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REVIEW

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Selected bone morphogenetic proteins — the possibility of their use in the diagnostics and therapy of severe asthma

The authors declare no financial disclosure

Abstract

Asthma is a chronic heterogeneous illness of the lower airway with an inflammatory basis, developing from hyperresponsiveness and bronchial obstruction. One of the more unfavourable processes occurring in the airway are the long-term changes of the respiratory tract known as remodelling, resulting in complete irreversible obstruction. Bone morphogenetic protein (BMP) is a member of the Transforming Growth Factor beta (TGF-β) superfamily, which regulates processes in embryonic and post-embryonic development. The role played by BMP is regulation of degradation and remodelling of the extracellular matrix, which is one of the elements involved in the reconstruction of the structure of the bronchi in severe asthma. This paper presents the antagonistic properties of BMP against TGF-β, anti-inflammatory and counteracting fibrosis in the respiratory tract. The current state of knowledge indicates that this group of cytokines are potential new markers of remodelling in severe asthma, and further studies on their therapeutic value are necessary.

Key word: bone morphogenetic proteins, BMP signalling pathway, inflammation, remodelling, asthma

Adv. Respir. Med. 2017; 85: 109–115

Introduction

Asthma is a heterogeneous, chronic inflammatory disease typified by airway hyperresponsiveness and paroxysmal variable bronchial obstruction provoked by specific and non-specific factors [1]. The pathophysiological basis of asthma stems from three phenomena: airway hyperresponsiveness to specific and non-specific factors, variable and reversible airway obturation, and chronic inflammation of the bronchial mucosa.

The inflammation process involves inflammatory cells such as Antigen Presenting Cells (APC), T lymphocytes, mast cells, eosinophils, macrophages and neutrophils, as well as structural cells including epithelial cells, myocytes, fibroblasts and myofibroblasts, nerve cells and vascular endothelial cells [2]. One of the causes of airway hyperresponsiveness is epithelial damage [3]. The CysLT1 receptor is activated with C4, D4 and E4 leukotrienes, secreted by mast cells, and this is followed by muscle spasms. Besides leukotrienes, mast cells also secrete a number of pro-inflammatory cytokines, prostaglandins and histamine, particularly following repetitive stimulation by allergens. Following the onset of the disease, the bronchial walls of the respiratory tract undergo an ongoing, highly-adverse process known as remodelling, which results in reduced elasticity, thickening of the muscular layer, increased angiogenesis and the deposition of an extracellular matrix (ECM) [4]. The activation of fibroblasts, and the differentiation and secretion of increased amounts of collagen is caused mainly by TGF-β1.

Type-β transforming growth factors (TGF-β) are pleiotropic compounds produced by most epithelial and fibroblastic cells. They share the

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DOI: 10.5603/ARM.2017.0017
Received: 15.01.2017

ISSN 2451–4934

action of cytokines, as well as of stimulators and inhibitors of growth and proliferation [5, 6]. The subfamily of the TGF-β superfamily includes Bone Morphogenetic Proteins (BMP), Growth Differentiation Factors (GDF) and Anti-Müllerian Hormone (AMH) [7].

Bone morphogenetic proteins regulate a number of developmental processes for both embryonic and post-embryonic organogenesis: they take part in bone formation, wound healing and immune response [8, 9]. BMP expression was first discovered in bones, but has also been found in other organs such as the bone primordia (BMP-2,4,5,7), kidneys (BMP-3,4,7), heart (BMP-2,4,6,7) and teeth (BMP-3,4,7). In addition, BMP subtypes 3, 4 and 7 have been observed in lung tissue [10–13]. Among the 20 known members of the BMP family, the strongest osteoinductive properties are demonstrated by isoforms BMP-2, 6 and 9, both in the bone tissue and heterotopic areas [14]. However, although BMP-3, 4 and 7 have less osteoinductive potential, they demonstrate regulatory activity in the development and differentiation of fibroblasts, which may take part in the remodelling of the respiratory tract [15, 16].

