Tumour promoting functions of TGF-β in CML-initiating cells

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Recent data have shown that transforming growth factor-β (TGF-β) plays bi-directional roles in the maintenance of cancer stem cells in a cell-type and context-dependent manner. Zhu et al. (TGF-β1-induced PI3K/Akt/NF-κB/MMP9 signalling pathway is activated in Philadelphia chromosome-positive chronic myeloid leukaemia hemangioblasts. J. Biochem. 2011;149:405–414) studied the functions of TGF-β in hemangioblasts from patients with chronic myeloid leukemia (CML), which displayed properties of leukemia-initiating cells. They have shown that the BCR/ABL oncoprotein induced the production of TGF-β in the CML hemangioblasts, and that TGF-β activated the phosphoinositide 3-kinase-Akt-NF-κB pathway in these cells. Activation of this pathway enhanced the production of matrix metalloproteinase-9 leading to increased synthesis of soluble Kit ligand and intercellular adhesion molecule-1. TGF-β is known to maintain the CML-initiating cells through the Akt-FoxO pathway. Together, these findings suggest that TGF-β may exhibit multiple functions in progression of CML through acting on leukemia-initiating cells.

Keywords: Akt/cancer stem cell/CML/MMP-9/TGF-β.

Abbreviations: CML, chronic myeloid leukemia; EMT, epithelial–mesenchymal transition; HTLV, human T-cell leukemia virus; MMP, matrix metalloproteinase; PI3K, phosphoinositide 3-kinase; s-ICAM-1, soluble intercellular adhesion molecule-1; s-KitL, soluble Kit ligand; TGF-β, transforming growth factor-β.

Transforming growth factor-β (TGF-β) is a multifunctional cytokine that regulates growth, differentiation, apoptosis and migration of various types of cells (1,2). TGF-β functions as a potent growth inhibitor for epithelial cells, endothelial cells, hematopoietic cells and lymphocytes, and thus, perturbations of TGF-β signalling result in progression of certain cancers, such as colorectal cancer and pancreatic cancer. Epithelial–mesenchymal transition (EMT) plays critical roles in invasion and metastasis of cancer, and TGF-β induces EMT in certain epithelial cells (3,4). TGF-β also induces angiogenesis in vivo and regulates immune cell functions at the advanced stages of cancer. Therefore, TGF-β plays both tumour suppressing and promoting functions in the development of cancer (5). In human acute leukemias, expression of certain oncoproteins in leukemia cells interferes with the growth inhibitory activity of TGF-β (6). The oncoprotein Evi1, which is responsible for the development of certain acute leukemia and other cancers, has been reported to repress TGF-β signalling and antagonize the growth inhibitory activity of TGF-β (7). The oncoprotein Tax from human T-cell leukemia virus-1 (HTLV-1) also represses TGF-β signalling through interaction with Smad2, 3 and 4 and by activation of c-Jun (8,9), although a recent report suggested the HTLV-1 basic region leucine zipper factor enhances TGF-β signalling through transcriptional co-activator p300 and enables HTLV-1 to convert T cells into regulatory T cells (10).

Chronic myeloid leukemia (CML) is a clonal hematopoietic cell disorder. Chromosomal translocation and formation of the BCR/ABL fusion gene are characteristically observed in this disorder. As the BCR/ABL fusion protein is a constitutively activated tyrosine kinase, inhibitors for the ABL kinase are effective and widely used in the treatment of chronic-phase CML patients. Zhu et al. (11) investigated the functions of TGF-β in hemangioblasts obtained from individuals with CML. The hemangioblasts from CML patients showed fibroblast-like morphology and contained the BCR/ABL fusion gene. The CML hemangioblasts expressed Flk1, CD29, CD44 and CD105 fusion gene. The CML hemangioblasts produced high levels of matrix metalloproteinase-9 (MMP-9), soluble Kit ligand (s-KitL) and soluble intercellular adhesion molecule-1 (s-ICAM-1) when compared with normal controls (11). The induction of mRNAs and proteins of s-KitL and s-ICAM-1 was dependent on the increase in MMP-9 because knockdown of the expression of MMP-9 resulted in the decrease in production of them. Interestingly, the CML hemangioblasts expressed higher levels of TGF-β1 than normal control, but the levels of expression of TGF-β2 or TGF-β3 were not significantly different between CML and control hemangioblasts. Imatinib, an inhibitor of the ABL tyrosine kinase, suppressed the production of TGF-β1 in the CML hemangioblasts, suggesting that the BCR/ABL oncoprotein upregulated the production of TGF-β1 (Fig. 1). Moreover, treatment of the CML hemangioblasts with TGF-β1 increased the production of MMP-9, s-KitL and s-ICAM-1. MMP-9 has been suggested to play versatile roles in the progression of CML (12). Increase in the s-ICAM-1 synthesis results...
in prevention of the recognition by T lymphocytes and natural killer cells, and that in the s-KitL synthesis leads to mobilization of CML cells to the peripheral circulation. Thus, TGF-β1 induced by the BCR/ABL oncoprotein may be responsible for these processes during progression of CML.

The TGF-β family proteins, such as TGF-βs, activins and bone morphogenetic proteins, transduce signals through binding to two different types of serine–threonine kinases, termed type II and type I receptors. Activated TGF-β family receptors transduce signals through Smad proteins, which, upon activation by type I receptors, move into the nucleus and regulate the transcription of target genes in cooperation with various transcription factors and transcriptional co-activators and/or co-repressors (13). In addition to the Smad signalling pathways, TGF-β also activates non-Smad signalling pathways, including Erk, JNK and p38 MAP kinase pathways, and the phosphoinositide 3-kinase (PI3K)-Akt pathway (14). Zhu et al. have shown that TGF-β activated the PI3K-Akt pathway in the CML hemangioblasts (15). The PI3K-Akt pathway then led to the activation of IKKα and degradation of 1κB, resulting in the activation of NF-κB. Since the inhibitors for PI3K, Akt or NF-κB suppressed the synthesis of MMP-9, the PI3K-Akt-NF-κB cascade may be responsible for this process. They have also shown that HSc025, an inhibitor of TGF-β-Smad signalling through the activation of nuclear translocation of Y-box binding protein 1 (16), failed to inhibit the effect of TGF-β on the induction of MMP-9. Thus, non-Smad signalling pathways may be important for the induction of MMP-9 by TGF-β, although it would still be interesting to knockdown the expression of Smad proteins to determine whether the activation of Smad signalling is involved or not in the production of MMP-9 in the CML hemangioblasts.

Other investigators have also reported that TGF-β signalling is a crucial pathway for maintenance of leukemia stem cells in CML. Naka et al. reported that TGF-β regulates the activation of Akt and localization of the forkhead O transcription factor FoxO3a in CML-initiating cells (16). They have further shown that the TGF-β-Akt-FoxO pathway plays an important role in the maintenance of the stem cell-like properties and tumorigenic activities of CML. Although discovery of imatinib is a breakthrough for CML therapy, imatinib is not able to completely eradicate the CML stem cells. Naka et al. proposed that a combination of TGF-β inhibition/FoxO3a depletion and imatinib treatment may lead to the efficient depletion of CML cells (17). The present findings by Zhu et al. (11) have further indicated the importance of TGF-β-Akt pathway for the progression of CML.

Conflict of interest
None declared.

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