Nodal and Hedgehog Signaling in Midline and Left-Right Axis Development

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Genetic screens in zebrafish have identified two classes of genes that lead to defects resembling human holoprosencephaly (Schier, 1997): mutations leading to cyclopia (cyclopic class) and mutations affecting the ventral midline of the neural tube and the crossing of retinal axons in the diencephalon (midline/retinotectal class). Cyclopic mutants such as cyclops, one-eyed pinhead and squint have ventral forebrain deficiencies, fused eyes or a single median eye. Molecular studies have indicated that these mutations affect signaling by TGF-beta factors of the Nodal family (Schier and Shen, 2000). Cyclops and squint encode Nodal-related proteins and one-eyed pinhead affects an EGF-CFC protein (Feldman et al., 1998; Rebagliati et al., 1998; Sampath et al., 1998; Zhang et al., 1998; Gritsman et al., 1999). Midline/retinotectal mutants such as sonic you, you-too and detour affect subregions in the ventral diencephalon. Molecular studies have indicated that these three genes encode components of the hedgehog signaling pathway: sonic you disrupts the signaling molecule sonic hedgehog and you-too and detour affect the transcription factors gli2 and gli1, respectively (Schauerte et al., 1998; Karlstrom et al., 1999; Karlstrom et al., in preparation). I will discusss how Nodal and Hedgehog signaling pattern vertebrate embryos and discuss the implications for understanding holoprosencephaly.

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