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The role of WNT4 in the non-canonical WNT/PCP pathway in thymic epithelial tumors

Autor: Xiaonan Zhang
Institut / Klinik: Pathologisches Institut
Doktorvater: Prof. Dr. M. Alexander

Background: WNT4-driven non-canonical signaling is crucial for homeostasis and age-related involution of the thymus. Abnormal WNT signaling is a central feature of many cancers but the role of WNT signaling in thymic tumors is largely unknown.
Materials & Methods: Expression, secretion, and function of WNT4 and frizzled receptor 6 were analyzed using qRT-PCR, western blot, ELISA, shRNA techniques, and functional assays in biopsies of non-neoplastic thymi (NTs), thymomas, thymic carcinomas [1] and primary thymic epithelial cells (pTECs) derived from those and the TC cell line, 1889c. Cells were conventionally (2D) grown and in three-dimensional (3D) spheroids.
Results: In biopsies, WHO type B3 thymomas and TCs showed increased WNT4 expression compared to NT. NTs, but not thymomas showed an age-dependent decline of WNT4 mRNA levels. During short-term 2D culture, WNT4 expression and secretion declined in neoplastic pTECs, but not in cultured as 3D spheroids or in medium supplemented with recombinant WNT4. Under the latter conditions, growth of pTECs was accompanied by increased expression of non-canonical targets RAC1 and JNK. Down-regulation of WNT4 by shRNA induced increased cell death in pTECs derived from B3 thymomas and led to decreased RAC1, but not JNK, protein phosphorylation. Vice versa, pharmacological inhibition of NFκB decreased both RAC1 and JNK phosphorylation in neoplastic TECs.
Conclusion: Lack of the age-related decline of non-canonical WNT4 expression in TETs and restoration of declining WNT4 expression through exogeneous WNT4 or 3D culture of pTECs, hints at an oncogenic role of WNT4 in thymic tumors and is compatible with a WNT4 autocrine loop model. Crosstalk between WNT4 and NFκB signaling may present a promising target for combined interventions in TETs.