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Review

TGF-β/BMPs: Crucial crossroad in neural autoimmune disorders

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ABSTRACT

Transforming growth factor beta (TGF-β) has a crucial role in the differentiation of ectodermal cells to neural or epidermal precursors. TGF-β and bone morphogenetic protein molecules (BMPs) are involved in many developmental processes, including cell proliferation and differentiation, apoptosis, mitotic arrest and intercellular interactions during morphogenesis. Additionally, the failure of central thymic tolerance mechanisms, leading to T cells with a skewed autoreactive response, is being described as a contributor in inflammatory processes in autoimmune diseases such as multiple sclerosis. Since TGF-β and BMP proteins are crucial for the development of the neural system and the thymus, as well as for the differentiation of T cells, it is essential to further investigate their role in the pathophysiology of this disorder by using references from embryonic experimental research. Available literature in the TGF/BMP signalling cascade, mostly during embryonic development of the nervous system is being reviewed. An attempt is made to further elucidate a potential role of TGF/BMP signalling in the pathophysiology of MS. During demyelination, BMP signaling, through various molecular mechanisms, directs the development of the adult neural stem cell in the astrocyte rather than the oligodendrocyte direction, therefore inhibiting the repair process. Further understanding of the above relationships could lead to the development of potentially efficient therapies for MS in the future.

1. Introduction

The TGF-β family of cytokines contributes to a plethora of different and distinct biologic processes such as cellular growth, differentiation and development as well as immune responses. Based on their structural features the 35 mammalian members of the TGF-β superfamily are divided into (i) TGF-β; (ii) activins/inhibins; (iii) BMPs/growth and differentiation factors (GDFs); (iv) the group of glial cell line-derived neurotrophic factor (GDNF) ligands which are vital to the development and maintenance of neural tissues; (v) decapentaplegic (DPP) which is a key morphogen involved in the development of the fruit fly *Drosophila melanogaster* (*Drosophila* homolog to vertebrate's BMPs); and (vi) Vg1 which was one of the first TGF-β related factors to be identified in vertebrate embryos, as a molecule localized to the vegetal pole of *Xenopus* embryos and involved in mesoderm induction (Weiskirchen et al., 2009).

Especially for the BMP subfamily, 20 members have been identified and have been further classified into several subgroups on the basis of sequence similarities and homology (Botchkarev, 2003). These include BMP2/4, BMP3, BMP5/6/7/8, BMP9/10, BMP11/12/13 and BMP15.

Cellular regulating functions which are critical for the developmental and homeostatic processes of the nervous system are reportedly controlled by the TGF-β (Gomes et al., 2005) and BMP signalling pathways (Christiansen et al., 2000).

In both pathways, the signalling process is initiated at the level of a cell-membrane receptor, which is a complex of single-pass transmembrane receptors that contain an intracellular kinase domain which phosphorylates serine and threonine residues. This receptor complex consists of two distinct transmembrane proteins, known as the type I and II receptors. Ligand binding leads to an unidirectional phosphorylation event in which the type II receptor phosphorylates the type I receptor, thereby activating its kinase domain (Attisano and Wrana, 2002).

A potential role in the differentiation of T cells has been proposed. It is well known that a diverse and self-tolerant population of T lymphocytes which is generated in the thymus and

Abbreviations: CNS, central nervous system; BMP, bone morphogenetic factor; TGF-β, transforming growth factor beta; GDFs, growth and differentiation factors; GDNF, glial cell line derived neurotrophic factor; SME, SMAD-binding elements SBE; XSmad4, *Xenopus* Smad4; R-SMAD, receptor-activated SMAD; CO-SMAD, contributing SMAD; I-SMAD, inhibitory-SMAD; FGF, fibroblast growth factor; SARA, anchor for receptor activation.

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maintained in the peripheral lymphoid organs is the predominant requirement for a functional immune system. The thymus provides the appropriate microenviroment, important for the differentiation of T cells, resulting in a well established maturation procedure. This process involves molecules such as the Hedgehog (Hh) proteins (Sacedon et al., 2003), Wnt proteins (Staal et al., 2001) and BMP2/4 (Cejalvo et al., 2007). The human thymus cortical epithelial cells are the main source of BMP2 and BMP4, while both thymocytes and thymic epithelium express all the molecular machinery required for the response to these proteins. In addition, BMP receptors, BMPRIA and BMPRII, are mainly expressed by cortical thymocytes while BMPRIB receptor is expressed in the majority of the human thymocytes (Cejalvo et al., 2007). Also, treatment with BMP4 on chimeric human-mouse fetal thymic organ cultures seeded with $CD34^+$ human thymic progenitors, result in reduced cell recovery and in the subsequent inhibition of the differentiation of human thymocytes from $CD4^-$ $CD8^-$ to $CD4^+$ $CD8^+$ cell stages, supporting the dominant role of BMP2/4 signalling in human T-cell maturation (Cejalvo et al., 2007).

