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Editorial Open Access

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 cytostatis 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

1. Massagué J (2008) TGFbeta in Cancer. Cell 134: 215-230.
2. Hata A, Davis BN (2009) Control of microRNA biogenesis by TGFbeta signaling pathway-A novel role of Smads in the nucleus. Cytokine Growth Factor Rev 20: 517-521.
3. Mu Y, Gudey SK, Landström M (2012) Non-Smad signaling pathways. Cell Tissue Res 347: 11-20.
4. Ellenrieder V (2008) TGFbeta regulated gene expression by Smads and Sp1/KLF-like transcription factors in cancer. Anticancer Res 28: 1531-1539.
5. Akhurst RJ, Derynck R (2001) TGF-beta signaling in cancer--a double-edged sword. Trends Cell Biol 11: S44-51.
6. Padua D, Massagué J (2009) Roles of TGFbeta in metastasis. Cell Res 19: 89-102.
7. Scandura JM, Boccuni P, Massagué J, Nimer SD (2004) Transforming growth factor beta-induced cell cycle arrest of human hematopoietic cells requires p57KIP2 up-regulation. Proc Natl Acad Sci U S A 101: 15231-15236.
8. Chen CR, Kang Y, Siegel PM, Massagué J (2002) E2F4/5 and p107 as Smad cofactors linking the TGFbeta receptor to c-myc repression. Cell 110: 19-32.
9. Siegel PM, Massagué J (2003) Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. Nat Rev Cancer 3: 807-821.
10. Latres E, Malumbres M, Sotillo R, Martin J, Ortega S, et al. (2000) Limited overlapping roles of P15(INK4b) and P18(INK4c) cell cycle inhibitors in proliferation and tumorigenesis. EMBO J 19: 3496-3506.
11. Chen CR, Kang Y, Massagué J (2001) Defective repression of c-myc in breast cancer cells: A loss at the core of the transforming growth factor beta growth arrest program. Proc Natl Acad Sci U S A 98: 992-999.
12. Thomas DA, Massagué J (2005) TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. Cancer Cell 8: 369-380.
13. Sánchez-Elsner T, Botella LM, Velasco B, Corbí A, Attisano L, et al. (2001) Synergistic cooperation between hypoxia and transforming growth factor-beta pathways on human vascular endothelial growth factor gene expression. J Biol Chem 276: 38527-38535.
14. Miettinen PJ, Ebner R, Lopez AR, Derynck R (1994) TGF-beta induced transdifferentiation of mammary epithelial cells to mesenchymal cells: involvement of type I receptors. 127: 2021-2036.
15. Bandyopadhyay A, Agyin JK, Wang L, Tang Y, Lei X, et al. (2006) Inhibition of pulmonary and skeletal metastasis by a transforming growth factor-beta type I receptor kinase inhibitor. Cancer Res 66: 6714-6721.
16. Yang YA, Dukhanina O, Tang B, Mamura M, Letterio JJ, et al. (2002) Lifetime exposure to a soluble TGF-beta antagonist protects mice against metastasis without adverse side effects. J Clin Invest 109: 1607-1615.
17. Inman GJ (2011) Switching TGFÎ² from a tumor suppressor to a tumor promoter. Curr Opin Genet Dev 21: 93-99.

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18. Wendt MK, Tian M, Schiemann WP (2012) Deconstructing the mechanisms and consequences of TGF-Î²-induced EMT during cancer progression. Cell Tissue Res 347: 85-101.

19. Roberts AB, Wakefield LM (2003) The two faces of transforming growth factor beta in carcinogenesis. Proc Natl Acad Sci U S A 100: 8621-8623.

20. Meng X, Vander Ark A, Lee P, Hostetter G, Bhowmick NA, et al. (2015) Myeloid-specific TGF-Î² signaling in bone promotes basic-FGF and breast cancer bone metastasis. Oncogene.

21. Pang Y, Gara SK, Achyut BR, Li Z, Yan HH, et al. (2013) TGF-Î² signaling in myeloid cells is required for tumor metastasis. Cancer Discov 3: 936-951.