Wnt Signaling Networks and Embryonic Patterning

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Abstract

Wnt signaling lies at the heart of metazoan development. The Wnt pathway bifurcates a number of times and regulates cell polarity, migration, adhesion and gene expression. I review the complexity of this network with a focus on the role of SOX proteins in its regulation.

Introduction

There is a growing consensus that the metazoans are monophyletic, descended from urmetazoans that lived ~1.2 Gya. While it seems likely that many inter- and intracellular signaling pathways were in place in this eumetazoan ancestor, there is much genomic sequence gazing and phylogenetic reconstruction remaining before we have a clear view of the metazoan Adam/Eve. Nevertheless, it is clear that a small number of conserved signaling pathways have been used repeatedly to establish body axes and tissue types. These include the Wnts, the receptor serine/threonine protein kinases, the receptor tyrosine kinases, hedgehogs and Notch/Delta. I will focus on the Wnt signaling system as a key player from the earliest stages of metazoan evolution (Fig. 1).

Wnt signaling typically occurs over short ranges (juxtacrine), involves components of the cadherin cell-cell adhesion system, and can directly modulate gene expression through the LEF/TCF-subfamily of sequence-specific HMG-box DNA binding proteins. In part their autocrine/juxtacrine activity is due to the fact that Wnts are lipid-modified. Molecular studies of the cnidarian Hydra vulgaris reveals the presence of Wnts and a number of downstream components of the Wnt signaling pathway. Whether Wnt signaling or Wnt signaling components are present in the more basal Porifera (sponges) or the protozoan sister group of the metazoans, the Choanoflagellates, is not yet known. Cadherin-like polypeptides have been identified in the unicellular and colonial Choanoflagellates Monosiga brevicollis and Proterospongia and catenin-like polypeptides are present in the cellular slime mold Dictyostelium discoideum. Wnt signaling has been implicated in a large number of morphogenic events during development as well as the maintenance of stem cells in their undifferentiated state. Wnt signaling plays a key role in the regulation of epithelial-mesenchymal transition during neural crest formation.
Wnts and Their Receptors

Wnts are secreted glycoproteins that act at short range to regulate cellular behavior. In the human there are 19 known Wnts. The downstream effects of Wnt signaling are complex and can affect cellular morphology, polarity and motility as well as gene expression through parallel, complementary and interacting pathways. The origin of this diversity begins with the membrane-bound Wnt receptors. Wnts bind to the extracellular domains of frizzled polypeptides. These are seven-pass transmembrane proteins that associate with the low-density lipoprotein receptor-related LRP5 and LPR6 polypeptides to form one type of Wnt receptor. The mouse LPR5 gene plays a critical role in cholesterol metabolism and, together with Wnts 3a and 5, regulates glucose-induced insulin secretion. LPR5 interacts directly with the downstream Wnt-signaling polypeptide Axin. Ten frizzleds have been identified in human and different frizzleds bind to differ Wnts with different affinities to produce different down-stream outcomes.

* Roel Nusse’s lab maintains the excellent Wnt Gene Homepage where you can usually find the latest information of all components of the Wnt signaling pathway. http://www.stanford.edu/~rnusse/wntwindow.html