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Somatic Cell Lineage Specification by Notch Signaling in Fetal Mouse Ovaries.
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Organogenesis of the ovary is a complex process involving germ and somatic cell lineage determination. Somatic cells in the fetal ovary give rise to the supporting or granulosa cell lineage and the interstitial cell populations. After birth, interstitial cells differentiate into the theca cells and ovarian stroma.

Interstitial cells not only play a critical role in steroidogenesis, but are also implicated in ovarian disorders such as polycystic ovarian syndrome, primary ovarian insufficiency, and androgen-producing tumors. Despite their role in normal ovarian functions and diseases, the developmental processes determining interstitial cell progression are not clearly defined. Here, we performed a time-course analysis of somatic cell fate progression with a focus on the interstitium by genetic lineage-tracing experiments in the mouse ovary. Before the onset of ovarian organogenesis, somatic cells are thought to be homogeneous with the expression of SF1 (Steroidogenic factor 1). To our surprise, we discovered a subpopulation of SF1 + somatic cell progenitors that expressed Hes1, a transcription factor indicative of NOTCH pathway activation. Expression of Hes1, which was absent in the supporting cell lineage, represented the earliest event that defines the interstitial cell lineage. We next investigated the importance of the interstitium-specific pattern of Hes1 expression by ectopically activating NOTCH signaling in all somatic cells in the fetal ovary. Constitutive activation of NOTCH resulted in defects of cell lineage specification and ovarian development. The steroidogenic interstitial cells and ovarian stromal cells were significantly reduced and follicular arrest occurred in neonatal ovaries that constitutively expressed NOTCH in both the supporting and the interstitial cell lineages. These results illustrate that the somatic cell pool in the undifferentiated ovary is heterogenous and not homogenous as previously thought. The interstitial cell lineage is defined earlier than the supporting cell lineage in the undifferentiated ovary by the activation of the NOTCH pathway. A properly tuned NOTCH pathway is absolutely essential for interstitial and supporting cell development and folliculogenesis. This research was supported by ---the National Institute of Environmental Health Sciences intramural research funds.