Paradoxical TGF β and Therapeutic Strategies

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Editorial

Transforming growth factor beta (TGFβ) signaling pathway is one of the key players during embryogenesis and maintaining tissue homeostasis [1]. Activated TGFβ binds to its receptor and regulates transcription, translation, miRNA biogenesis, protein synthesis and post-translational modifications through canonical SMAD and non-SMAD pathways ultimately mediating cell proliferation, differentiation, apoptosis, adhesion, invasion and cellular micro-environment [2-4]. Alterations in TGFβ signaling lead to tumor initiation and progression. For over three decades of research since its discovery, researchers found that TGFβ has diverse and contrasting functions as tumor suppressor and tumor promoter [5,6]. One of the key mechanisms by which TGFβ elicits its tumor suppressive functions is by simultaneously inhibiting the CDK functions and eliminating proliferative drivers [7]. However, it has to be noted that TGFβ is not a universal proliferation regulator and exerts its anti-proliferative actions depending upon the context [6]. It has been shown that it is a powerful growth inhibitor in cells that lack either p15Ink4b or the c-Myc response alone and results in effective evasion of cytostasis upon combined loss of these two genes [8-11]. Cancer cells that bypass the anti-proliferative effect of TGFβ take advantage of its immunosuppressive, pro-angiogenic and epithelial-mesenchymal transdifferentiation in order to establish and gain control over the surrounding cellular environment [12-14]. Evidence from several animal studies implicated that it has also a role in bone and lung metastasis [15,16].

Several studies showed that TGFβ can have potent tumor suppressive properties in early stages of cancer but switches to tumor promoting nature at later stages [17-19]. Therefore therapies targeting TGFβ should be cautious as the timing of the treatment is very critical. However, the precise molecular mechanisms determining when the TGFβ switches from a tumor suppressor to promoter poses a great challenge in the field. Recent studies have showed that host immune cells play a critical role in switching the activity of TGFβ [20,21]. Genetic abrogation of TGFβ signaling specifically in myeloid cells resulted in reduction of bone and lung metastasis in an in vivo mouse model system [20,21]. These two studies have unequivocally suggested that specific targeting of TGFβ signaling in myeloid cells reduces tumor metastasis.

Currently, multiple drugs have been developed targeting TGFβ. The three major approaches that took into consideration while designing the drugs include: prevention of TGFβ synthesis (using antisense molecules), inhibition of binding to cell membrane receptor (using neutralizing monoclonal antibodies or trapping TGFβ ligand with soluble receptors), and inhibition of receptor mediated signaling (TGFβ receptor kinase inhibitors) [6]. As mentioned before, considering the contrasting functions of this cytokine, the judgment has to be made since it could dramatically alter the outcome of patient survival.

Although, there are hints suggesting that specific targeting of TGFβ signaling in myeloid cells could reduce the tumor metastasis, further studies have yet to perform to develop myeloid specific targeting of TGFβ neutralizing antibodies or TGFβ blockers that could rescue tumor metastasis.

References


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