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Titel des Beitrags: EZH2 is a mediator of EWS/FLI1 driven tumor growth and metastasis blocking endothelial and neuro-ectodermal differentiation.
Abstract: Ewing tumors (ET) are highly malignant, localized in bone or soft tissue, and are molecularly defined by ews/ets translocations. DNA microarray analysis revealed a relationship of ET to both endothelium and fetal neural crest. We identified expression of histone methyltransferase enhancer of Zeste, Drosophila, Homolog 2 (EZH2) to be increased in ET. Suppressive activity of EZH2 maintains stemness in normal and malignant cells. Here, we found EWS/FLI1 bound to the EZH2 promoter in vivo, and induced EZH2 expression in ET and mesenchymal stem cells. Down-regulation of EZH2 by RNA interference in ET suppressed oncogenic transformation by inhibiting clonogenicity in vitro. Similarly, tumor development and metastasis was suppressed in immunodeficient Rag2(-/-)gamma(C)(-/-) mice. EZH2-mediated gene silencing was shown to be dependent on histone deacetylase (HDAC) activity. Subsequent microarray analysis of EZH2 knock down, HDAC-inhibitor treatment and confirmation in independent assays revealed an undifferentiated phenotype maintained by EZH2 in ET. EZH2 regulated stemness genes such as nerve growth factor receptor (NGFR), as well as genes involved in neuroectodermal
and endothelial differentiation (EMP1, EPHB2, GFAP, and GAP43). These data suggest that EZH2 might have a central role in ET pathology by shaping the oncogenicity and stem cell phenotype of this tumor.

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