
Transforming growth factor β (TGF-β) and bone morphogenetic protein (BMP) signaling pathways are involved in many physiological processes during embryonic and adult life. TGF-β promotes epithelial to mesenchymal transition (EMT). We identified a gene target of TGF-β signaling, encoding the salt-inducible kinase 1 (SIK1). A potential substrate of this kinase, the polarity protein Par3, is an established regulator of tight junction assembly. SIK1 associates with Par3, can potentially phosphorylate Par3 and leads to its degradation, contributing to tight junction disassembly.

Glioblastoma multiforme (GBM) is a common malignancy in the central nervous system, characterized by high heterogeneity, invasiveness, and resistance to therapy. One of the causes of heterogeneity and therapy-resistance is the existence of glioblastoma stem cells (GSCs). TGF-β signaling promotes self-renewal while BMP signaling induces differentiation of GSCs. Snail is a potent inducer of the EMT in carcinomas. However, in the context of GBM, Snail induces BMP signaling and represses TGF-β signaling through interaction with SMADs, the signaling mediators of TGF-β and BMP. In conclusion, Snail differentially regulates the activity of the opposing BMP and TGF-β pathways, thus promoting an astrocytic fate switch and repressing stemness in GSCs.

Although profound changes in cell polarity is a hallmark of invasive malignancies, little is known about the role of the polarity machinery in tumor suppression. Patient transcriptomic data suggested low Par3 expression, correlating with poor survival of the GBM patients. Par3 silencing decreased the GSC self-renewal capacity and enhanced their invasiveness. Transcriptomic analysis indicates that loss of Par3 leads to downregulation of genes encoding mitochondrial enzymes that generate ATP. These results support a novel role of Par3 in GBM, beyond its contribution to junctional contacts between cells.

Another regulator of TGF-β and BMP signaling is the liver kinase B1 (LKB1). According to GBM patient mRNA analysis, high levels of LKB1 correlate with poor prognosis. Silencing of LKB1 in GSCs impairs invasion and self-renewal capacity due to downregulation of genes involved in these processes. Moreover, loss of LKB1 induces mitochondrial dysfunction, leading to decreased ATP levels. Collectively, this thesis has delivered a group of novel regulatory pathways that control critical aspects of cancer cell polarity, invasion and stemness.

*Keywords*: Cancer, cancer stem cells, invasion, metastasis, polarity, TGF-β signaling.

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