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Wnt signalling, TCF/LEF transcription factors, colorectal cancer

Research topics

The main focus of the newly formed department lies on the molecular mechanisms of Wnt signalling in mammalian cells and signalling pathways influencing behaviour of normal and diseased intestinal epithelial cells.

The most important result in the current years was the identification of the HIC1 (Hypermethylated In Cancer 1) tumour suppressor as a novel modulator of the Wnt signalling cascade. The *HIC1* gene is frequently epigenetically silenced or deleted in different types of solid tumours. When expressed, the HIC1 protein localizes into the nuclear dot-like structures called the HIC bodies. We showed that HIC1 interacts with the Wnt signalling effector TCF-4. Interestingly, HIC1 relocates TCF-4 to the HIC bodies and the effectiveness of this relocation is partly dependent on the structural function of CtBP (C-terminal binding protein). Furthermore, we demonstrated that HIC1 inhibits transcriptional activation of various Wnt-specific target genes. This inhibitory action is based just on the ability of HIC1 to sequestrate TCF-4 into the HIC bodies. Such sequestration results in uncoupling TCF-4/β-catenin complexes from the Wnt-responsive promoters and, ultimately, leaves these promoters irresponsive to the Wnt signals. In conclusion, we predict that the hyperactivity of the Wnt/β-catenin pathway might contribute to the development of tumours from cells in which the expression of HIC1 has been inactivated.

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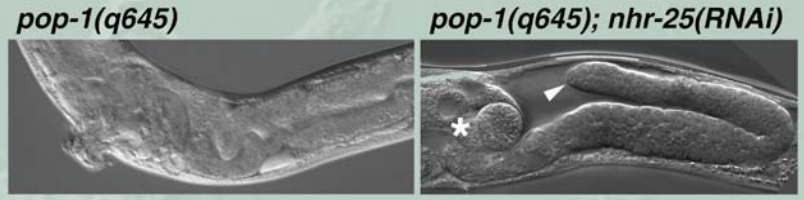
Selected recent papers

1. Valenta T, Lukas J, Doubravska L, Korinek V. HIC1 attenuates Wnt signaling by recruitment of TCF-4 and β-catenin to the nuclear bodies. **EMBO J.** 2006;25:2326-2337.
2. Asahina M, Valenta T, Šilhánkova M, Kořínek V, Jindra M. Crosstalk between a nuclear receptor and β-catenin signaling decides cell fates in the C..elegans somatic gonad. **Developmental Cell.** 2006;11:203-211.
3. Psahoulia FH, Drosopoulos KG, Doubravska L, Andera L, Pintzas A. Quercetin enhances TRAIL-mediated apoptosis in colon cancer cells by inducing the accumulation of death receptors in lipid rafts. **Mol Cancer Ther.** 2007;6:2591-2599.
4. Doubravská L, Šímová Š, Čermák L, Valenta T, Kořínek V, Anděra L. Wnt-expressing rat embryonic fibroblasts suppress Apo2L/TRAIL-induced apoptosis of human leukemia cells. **Apoptosis.** 2008;13:573-587.
5. Vojtechova M, Tureckova J, Kucerova D, Sloncova E, Vachtenheim J, Tuhackova Z. Regulation of mTORC1 signaling by Src kinase activity is Akt1-independent in RSV-transformed cells. **Neoplasia.** 2008;10:99-107.



Nuclear receptor NHR-25 counteracts β-catenin signalling during gonad development in C. elegans. The absence of gonadal arms caused in hermaphrodites by mutations in the pop-1/Tcf gene [pop-1(q645); left] can be reverted by nhr-25 knockdown (right). Arrowhead points to distal tip cell; asterisk indicates an embryo (Asahina et al., 2006).

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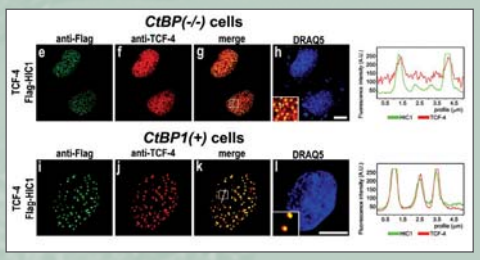
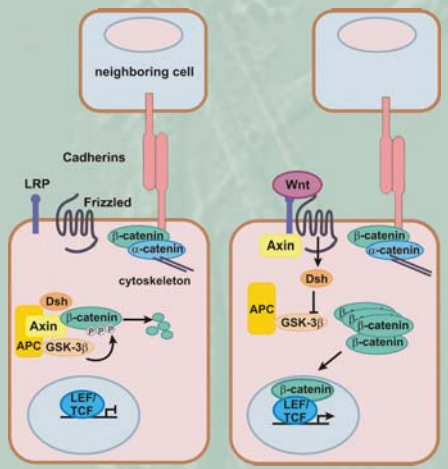


A simultaneous interaction between CtBP, TCF-4 and HIC1 is essential for the efficient nuclear sequestration of TCF-4 into the HIC1 bodies. *Confocal microscopy images of CtBP(-/-) (no CtBP expression, upper panel) and CtBP1(+) cells (expressing CtBP1, lower panel) transfected with the indicated constructs (left) and stained with anti-Flag and anti-TCF-4 antibody. The right panels show the overlap of fluorescence intensity peaks along profiles as indicated in the merged micrographs.*



The canonical Wnt/β-catenin signalling pathway (adopted from Reya and Clevers, Nature, 2005)