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Commentary

Function of Transforming Growth Factor β (*TGF-β*) in the Development of Cancer Cells

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DESCRIPTION

The Bone Morphogenetic Proteins (BMPs), activins, and other members of the Transforming Growth Factor β (*TGF-β*) family are secreted cytokines that play important roles in tissue homeostasis and embryonic development. Perturbation of these cytokine's functions can result in a number of illnesses, including cancer. Specific transmembrane type I and type II serine/threonine kinase receptors and intracellular SMAD transcriptional effector proteins are used by members of the *TGF-β* family to communicate.

The cell surface ligand-receptor complex's type I receptors, which are phosphorylated by type II kinases, control the specificity of the signaling. In contrast to *TGF-β* and activin type I receptors, which signal via SMAD2 and SMAD3 and two Receptor-regulated SMADs (R-SMADs), respectively, BMP type I receptors (ALK1, ALK2, BMPRIA or ALK3, and BMPRIB or ALK6) directly phosphorylate three R-SMADs, namely SMAD1, -5, and -8, at their C-terminus. In the presence of the common mediator SMAD4, activated R-SMADs assemble into Smad complexes, which then build up inside the nucleus. To control particular gene transcriptional responses, they collaborate with transcriptional co-activators/co-repressors and epigenic regulators. *TGF-β* family receptors can communicate outside of the established SMAD signaling pathway.

Members of the *TGF-β* family of cytokines are multifunctional and their effects are greatly influenced by the cellular environment. Members of the *TGF-β* family have been linked to both tumor-suppressing and tumor-promoting effects in cancer. Of all the members of its family, *TGF-β* has been the subject of the greatest research. Many of the *TGF-β* related observations probably also apply to other family members (with some variations). *TGF-β* limits cell proliferation, triggers apoptosis, and aids in genome integrity in normal cells, pre-malignant tumor cells, and even some malignant tumor cells.

When receptors or SMADs develop mutations or other forms of dysfunction, cancer cells may become resistant to these tumor suppressive activities. These cells could expand out of control as a result. Aside from becoming resistant to *TGF-β* induced cytostatic and pro-apoptotic effects, advanced cancer cells that have their proto-oncogenes and tumor suppressor genes activated or inactivated may also use the SMAD pathway to stimulate pro-oncogenic effects, such as inducing the Epithelial-to-Mesenchymal Transition (EMT) program and thereby promoting cancer cell invasion and metastasis.

Additionally, in addition to cancer cells, host cells have a great capacity for secreting *TGF-β*, which not only affects cancer cells but also cells in the tumor microenvironment, promoting tumor angiogenesis and immune evasion. Despite efforts by numerous academic and commercial laboratories to target *TGF-β* signaling by preventing *TGF-β* receptor contact or decreasing receptor kinase activity for cancer therapy, no *TGF-β* inhibitor has yet received clinical approval. This is partially explained by the fact that the inhibitors used in clinical trials do not work in a cell type-specific manner and have on-target harmful side effects when given systemically.

However, there has recently been a renewed interest in targeting this route by (selectively) inhibiting the *TGF-β* induced immune suppression since it may make immune checkpoint inhibitor therapy more effective. The varied role that *TGF-β* members play therein is further explored in new paths for future research. We hope that fundamental and translational research efforts will soon result in the clinical approval of a medication that targets a member of the *TGF-β* family for the treatment of particular cancer subtypes.

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