The BMP-SMAD signalling pathway

Cellular transduction of signalling by BMP occurs through the SMAD protein (mothers against decapentaplegic homolog), in a similar way to proteins from the TGF-β family. Two types of BMP receptors are required to carry the signal: the serine-threonine kinases BMPR-I and BMPR-II (BMPR- bone morphogenetic protein receptor). BMPR-I comprises two receptor subtypes, BMPR-1A (ALK-3) and BMPR-1B (ALK-6), and activin receptor-like kinase-2 (ALK-2), binding activin and BMP-7, while BMPR-II includes BMPR-2, a type II activin receptor (ActRII) and type IIB activin receptor (ActRIIB) [17]. The signal can be passed into the cell nucleus via the canonical pathway (with the participation of SMAD), or a non-canonical pathway by MAP kinases (MAPK-mitogen activated protein kinases), N-terminal kinase (JNK), p38 kinase or Phosphoinositide-3-kinase (PIK3), RAS proteins.

The SMAD family of mediating proteins are derived from two homologous proteins: Sma, occurring in *Caenorhabditis elegans*, and Mad, present in *Drosophila melanogaster*. The SMAD family can be divided into three groups: proteins activated by the R-SMAD receptor, such as SMAD-1,2,3,5 or 8; Co-SMAD, i.e. co-mediating protein SMAD4 ; and the I-SMAD inhibitory proteins, represented by SMAD 6 and 7. SMAD 1, 5 and 8 are activated by BMP signalling. In canonical signalling, after merging, the complex formed by BMP and SMAD-1, 5 or 8 links to the common mediator Co-SMAD4, which allows transport to the cell nucleus [18]. In the cell nucleus, the R-SMAD/Co-SMAD complex binds to the promotors associated with the SRE sequence (SMAD-Response Elements) and following that binding, it regulates their transcription [19].

The genes responsible for mediating SMAD with BMP depend on the type of cell or tissue [20]. SMAD acts as a mediator in inflammation and fibrosis, as well as in epithelial-to-mesenchymal transition (EMT) induced by TGF-β1 [21]. BMP-6 and BMP-7 activate only two of the three R-SMADs , i.e. SMAD1 and SMAD5, whereas BMP-2 activates all SMAD subtypes [22]. It is suggested that some proteins from the BMP family are able to deactivate parts of the SMAD1 and SMAD5 regulatory proteins [23]. BMPs, together with their BMPR-SMAD signal pathway, TGF-β and TGFβR-SMAD undergo mutual interactions. The co-mediating protein Co-SMAD 4 is the common link. When the intracellular level of SMAD4 is limited, ligands of the TGFβR and BMPR receptors modulate its competing activity towards SMAD4 [24]. Correct BMP signalling is essential for the correct promotion and regulation of regeneration, repair and maintenance of tissues where BMP expression is found.

Due to the fact that BMPs belong to the TGF-β superfamily, they have similar signal transduction mechanisms and common co-mediating protein and the confirmed expression of certain subtypes of BMP in the respiratory tract, which results in the need for further studies concerning the possible role of BMPs in the pathological mechanism of bronchial asthma development and subsequent remodelling. Besides, BMPs may be hypothetically used as biomarkers of disease progress in patients.

The BMP protein and BMPR receptor: expression, function and role in the respiratory tract

Although BMP-3 remains not fully understood, the BMP-3 gene is known to be present in chromosome 4q21.21 [26]. The BMP-3 molecule demonstrates high affinity to the activin receptor ActRII, but lower to ActRIIb. Next, the signal is carried to the cell nucleus using the SMAD protein [27]. Expression is located mainly in the neuroectodermis and the forming s periosteum, which suggests that BMP-3 may be engaged in

