Antagonism or synergy between BMP and TGFβ pathways in cancer

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Transforming growth factor β (TGF-β) promotes epithelial-mesenchymal transition (EMT), tumor cell invasiveness, cancer stemness and metastasis. Bone morphogenetic protein (BMP) signaling can also induce EMT, yet relates more frequently to differentiation of diverse tissues, including cancer stem cells (CSCs). Our work focuses on glioblastoma multiforme, a brain malignancy characterized by high heterogeneity, invasiveness, and resistance to current therapies, attributes related to the occurrence of CSCs. We also examine the role of long non-coding RNAs (lncRNAs) downstream of TGFβ and BMP signaling.

After screening for lncRNAs, whose expression is regulated by TGF-β signaling, we focused on TGFB2 antisense RNA 1 (TGFB2-AS1), which is induced by TGF-β. RNA in situ hybridization revealed a predominant nuclear localization of TGFB2-AS1. Depletion of TGFB2-AS1 enhanced TGF-β and Smad-mediated transcriptional responses. On the other hand, cells stably over-expressing TGFB2-AS1 showed marked reduction in several BMP ligands and signaling mediators. We have identified a novel TGF-β-target lncRNA with an inhibitory role on BMP and TGF-β signaling output, suggesting that TGFB2-AS1 is part of an auto-regulatory negative feedback loop that balances BMP- and TGF-β-mediated responses.

In the context of glioblastoma multiforme, we demonstrated that BMPs induce the transcription factor Snail to promote astrocytic differentiation in CSCs and suppress tumor growth in vivo. Snail interacts with Smad signaling mediators, generates a positive feedback loop of BMP signaling and transcriptionally represses the TGFβ1 gene, decreasing TGFβ1 signaling activity. Exogenous TGFβ1 counteracts Snail function in vitro, and in vivo promotes proliferation and re-expression of Nestin, confirming the importance of TGFβ1 gene repression by Snail. Our work explains in molecular detail how transcription factors such as Snail and lncRNAs provide coordinated control of gene expression, thus promoting cancer stemness and tumor invasiveness, while suppressing beneficial signaling actions in the context of tumor differentiation, mainly driven by BMPs.
SCIENTIFIC BIOSKETCH

Born in Greece, got a Bachelor's degree in Biology at the Aristotelian University of Thessaloniki, Greece, earned his Ph. D. in Genetics at the University of Minnesota, USA, and joined the laboratory of Dr. Harvey Lodish at the Whitehead Institute for Biomedical Research/MIT in Cambridge, USA, where he began to investigate the transforming growth factor β (TGFβ), a cell-to-cell signaling protein that regulates a wide spectrum of biological processes.

He moved to the University of Crete at Heraklion as adjunct Assistant Professor in 1996 and to Sweden in 1998 where he joined the Ludwig Institute for Cancer Research-Uppsala Branch as an Assistant Member. He became Associate Member in 2004 and Full Member in 2010, when he also received a prestigious Senior Investigator position by the Swedish Cancer Society. In 2010 he also became affiliated with the Dept of Medical Biochemistry and Microbiology at Uppsala University, where he currently is a Professor.

In Uppsala he established the TGFβ Signaling Group in 1999 and his second laboratory, Signal Transduction and Epithelial Plasticity at the Dept of Medical Biochemistry and Microbiology in 2012, which today include fourteen members of eight different nationalities researching on signal transduction and cancer biology.

RESEARCH FOCUS

Aristidis Moustakas is a molecular and cell biologist with special expertise in signal transduction and cell differentiation. He studies these biological processes in the context of cancer. This approach generates significant opportunities for the generation of new methods of treating cancers, collectively called differentiation therapy methods.

More specifically his research focuses on some of the major signal transduction pathways, namely the transforming growth factor β (TGFβ) and the related bone morphogenetic protein (BMP) pathway, which play central roles in controlling the differentiation of many cell types. The TGFβ/BMP pathways also take central stage in the progression and ultimate metastasis of essentially all cancers. His research scans several tumor types, breast, lung, liver and brain cancer, aiming at uncovering common, general principles that drive the behavior of these tumor types. His research group gradually maps the complex signaling routes and their connections to transcription factors and gene networks that orchestrate the behavior of malignant cells.

MAJOR RECENT RESEARCH CONTRIBUTIONS (2015-18)

Epithelial-mesenchymal transition (EMT) has become a central aspect of basic cancer research. Following our pioneering work (1999-2010) on TGFβ
signaling and EMT, we have recently explained how the chromatin protein HMGA2 (high mobility group A2) acts as a central regulatory node that orchestrates the EMT and the ability of tumor cells to generate cancer stem cells. Our effort to generate drugs that inhibit the EMT brought us, through serendipity, to the understanding that nuclear receptors, such as LXRα, well known for regulating liver metabolism and lipid homeostasis, they also act by limiting the EMT and protecting from the pro-tumorigenic actions of fibroblasts.

The bone morphogenetic protein (BMP) pathway has been proposed to eradicate the cancer stem cells of glioblastoma multiforme (GBM). GBM is a group of brain tumors that present notorious difficulty in terms of treatment. BMPs have been proposed as differentiation therapy against GBM. Our work has placed the transcription factor Snail as a central mediator of the action of BMPs in GBMs. We now understand that although BMP-mediated differentiation therapy can work in terms of eradicating partially cancer stem cells, Snail acting downstream of BMPs explains why BMPs also promote invasiveness of the tumor cells, which is a strong and undesirable adverse effect.

**SELECTED PRIMARY PUBLICATIONS (2015-18)**


