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Review

The clinical and biological roles of transforming growth factor beta in colon cancer stem cells: A systematic review

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ABSTRACT

Background: Transforming growth factor beta (TGF-β) is a multipurpose cytokine, which plays a role in many cellular functions such as proliferation, differentiation, migration, apoptosis, cell adhesion and regulation of epithelial to mesenchymal transition. Despite many studies having observed the effect that TGF-β plays in colorectal cancer, its role in the colorectal stem cell population has not been widely observed.
Method: This systematic review will analyse the role of TGF-β in the stem cell population of colorectal cancer.
Results: The effects on the stem cell phenotype are through the downstream proteins involved in activation of the TGF-β pathway. Its involvement in the initiation of the epithelial to mesenchymal transition (EMT), the effect of colorectal invasion and metastasis regulated through the Smad protein involvement in the EMT, initiation of angiogenesis, promotion of metastasis of colorectal cancer to the liver and its ability to cross-talk with other pathways.
Conclusion: TGF-β is a key player in angiogenesis, tumour growth and metastasis in colon cancer.

1. Introduction

There are two kinds of transforming growth factors, transforming growth factor (TGF) alpha and beta. TGF-α plays an important role in cell proliferation, differentiation and development through binding to the epidermal growth factor receptor, and belongs to the epidermal growth factor family (Zhao et al., 2014). It could play a role in pathogenesis in cancer (Ak et al., 2011).

The transforming growth factor beta (TGF-β) is a pleiotropic cytokine with the ability to affect a range of biological functions and activities such as regulating inflammatory and cell cycle responses (Pokharel et al., 2016). TGF-β belongs to a superfamily consisting of over thirty proteins including activins, inhibins, bone morphogenetic proteins (BMP), and differentiation and growth factors (Abetov et al., 2015; Katz et al., 2016). The pathway is one the most commonly altered signalling pathways in human cancers (Mishra et al., 2009; Roy and Majumdar, 2012). There are three isoforms of TGF-β in mammalian cells, including the most abundant TGF-β1, and more rare ones: TGF-β2 and TGF-β3 (Katz et al., 2016). In normal cellular microenvironment, TGF-β regulates immune and inflammatory responses (Pokharel et al., 2016). Also, it acts as a tumour suppressor through its ability to inhibit cell proliferation and instigate apoptosis by targeting downstream cell-cycle checkpoint genes (Abetov et al., 2015; Buhrmann et al., 2014; Katz et al., 2016; Roy and Majumdar, 2012; Saif and Chu, 2010; Stelzner et al., 2012; Thenappan et al., 2009; Yu et al., 2012).

The TGF-β signalling pathway plays important roles in many cellular functions. These may include cellular proliferation, differentiation, migration, apoptosis, cell adhesion, regulation of the epithelial to mesenchymal transition (EMT) and maintenance of stemness (Abetov et al., 2015; Bach et al., 2000; Buhrmann et al., 2014; Roy and Majumdar, 2012; Saif and Chu, 2010; Sipos and Galamb, 2012; Thenappan et al., 2009; Yu et al., 2012; Zhai et al., 2015). These processes result from the sequential activation of various components of the TGF-β pathway leading to regulation of gene expression.

Despite the emerging evidence of TGF-β regulated molecular carcinogenesis, its roles in colon cancer stem cells is still unclear. This review aims to analyse the role of TGF-β and its pathway in the colon stem cell population.

2. Methodology

A systematic review of journal articles published in PubMed between 1992 and 2016 was utilised for this review. The search terms included: *TGF-beta, colorectal, colon, stem cell, tumour initiating cells*. Eighty-six articles were found using these search terms. Studies not focusing on TGF-β, stem cells or colorectal cancer were excluded from analysis. There have been very few studies (n = 5) which observe the role of TGF-β in the colorectal stem cell population. Their findings

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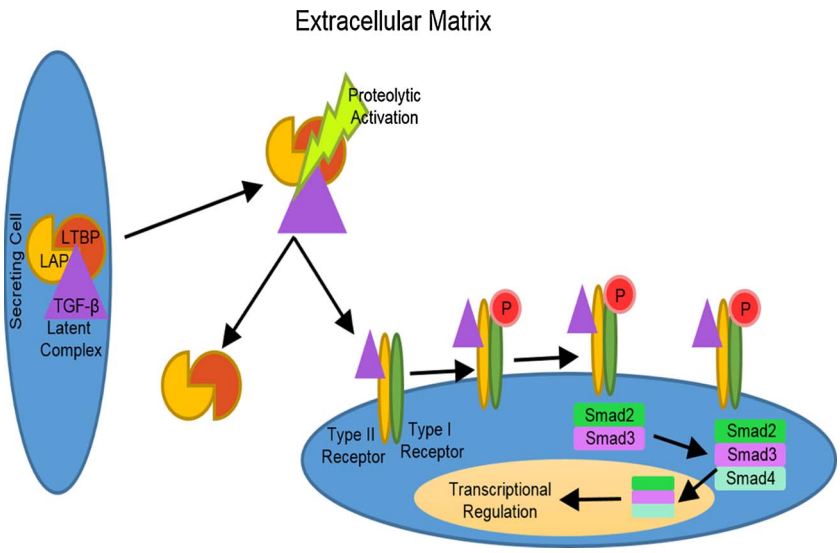

Fig. 1. Activation of TGF-beta protein: The latent complex comprised of three proteins, LAP: latency-associated peptide; LTBP: latent TGF-β binding protein, TGF-β: transforming growth factor beta is secreted via the cell into the extracellular matrix. Following proteolytic activation, the TGF- β cytokine is released from the latent complex and activated. The active TGF- β protein binds with the Type II TGF- β receptor, which then recruits and phosphorylates (P) the Type I TGF-β receptor. The active complex recruits and phosphorylates the Smad2 and Smad3 proteins that form a hetero-oligomeric complex with Smad4 protein. The active complex moves into the nucleus where it interacts with transcriptional factors to regulate gene expression.

indicate that TGF-β plays an important role in regulating the stem cell phenotype, epithelial-to-mesenchymal transition (EMT), invasiveness and migration, angiogenesis, tumour growth and metastasis and cell signalling.

