

## Drosophila as a model system for atypical teratoid/rhabdoid tumors

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Atypical teratoid/rhabdoid tumors (ATRTs) are highly malignant brain tumors, mainly affecting infants and children. Mutations causing loss of SMARCB1 function, a core component of SWI/SNF chromatin remodeling complex are a hallmark genetic feature. Even though other recurrent genetic alterations are absent, ATRTs are highly heterogeneous with regard to epigenetic features, gene expression profiles and clinical features. Based on DNA methylation profiles, ATRTs segregate into three molecular groups, i.e. ATRT-TYR, ATRT-MYC and ATRT-SHH. ATRT-SHH represents the largest molecular group and is characterized by active sonic hedgehog and notch pathways. In contrast to other cancers, however, mutations in sonic hedgehog and notch related genes are not encountered and little is known about mechanisms involved in dysregulation of these pathways relevant for tumor formation, maintenance and progression upon SMARCB1- deficiency.

In order to explore the role of hedgehog (hh) and notch pathway dysregulation upon SMARCB1-deficiency, we used *Drosophila melanogaster* as a model. We applied UAS/GAL4 system to knock down *Snr1*, the fly homolog of SMARCB1, in the wing disc of *Drosophila* larvae. In contrast to ubiquitous (*Tubulin*- or *Actin*- GAL4), wing disc specific (*ms1096* and *ap*- GAL4) or *hh* repressed regions (*ptc* or *dpp*-GAL4), tumor-like structures developed when *Snr1* was down regulated in the posterior, *hh* expressing region (*en*- or *hh*-GAL4). Presence of such features was accompanied by abnormalities in hh and notch pathway activation. Furthermore, in affected regions not only proliferation but also cell cycle was disrupted, underlining the role of *Snr1* in growth control. Remarkably, a high diversity of phenotypes was encountered, suggesting clonal aspects and involvement of other genes. Further studies are required to identify these genes in modifier screens i.e, testing fly orthologs of genes up-regulated in ATRT and active in the wing imaginal discs.

**Hauptautor:** MISKIEWICZ, Katarzyna

**Co-Autor:** Prof. HASSELBLATT, Martin

**Vortragende(r):** MISKIEWICZ, Katarzyna