A Hh-Gli signalling network and therapeutic potential.

The Hedgehog-Gli (Hh-Gli) signaling pathway is a developmental pathway, which is often found aberrantly activated in various tumors. Canonical pathway activation begins when the ligand Shh binds to its receptor, Patched (PTCH1), resulting in the de-repression of the co-receptor Smoothened (SMO). This triggers a cascade of events in the cytoplasm leading to activation of the transcription factors GLI and transcription of their target genes. The GLI proteins are regulated by the Suppressor of Fused (SUFU), and 3 kinases, including GSK3β, that regulate the processing of Gli proteins. First discoveries related to the pathway and human disorders were made on a range of PTCH1 alteration profiles, including genetic mutation, LOH, and promoter hypermethylation (Hahn et al 1996, Shimkets et al 1996, Levanat et al 1996, Cretnik et al 2007, Car et al 2010, Musani et al 2009). At this level, the key player in the pathway is PTCH1. Inactivation of PTCH1 allows hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway that may lead to neoplastic growth. Mutations in the PTCH1 gene are the underlying cause of Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Gorlin syndrome. We are mainly interested in mechanisms of Hh-Gli signaling pathway deregulation that may lead to cancer development. In our research we have observed upregulation of the Hh-Gli pathway genes PTCH1, SMO, GLI1 and SUFU, in ovarian tumors compared to healthy tissue. This effect is very similar in both carcinoma and borderline tumors, suggesting that Hh-Gli signaling plays a role in both tumor types. However, expression of the SHH gene was significantly higher in borderline tumors compared to carcinoma, which supports the theory in which borderline tumors are a distinct tumor type, and not an early stage in the development of ovarian carcinoma. The upregulation of Hh-Gli signaling in almost all tested samples suggests that this is an early event in ovarian tumorigenesis regardless of tumor type. On the other hand, in breast cancer we observed a cross-talk between Hh-Gli signaling (SHH ligand) and the Estrogen receptor, creating a potentially new signaling network (Sabol et al, 2014, Uzarevic 2011). Furthermore, in colon cancer cells we observed noncanonical hyperactivation of the pathway caused by the deregulated regulatory kinase GSK3β. Deregulated GSK3β activity leads to overproduction of activator form of Gli3 and to pathway hyperactivation. Inhibition of GSK3β leads to increased co-localization of GSK3β and Gli3 indicating improved regulation of Gli3 processing and results in pathway downregulation (Gojevic 2011, Trnski 2015). This suggests a major role for the interplay of GSK3β and Gli3 in the regulation of this pathway in colon cancer (publication in preparation).