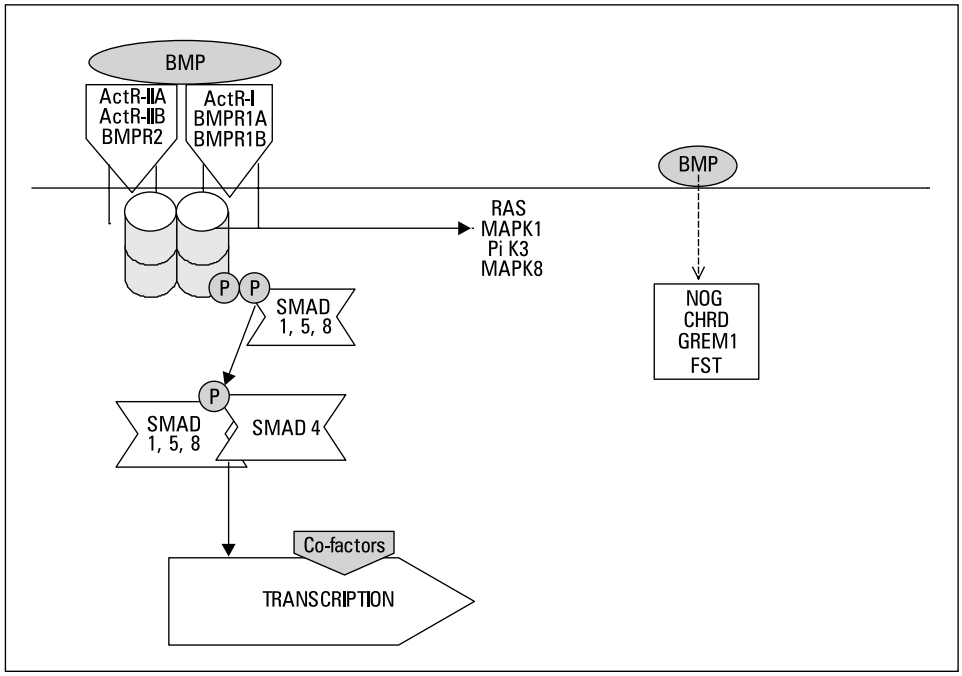

Figure 1. BMP signalling pathways based on [25], own modified. In canonical pathway of BMP signal is transduced through the heteromeric complex with BMP ligand and type I and type II BMP receptors. That complex after phosphorylation is binded with phosporylated SMAD 1, 5, 8 and then merged with co-mediating protein SMAD4, then this newly-formed complex is transported into the nucleus for initiating the transcription. In the non-canonical pathway signal may be transduced via MAPK1, PIK3, MAPK8, RAS. There are also several extracellular inhibitors for BMP, i.e. NOG, CHRD (chordin), GREM1 (Gremlin) and FST (follistatin) or by the receptor BAMBI

the early development of bones during embryogenesis [26]. Studies of six-week-old embryos have revealed the expression of BMP-3 mRNA in epithelial stem cells of the bronchial epithelium, and later in epithelial cells lining the buds of bronchial branches [11]. Some studies propose that BMP-3 may act as an inhibitor for other members of the BMP family. This hypothesis has been confirmed by tests on double knockout mice in which a significant increase in bone mass was observed; however, more frequent spontaneous fractures were observed in the case of mice with BMP-3 overexpression [28]. In a study of allergic rhinitis in a mouse model, a significant reduction in the expression of BMP-3 and BMP-5 was observed following exposure to the allergen *Aspergillus fumigatus*. In the same test, the expression of a range of cytokines from Fibroblast Growth Factors (FGF) and Matrix Metalloproteinases (MMP) was found to be elevated after exposure to a specific allergen. These findings suggest that signal transduction in cells intended for initiating the process of fibrogenesis and remodelling is initiated earlier in inflammatory illnesses [29].