In addition, it has been reported that, during embryogenesis, BMP signalling is involved in the procedure of the normal thymus development (Revest et al., 2001). The differentiation phase of thymus development is characterized by the interaction of epithelial cells with neural-crest mesenchymal cells, a procedure that is still not fully investigated. This interaction is a common feature in the organogenesis of a plethora of organs involving pleiotropic morphogens such as FGF (Revest et al., 2001) (fibroblast growth factors that serve as key players in the processes of proliferation and differentiation of a wide variety of cells and tissues including angiogenesis, wound healing, and embryonic development), Hh proteins, the role of which has been reported (Shah et al., 2004), and BMP the role of which has been investigated in recent studies (Bleul and Boehm, 2005). According to these, the inhibition of BMP signals by the transgenic expression of Noggin (a signaling molecule involved in neural induction, via inhibition of BMP4, along with other TGF-β signaling inhibitors as well as in neural tube fusion, as proven by mouse knockout experiments (McMahon et al., 1998) results in the formation of dysplastic thymic lobes of drastically reduced size that do not descend to the mediastinum but remain in their embryonic location on the level of the hyoid bone. It appears that it is the thymic stroma that requires uninterrupted BMP signaling for normal development, rather than the thymocytes themselves that develop with normal kinetics in a thymus expressing the BMP antagonist Noggin. Finally, the fact that the expression of Msx-1 and the phosphorylation of Smad 1/5/8 proteins in capsular mesenchymal cells is abolished by the transgenic Noggin, implies that BMP signalling ensures the communication between epithelial and mesenchymal cells (Bleul and Boehm, 2005).

Autoimmune diseases such as multiple sclerosis (MS) (Korn, 2008) are characterized mainly by a failure of central thymic tolerance mechanisms which leads to skewed autoreactive T cells and exacerbat on of the inflammatory process during the progression of the disease. Since BMP proteins are crucial for the development of thymus as well as the differentiation of T cells, the impact of BMP signalling in this imbalance is of great interest. A further elucidation of the causes of immunological disturbances taking place during the progression of MS, the role of TGF-β/BMP signaling and the emergence of a possible switch-regulator factor, that could be utilized as a novel target of future MS therapeutics, is the main goal of this review.

2. Methods

Three authors (R.A., D.K., and K.V.) independently performed the literature search, study selection, and data extraction. The following terms were used in searches of the Entrez-PubMed database (1966–2009): transforming growth factor-beta (TGF-β), bone morphogenetic protein molecule (BMPs), neuronal development, skin development, SMAD proteins, multiple sclerosis, urticaria, and atopic dermatitis. The term SMAD proteins refers to intracellular proteins that serve as signal transducers for the members of the TGF-β superfamily. More specifically extracellular signals from TGF-β ligands are transduced by SMADs to the nucleus where downstream TGF-β gene transcription is further activated (Miyazono, 2000). We also screened articles related to the initially identified publications to expand our data sources.

2.1. TGF-β/BMP and SMAD

The transduction of the TGF-β/BMP signal from the cell surface to the nucleus requires the presence of cytoplasmatic mediators, for the integration of this cascade, like SMAD proteins (Graff et al., 1996). SMAD proteins are vertebrate proteins, products of the Sma and Mad genes and represent components of the signal transduction pathway downstream of the serine-threonine kinase receptors. They interact with the TGF-β/BMP type I receptors to mediate this process. There are 5 different classes of SMAD proteins: (i) R-SMAD proteins [(receptor-regulated SMAD or receptor-associated SMAD) i.e. SMAD proteins that bind directly to TGF-β superfamily type 1 receptors and upon phosphorylation oligomerize with co-activating SMAD protein, and subsequently translocate to the nucleus where the complex directs transcription of downstream target genes.]; (ii) co-SMAD proteins [(cooperating SMAD or co-activating SMAD or C-SMAD) a term referring to a common pathway SMAD protein e.g. SMAD4 that does not become phosphorylated by the TGF-β type 1 receptor]; (iii) I-SMAD proteins [(inhibitory SMAD or anti-SMAD) that downregulate signaling through the TGF-β receptor and block receptor-mediated phosphorylation of R-SMAD proteins such as SMAD6 and SMAD7] (Imamura et al., 1997; Nakao et al., 1997; Zhang et al., 1996); (iv) AR-SMAD proteins (Activin/TGF-β-specific receptor-regulated SMAD proteins that bind to specific receptors for TGF-β and Activins such as SMAD2 and SMAD3); and (v) BR-SMAD proteins (BMP-specific receptor-regulated SMAD proteins that are activated by the BMP type 1 receptor such as SMAD1, SMAD5, SMAD8 and SMAD9). According to the "canonical" pathway of BMP-SMAD (Botchkarev, 2003), R-SMAD proteins (including SMAD1, SMAD2, SMAD3, SMAD5, SMAD8) are directly phosphorylated and activated by the type I receptor. In addition, the activation of R-SMAD is integrated with another protein, the SMAD Anchor for Receptor Activation (SARA). SMAD2 and SMAD3 are phosphorylated and translocated to the nucleus after TGF-β stimulation (Chen et al., 1996; Tsukazaki et al., 1998) (Fig. 1A) while SMAD1/SMAD5/SMAD8 after BMP stimulation (Hoodless et al., 1996; Liu et al., 1996) (Fig. 1B).

Co-SMAD, SMAD4 and SMAD10 (Lagna et al., 1996; LeSueur et al., 2002) form hetero-oligomers with R-SMAD and translocate into the nucleus where they activate the transcriptional process (Hill, 2009) (Fig. 1A and B). More specifically, nuclear SMAD complex can bind to DNA directly through specific DNA sequences, called SMAD-binding elements (SBE) or via cytosine–guanine (CG) regions (Kim et al., 1997; Shi et al., 1998).

SMAD10, also known as *Xenopus* Smad4 (XSmad4), is a recently described SMAD that is structurally similar to SMAD4 (65% homology). Gain-of-function studies have identified the endogenous role of SMAD10. Its function includes developmental processes such as the formation of anterior and posterior neuronal tissue and induction and formation of the mesoderm (Howell et al., 1999; LeSueur and Graff, 1999; Masuyama et al., 1999).

I-SMAD proteins (SMAD6 and SMAD7) (Fig. 1A and B) inhibit the TGF-β/BMP signaling pathway. TGF-β cytokines induce the I-SMAD transcription. I-SMAD down regulates the TGF-β signaling