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New Strategies to Target the TGF-β/Smad Signaling Pathway in Cancer

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Description

The Transforming Growth Factor (TGF)-β signaling pathway governs key cellular processes under physiologic conditions and is deregulated in many pathologies, including cancer. TGF-β is a ubiquitous, multifunctional cytokine secreted by nearly all cell types that binds transmembrane TGF-β type I and II receptors to activate downstream pathways through intercellular SMAD transcriptional effectors.

Deregulated inter-and intracellular TGF-β signaling contributes to cancer initiation and progression. In healthy cells and early stage cancers, TGF-β arrests epithelial growth and functions as a tumor suppressor. Later, after cancers have progressed, the cytostatic effects of TGF-β are circumvented, and TGF-β signaling exerts tumor promoting activities. TGF-β has been shown to induce epithelial-to-mesenchymal transition, stimulate angiogenesis, and contribute to immune evasion [1-3]. Collectively, the pleiotropic nature of TGF-β signaling contributes to drug resistance, tumor escape and undermines clinical response to therapy. Thus, based upon a wealth of preclinical and translational studies, the TGF-β signaling pathway has emerged as a highly attractive, actionable target that can be pharmacologically modulated to reduce tumor growth and improve the outcomes of cancer patients. Here, we comment on recent exciting and highly promising strategies that have been employed to target the TGF-β signaling pathway.

Recently, we evaluated the safety and efficacy of a number of TGF-β pathway antagonists from multiple drug classes that have been developed or are being evaluated in clinical trials with cancer patients [3]. Vactosertib is a highly promising and potent small molecule TGF-β type 1 receptor kinase inhibitor that is well-tolerated in patients and demonstrates an acceptable safety profile. Importantly, Vactosertib demonstrateseefficacyagainst multiplecancertypes, includingthe plasma cell malignancy Multiple Myeloma (MM). TGF-β supports myeloma progression through its role in stimulation of IL-6, the development of Th17/regulatory T cells, hematopoietic suppression, and promotion of catabolic bone remodeling [4]. Proteasome inhibitors have emerged as standard-of-care therapy for MM patients and remarkably improved quality-of-life and overall survival [5]. However, despite recent therapeutic advances, MM patients frequently develop drug resistance which contributes to poor outcomes. Vactosertib suppresses the viability of MM cells, is associated with a potent anti-myeloma effect, suppresses bone resorption and modulates the tumor microenvironment in immunocompetent models [6]. These data provided a rationale for clinical evaluation of the combination therapy of Vactosertib and the proteasome inhibitor ixazomib as a potential therapeutic strategy to improve outcomes in patients with MM [7]. Preclinical studies in the syngeneic 5T33MM immunocompetent mouse model also assessed the efficacy of Vactosertib single agent activity as well as synergistic activity with the third generation immunomodulatory drug, pomalidomide. Promising results from these studies prompted a corticosteroid-free phase I clinical trial to test the safety and efficacy of this combination in relapsed and/or refractory MM patients (NCT03143985).

The TGF-β pathway has also been pharmacologically targeted using small molecule inhibitors, TGF-β-directed chimeric monoclonal antibodies, ligand traps, antisense oligonucleotides and vaccines that have been now or are now being evaluated in clinical trials. Bintrafusp alfa is a TGF-β ligand trap that consists of a bifunctional conjugate that binds TGF-β and PD-L1 [8]. AVID200 is a computationally designed trap of TGF-β receptor ectodomains fused to an Fc domain [9]. Luspatercept is a recombinant fusion that links the activin receptor IIb to IgG and offers new ways to fight difficult-to-treat cancers [10].

Conclusion

In summary, many exciting TGF-β pathway antagonists are rapidly emerging as highly promising, safe and effective anticancer agents. However, significant challenges remain. Minimizing the unintentional inhibition of tumor-suppressing activity and inflammatory effects with the desired restraint on tumor-promoting activities still impedes clinical development of TGF-β pathway antagonists. A better understanding of the mechanistic details of the TGF-β pathway should lead to more effective TGF-β antagonists and uncover biomarkers that better stratify patient selection, improve patient responses and further the clinical development of TGF-β antagonists.

Author Contribution and Disclosures

JJD and BGK wrote the commentary. The authors disclose no conflicts to disclose.

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