

## **Abstract**

This dissertation delves into the intricate role of the Hedgehog signaling pathway (HH) in melanoma, aiming to provide a comprehensive understanding of its involvement in melanomagenesis and its potential as a therapeutic target. Hedgehog signaling pathway is a crucial cellular communication system that regulates various developmental processes and tissue homeostasis. Aberrations in this pathway can lead to the development of various diseases, including cancers such as melanoma. This form of skin cancer is known to be aggressive and often deadly. It is also denoted by the presence a subpopulation of cells known as cancer stem cells (CSCs) within formed neoplasm. According to available data on CSCs, they are assumed to be crucial for tumor initiation, progression, and its resistance to therapy. In this work, we focus on the role of CSCs in tumor progression and how HH contributes to maintaining the stem cell phenotype. Current analytical and therapeutic strategies targeting CSCs and HH will be discussed. Our findings suggest that targeting CSCs and the Hedgehog pathway may hold promise for the development of effective therapies for melanoma.

We aim to provide novel insights to HH signaling pathway and its interactions within the cell. We have succeeded to identify a brand-new transcriptional target of this pathway – Slug transcription factor. Slug protein involved in development of the neural crest and maintenance of the CSC phenotype. We found out that its cellular levels decrease upon the inhibition of HH effector proteins – the GLI transcription factors – by GANT61. Furthermore, we demonstrate that elements of the HH signaling pathway are present in more than 50 cancer cell lines.

We also revisited the so-called “rheostat model” on Microphthalmia-associated transcription factor (MITF) influence on cancerous phenotype on cell lines with inducibly regulated MITF levels. In the past, it was documented that high-MITF levels are manifested by high differentiation rate and low invasiveness and the low-MITF level is associated with low differentiation and proliferation rates combined with high invasiveness. Our data disprove of this postulate as we report a contradictory effect of MITF decrease. Lastly, it was shown, that MITF directly targets a SCF E3 ligase complex subunit - FBXO32 and in concert with chromatin-remodeling complex plays a significant role in regulation of ubiquitination in melanoma cells on epigenetic level.

**Key words:** Hedgehog signaling pathway, Slug, CSC, marker