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Epigenetic mechanisms downstream of Wnt in carcinomas and cancer stem cells

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Head and Neck Squamous Cell Carcinomas (HNSCCs) of the upper airways, which also include salivary gland cancers, are the fifth frequent human malignancy. The most important risk factors for HNSCCs are smoking, excess alcohol consumption and infection by high-risk human papillomaviruses. Patients with advanced tumors exhibit high mortality due to lack of effective molecular therapies. We found in a mouse model of salivary glands squamous cell carcinoma with conditional beta-catenin gain-of-function mutation that a histone modifier, which induces H3K4me3, acts downstream of Wnt/beta-catenin signaling. Conditional ablation of the histone modifier gene prevented tumor formation, reduced proliferation and induced apoptosis. ChIP-seq revealed a genome-wide increase in the active histone mark H3K4me3 and chromatin opening in Cancer Stem Cells (CSCs). Mutations by CRISPR/Cas9 of the histone modifier at the β -catenin-, Menin-, Brd4-, and Wdr5-binding and Set-H3K4me3 enzymatic sites in mice strongly reduced CSC self-renewal. Pharmacological interference that disrupted these interactions also strongly reduced the self-renewal of mouse and human CSCs. We thus identified an essential downstream layer downstream of Wnt/ β -catenin, which are H3K4me3 and opening of chromatin that are essential in HNSCC formation. Targeting the histone modifier and its interactions with small interfering molecules allow promising new therapies for head and neck squamous cell carcinomas.

Biography

Walter Birchmeir is a graduate in biology of Zürich University in 1973. After postdoctoral years at Cornell University, Ithaca, the Biocenter Basel and the University of California at San Diego, he became laboratory head at the Max-Planck-Institute Tübingen in 1982 and full Professor at the University of Essen Medical School in 1988. He joined the Max-Delbrück-Center for Molecular Medicine in Berlin in 1993. He was Director of the Max-Delbrück-Center from 04/2004 to 12/2008 and is Professor at the Charité/Humboldt University Berlin. His major research interests have been the role of cell adhesion and signal transduction in development and tumor progression.

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