, as seen during cartilage development, or by a direct effect on *Sox9* transcription. However, in XY supporting cell precursors, increasing levels of *SF1* activate *Sry* expression and then *SRY*, together with *SF1*, boosts *Sox9* expression. Once *SOX9* levels reach a critical threshold, several positive regulatory loops are initiated, including autoregulation of its own expression and formation of feed-forward loops via *FGF9* or *PGD2* signaling. If *SRY* activity is weak, low or late, it fails to boost *Sox9* expression before *β-catenin* levels accumulate sufficiently to shut it down. At later stages, *FOXL2* increases, which might help, perhaps in concert with ERs, to maintain granulosa (follicle) cell differentiation by repressing *Sox9* expression. In the testis, *SOX9* promotes the testis pathway, including *Amh* activation, and it also probably represses ovarian genes, including *Wnt4* and *Foxl2*. However, any mechanism that increases *Sox9* expression sufficiently will trigger Sertoli cell development, even in the absence of *SRY*" (Sekido et al., 2009).

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