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Survey

Bone morphogenetic proteins in inflammation, glucose homeostasis and adipose tissue energy metabolism

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ABSTRACT

Bore morphogenetic proteins (BMPs) are members of the transforming growth factor (TGF)-β superfamily, a group of secreted proteins that regulate embryonic development. This review summarizes the effects of BMPs on physiological processes not exclusively linked to the musculoskeletal system. Specifically, we focus on the involvement of BMPs in inflammatory disorders, *e.g.* fibrosis, inflammatory bowel disease, anchylosing spondylitis, rheumatoid arthritis. Moreover, we discuss the role of BMPs in the context of vascular disorders, and explore the role of these signalling proteins in iron homeostasis (anaemia, hemochromatosis) and oxidative damage. The second and third parts of this review focus on BMPs in the development of metabolic pathologies such as type-2 diabetes mellitus and obesity. The pancreatic beta cells are the sole source of the hormone insulin and BMPs have recently been implicated in pancreas development as well as control of adult glucose homeostasis. Lastly, we review the recently recognized role of BMPs in brown adipose tissue formation and their consequences for energy expenditure and adiposity. In summary, BMPs play a pivotal role in metabolism beyond their role in skeletal homeostasis. However, increased understanding of these pleiotropic functions also highlights the necessity of tissue-specific strategies when harnessing BMP action as a therapeutic target.
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1. Introduction

BMPs are large dimeric proteins synthesized and folded in the cytoplasm and cleaved by proteases during secretion. They are highly conserved molecules whose biologically active C-terminal peptide is released into the extracellular compartment to bind membrane receptors on target cells. Ligand binding induces constitutively-active BMP type II receptors to trans phosphorylate the BMP type I receptor which in turn phosphorylates the intracellular BMP effector proteins SMAD1/5/8 whereas TGFβ1 typically activates Smad2 and Smad3 [1–5]. The activated Smads translocate from the cytosol to the nucleus and form complexes with other transcription factors to bind and activate the expression of target genes. "Canonical" signalling appears to mediate the principal effects of BMPs, although activation of other signalling pathways could be crucial in their role in several biological responses including inflammation, glucose regulation and energy metabolism, which will be covered in this review.

2. Bone morphogenetic proteins in inflammation

The role of BMPs in inflammatory disorders includes chronic liver disease, inflammatory bowel disease, iron deficiency anemia, vascular disease, atherosclerosis, rheumatoid arthritis, ankylosing spondylitis, rare bone disorders and implantation of commercially available bone devices containing BMP2 and BMP7 [6].

2.1. BMPs role in inflammatory disorders of the gastrointestinal system

The liver provides a generic model of inflammation and repair, demonstrating an intensive interplay between the epithelial, inflammatory cells and myofibroblasts [7], following intoxication and hepatocyte damage. Fibrogenesis is one of the most prominent pathophysiological processes in a number of chronic diffuse liver diseases including viral hepatitis, fatty liver, autoimmune diseases and alcoholic liver disease [8]. Numerous animal models and human studies showed a correlation between inflammation and fibrosis leading to cirrhosis that is characterized by an excessive extracellular matrix deposition that leads to progressive liver dysfunction. In response to various factors that may cause liver damage, inflammation promotes fibrosis through a number of mechanisms and cell mediators (inflammatory cytokines and chemical neurotransmitters) (Fig. 1). A characteristic feature of inflammation is the activation of hepatic stellate cells (HSCs) to a myofibroblast-like phenotype that is proliferative, fibrogenic and contractile, synthesizing a large amount of ECM components.