3. Secretion and activation of TGF-β and its pathway

The TGF-β cytokine is secreted from cells as a latent complex between TGF-β, latency-associated peptide (LAP) and latent TGF-β binding protein (LTBP) and is activated through its detachment from the complex by proteolytic activation and integrin binding (Barcellos-Hoff and Dix, 1996; Dietzel et al., 2017) (Fig. 1). The active TGF-β molecules initiate the signal cascade upon binding with TGF-β serine/threonine kinase receptors, Type I and Type II, which form a transmembrane complex responsible for protein phosphorylation. The complex is activated through the binding of TGF-β to the type II receptor, activating the TGF-β receptor II protein (TGFBR2) which is responsible for the recruitment and phosphorylation of the TGF-β type I receptor (Abetov et al., 2015; Hasson et al., 2014; Katz et al., 2016; Roy and Majumdar, 2012; Saif and Chu, 2010; Thenappan et al., 2009; Yu et al., 2012; Zubeldia et al., 2013). This active complex stimulates the Smad proteins, which are responsible for TGF-β signalling pathway regulated gene transcription. There are three classes of Smad proteins including receptor-activated Smads (R-Smads), co-mediator Smads (co-Smads) and inhibitory Smads (i-Smads) (Katz et al., 2016; Mishra et al., 2009). TGF-β type I receptor phosphorylates Smad2 and Smad3 proteins (R-Smads), which lead to the emergence of an active hetero-oligomeric complex with the Smad4 (co-Smad) protein (Abetov et al., 2015; Bach et al., 2000; Buhrmann et al., 2014; Hasson et al., 2014; Katz et al., 2016; Roy and Majumdar, 2012; Saif and Chu, 2010; Yu et al., 2012).

The active hetero-oligomeric complex moves into the nucleus where it interacts with transcriptional factors. These factors include c-jun, p300/CPB, c-myc, cyclin D1, cyclin-dependent kinase 4, CDK-interacting protein 1 (p21), cyclin-dependent kinase inhibitor 1B (p27Kip1), cyclin-dependent kinase 4 inhibitor B/multiple tumour suppressor 2 (p15), retinoblastoma protein (Rb), integrins, E-cadherin, collagen and other DNA-binding proteins (Abetov et al., 2015; Buhrmann et al., 2014; Katz et al., 2016; Roy and Majumdar, 2012; Saif and Chu, 2010) (Fig. 1). This interaction of the hetero-oligometric complex leads to regulation of gene expression and plays a role in determining the fate of the stem cells (Di Benedetto et al., 2015; Dutta et al., 2016; Huynh et al., 2016; Kanatsu-shinohara et al., 2016; Lee et al., 2013; Oh et al., 2016; Xie et al., 2017).

4. TGF-β and maintenance of tumour microenvironment

The tumour microenvironment plays a key role in the initiation, progression and metastatic potential of a tumour (Shen et al., 2017). A recent study has noted that the tumour microenvironment increases the interaction between cancer cells and TGF- β (Shen et al., 2017). Furthermore, the endogenous TGF-β has been shown to play a role in the promotion of tumour progression through its ability to subdue the innate immune response (Owyang et al., 2017). Interestingly, lowering the level of TGF-β below its minimum leads to the improvement of T cell-dependent immunity against cancer, while its overexpression may stimulate tumour growth suggesting that the tumour suppressive/oncogenic properties of TGF-β is dependent on the immune system (Owyang et al., 2017). The interlaced contact between anti-tumour T cells and regulatory T cells within the tumour microenvironment has been shown to hinder the cancer targetting immune cells in a TGF-β dependent manner (Budhu et al., 2017).

The ability of TGF-β to act as a tumour suppressor and an oncogenic agent is mediated through the cell to cell communications which take place within the tumour microenvironment (Villalba et al., 2017). Although the direct mechanisms responsible for this occurrence have not yet been identified, it is believed that mutations in the TGF-β signalling pathway and its ability to activate alternative pathways may occur due to high levels of TGF-β within the microenvironment (Villalba et al., 2017). In colon cancer, the tumour microenvironment is altered in high levels of active TGF-β which corrupts the cancer cell and cancer-stroma interactions (Villalba et al., 2017). Moreover, TGF-β has been shown to trigger cancer cells to promote metastatic factors which act upon the tumour microenvironment through the expression interleukin 11, tenascin-C, PTHLH and ANGPTL4 (Villalba et al., 2017).

5. TGF-β and colorectal cancer

Colorectal cancer could evade the tumour-suppressing effects of the TGF-β pathway through the loss of Smad proteins, and by TGF-β type II receptor-mediated cell cycle deregulation (Mishra et al., 2009). TGF-β signalling pathway regulates normal growth of cells in the colonic crypt and villi (Bach et al., 2000). Deregulated activity of TGF-β is frequently observed in colorectal cancers (Bach et al., 2000; Buhrmann et al., 2014; Chandrakesan et al., 2014; Hasson et al., 2014; Kim et al., 2014; Saif and Chu, 2010; Thenappan et al., 2009; Yu et al., 2012; Yusra et al., 2012; Zhai et al., 2015; Zubeldia et al., 2013).

TGF-β signalling pathway is the most commonly altered signalling pathway in human cancers (Roy and Majumdar, 2012; Thenappan