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Talk Title: **The Role of Cilia in Tumorigenesis**

Abstract:
Melanoma is the most aggressive skin cancer. Despite recent progress, success of therapy is limited due to acquisition of resistance in many patients. The aggressiveness of melanoma has been associated with the capacity of its tumor cells to dynamically adapt to new extracellular cues, including drugs. The fact that melanoma cells can transiently and reversibly switch their phenotype indicates that, apart from genetic factors, epigenetic mechanisms are likely involved in emergence, malignant progression, and therapy response of melanoma cells. A prominent epigenetic regulator is enhancer of zeste homologue 2 (EZH2), which is a component of the polycomb repressive complex (PRC)2. Elevated PRC2 activity was shown to promote breast, prostate, lymphoma, and lung epithelial neoplasia in mice. Recently, we demonstrated a crucial role of EZH2 in melanoma initiation and metastasis formation. Using genetically engineered mouse melanoma models, in combination with pharmacological inhibition in human melanoma cells, we revealed that, among others, EZH2 directly suppresses formation of cilia in melanoma cells. Loss of this signaling organelle in turn was associated with increased canonical Wnt signaling and de-differentiation and promoted melanoma initiation in benign nevus cells. However, despite their prominent role in melanoma, cilia genes are not a major target of oncogenic mutations in human melanoma, suggesting that cilia might be required by melanoma cells at certain stages possibly associated with phenotype switching during metastasis formation and in response to therapy. Likewise, we found that malignant peripheral nerve sheath tumors (MPNST) – a skin tumor developmentally related to melanoma – exhibit low EZH2 expression and are highly ciliated, in contrast to melanoma. Thus, epigenetic control of cilia and the role of cilia in tumorigenesis appear to be context-dependent, which needs to be taken into account when designing therapeutic strategies targeting cilia-associated processes in cancer.