There is a close topographical relationship between the site of inflammation and the development of fibrosis *in vivo*. Although there are substantial numbers of leukocytes in the resting liver, injury results in a massive accumulation and contemporaneous activation of resident and recruited inflammatory cells. A variety of signal transduction pathways and cytokines has effects in the development of liver fibrosis such as TGFβ1, BMP7 and Smads [9]. TGFβ1 has been identified as the profibrogenic master cytokine, promoting transition of HSC to a myofibroblast-like phenotype, and inhibition of ECM degradation by HSCs through the expression of tissue inhibitor of metalloproteinases (TIMPs). Platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF) and tumor necrosis factor (TNFα) have emerged as most potent proliferative HSC cytokines [10], while, BMPs are important in hepatic development and liver regeneration. BMP9 is specifically expressed in the liver tissue and may induce liver fibrosis through ALK1, endoglin, Id1, hepcidin and Snail [11]. BMP7 has been shown to inhibit TGFβ dependent epithelial to mesenchymal transition (EMT) of hepatocytes and also has an antiapoptotic and anti-inflammatory effect [10]. For example, it reduces the progression of fibrosis in mice intoxicated with CCl4 and prevents EMT of hepatocytes accelerating liver regeneration after partial hepatectomy which is reduced after administration of an anti-BMP7 antibody [12]. The expression of BMP7 in the liver increases with increased hepatic inflammatory grade and fibrosis. Anti-inflammatory and anti-fibrogenic effects of BMP7 have also been shown in patients with chronic hepatitis B [13]. Various cytokines contribute to the control of hepatitis C virus (HCV) replication. BMP7 inhibits the intracellular replication of the HCV subgenome in a dose-dependent manner *via* a cell-cycle mediated arrest in host Huh7/Rep-Feo cells. Recombinant adenovirus carrying BMP7 (AAV-BMP7) in a rat experimental model of induced hepatic fibrosis suggests that BMP7 inhibits the hepatic fibrosis and promotes liver regeneration [14]. Expression of BMP7 was also confirmed in mesenchymal stem cells (MSCs) which have therapeutic effects in various diseases. MSC mitigate cirrhosis through their production of BMP7 against the fibrogenic effect of TGFβ1 in the injured liver [15]. In contrast, BMP2 inhibits the division of hepatocytes, thereby reducing the liver regeneration after hepatectomy [16]. BMPs are also involved in the process of pancreatic fibrosis which is a common pathological characteristic of chronic pancreatitis (CP), a major cause of pancreatic cancer. During early progression of pancreatic fibrosis, BMP2 and phosphorylated Smad1 (pSmad1) levels increase, followed by a

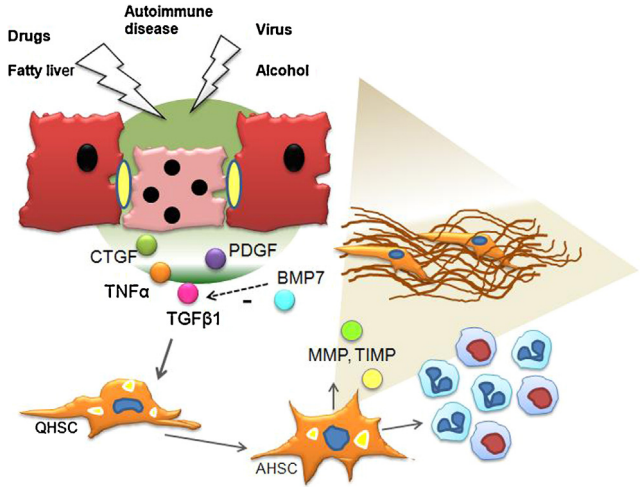

Fig. 1. The role of BMPs in liver fibrogenesis. After persistent and chronic liver injury which is associated with inflammatory response, liver regeneration fails and large number of cytokines are released from damaged tissue. The most important fibrogenic mediators such as transforming growth factor-beta (TGFβ), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNFα) and connective tissue growth factor (CTGF) induce the recruitment of inflammatory cells. Apoptosis of damaged hepatocytes and inflammatory cells stimulates activation of QHSC and their transdifferentiation to myofibroblasts through activated hepatic stellate cells which secrete large number of ECM components. BMP7 inhibits TGFβ activity and also has an antiapoptotic and anti-inflammatory effect.

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