Two sides of the same coin: the roles of TGF-β in colorectal carcinogenesis

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Dear Editor,

We read with great interest the article by Gu et al[1]. which investigated the impaired TGF beta signalling and its link with carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family and microbiome in colorectal carcinogenesis (CRC). The authors found that TGF-β signaling-deficient mice spontaneously developed adenomas and CRC with altered health microbiome in the gut. Moreover, the authors found that overexpression of CEACAM promoted cell proliferation and colony formation via inhibition of TGF-β pathway activity. Intriguingly, the authors showed that the stemness of CRC was inversely correlated with the TGF-β pathway activity, which is different with the scenarios in breast cancer, liver cancer, gastric cancer, skin cancer, glioblastoma and leukemia showing TGF-β is a positive regulator for cancer stem cell identity [2]. This finding further supports the notion that TGF-β can either work as tumor suppressor or inducer depending on different contexts (e.g. TGF-β is a tumour suppressor in normal tissue and early cancer cells, while TGF-β frequently plays a pro-tumorigenic role in advanced stage of cancer)[3]. For example, TGF-β can promote epithelial-to-mesenchymal transition (EMT), cell proliferation, promote metastasis and suppress the immune response, which are critical for cancer progression. Furthermore, TGF-β maintains the self-renewal and pluripotency of human embryonic stem cells, and has been similarly implicated in promoting the stem cell-like characteristics of cancer stem cell by promoting their self-renewal and expression of stem cell factors. In other cell types, TGF-β signalling can induce cell cycle arrest by upregulating cyclin-dependent kinase inhibitors, induce apoptosis, regulate autophagy and suppress inflammation[3]. Considering this dual function of the pathway, cellular heterogeneity and dynamics of colorectal cancer stem cells[4], it will be interesting to compare the activity and functionality of TGF-β signalling pathway in the cancer stem cells from primary and metastatic CRC.

The multitude, contrasting and context-dependent function of TGF-β signalling pathway makes it also challenging to use as a target for therapeutic applications. Currently, monoclonal antibodies and inhibitors targeting TGF-β have been used in clinical trial (ClinicalTrials.gov Identifier: NCT01291784, NCT00043706, NCT02452008, NCT02581787) to treat myofibrosis, systemic sclerosis, metastatic prostate and non-small cell lung cancer respectively. Considering the difficulty to predict the effects of all TGF-β blocking from the current strategies, especially the potential CRC risk inferred from the study by Gu et al, it might be important to monitor the gut microbiome and incidence of CRC in the patients during long-term follow up.

Moreover, as TGF-β is a critical regulator in the balancing of tolerance and response of the gut immune system[5], the impact of anti-TGF-β therapy on the immune homeostasis of the gut should not be overlooked.

Mechanistically, the pleiotropic nature of TGF-β signalling pathway may largely rely on the interaction partners of Smad2/3 transcription factors and the functionality of Smad4 in the TGF-β pathway. For example, FoxH1, ID1 or other cofactors that can facilitate the activation of specific transcriptional programs to enhance the pro-tumorigenic arm of TGF-β signalling (e.g. upregulation of stem cell factors and developmental plasticity of cancer stem cells, stimulation of EMT, cell migration, angiogenesis, chemoresistance, immune-suppressive functions etc.) while removing its anti-tumorigenic arm (e.g. induction of cell cycle arrest, apoptosis, autophagy, tissue inflammation etc.)[6]. Thus, in the future, it will be vital to specifically manipulate the downstream signaling interaction partners/cofactors of the TGF-β other than non-selective targeting of the whole TGF-β signalling pathway with its multiple branching signalling cascades and locus-specific functions of Smad2/3 with its transcriptional cofactors and epigenetic regulators. Moreover, by integrating the development of novel cell delivery approaches (e.g. CELL-SELEX[7], engineered exosomes[8]), it will be possible to achieve cell-type specific TGF-β targeting and provides long-term effectiveness and safety in clinical practise.

References

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