BMP-4 is an important regulatory molecule, inducing mesoderm formation and tooth and limb growth during embryogenesis, and the later formation of bone tissue and healing of fractures [17]. The gene for BMP-4, mapped onto chromosome 14q-22.2, has two promotor regions, which are subject to expression occurring in a cell type-specific manner. It is important to note that construction of BMP-4 includes the propeptide TGF-β1 domain and the TGF-β domain to form an active dimer [30]. BMP-4 is an important signalling molecule for lung embryogenesis [13], with the epithelium of the distal tips of the terminal buds demonstrating greater BMP-4 mRNA expression than the adjoining mesenchyme. Tests on transgenic mice have revealed that BMP-4 misexpression, controlled by the enhancer sequences of the Surfactant Protein C (SP-C) promotor, leads to a reduction in lung size, hyperinflation of the bronchiole tips and impaired gas exchange after birth [15]. It has been postulated that BMP-4 may play a role in the local inhibition of bronchial epithelial cell proliferation, which would inhibit the signal modulating FGFs. This theory has been demonstrated by the presence of hypoplastic epithelial tissue production in studies of transgenic mice with BMP-4 misexpression, and in studies where the BMP-4 ligand was added to *in vitro* epithelial cultures lacking BMP-4 expression [31].

Jefferey *et al.* [32] also note that BMP-4 has an inhibitory effect on fibrogenesis. It was found that BMP-4 has both antiproliferative and pro-

-differentiation effects on the lung epithelium. After examining the BMP-4 signalling pathway, using both the SMAD and mitogen-activated protein kinase (MAPK) pathways, it can be suggested that while the promotion of proliferation is dependent on the action of SMAD1 and c-Jun N-terminal kinase (JNK), the antiproliferative properties are dependent on SMAD1. As SMAD1 is the predominant signalling molecule engaged in the proliferation and differentiation of fibroblasts, it may inhibit the processes using BMP-4. Although the role of BMP-4 in the degradation of the ECM is not fully understood, BMP-4 is believed to be able to counter its growth and induce the proliferation of normal human lung fibroblasts (NHLF) using TGF-β1 [33]. Most importantly, studies which have been recently conducted reveal that BMP-4 not only regulates the level of MMP-13 expression connected with fibroblasts, but also the expression of MMP-13 induced by TGF-β1 [16, 34]. However, although these studies do not confirm that BMP-4 has a direct influence on fibroblast proliferation, they do indicate that it has an indirect action, which encourages the search for new diagnostic and therapeutic applications. The possibility of the partial reversal or inhibition of remodelling translates into improvements in the quality of life of patients and prevents some of the effects of severe asthma.

BMP-7, also known as osteogenic protein 1 (OP1), is mapped on chromosome 20q13.31. BMP-7 is expressed in the limb buds, heart, the retinal neuroepithelium, the lens and cornea, kidney and lung fibroblasts [35]. BMP-7 can bind to ALK-2, which activates the SMAD1 and SMAD5 transport proteins. SMAD1 carries the signal for initiating the formation and differentiation of fibroblasts. BMP-7 is known to have an affinity with ActRI, which may suggest that BMP-7 plays a role in these processes [36]. It is also noted that the absence of BMP-7 is associated with the preferential activation of the TGF-β receptor, the phosphorylation and activation of SMAD2 and SMAD3, followed by their translocation to the nucleus to begin the translation of TGF-β products [37].

BMP-7 plays a role in the differentiation of stem cells into osteoblasts and induction of osteogenesis [38], as well as in fibrogenesis and the differentiation of myofibroblasts [39]. It is important to note that BMP-7 has the potential to partially reverse fibrogenesis induced by TGF-β1 in the kidneys, heart and colon [40, 41]. In addition, it is able to inhibit epithelium-to-mesenchymal transition (EMT), whose constant activation induces chronic inflammation and fibrosis of tissues and organs [42]. Mesenchymal tissues, fibroblasts and myofibroblasts are the primary cells producing the ECM during fibrogenesis. At this stage, BMP-7 is able to inhibit collagen type I (COL1A2) production induced by TGF-β1. BMP-7 inhibits the expression of collagen type I mRNA, A-Smooth Muscle Actin (A-SMA) and Tissue Inhibitor of Metalloproteinase Protein-2 (TIMP) by the induction of Id2 (Inhibitor of Differentiation 2). BMP-7 and Id2 reduce the secretion of collagen dependent on TGF-β1 [43]. Transforming growth factor (TGF. Collagen types I and III, produced by the action of TGF-β1, are the main components of the ECM involved in airway remodelling alongside laminins, elastins and fibronectins [44]. Therefore BMP-7 acts against remodelling by reducing the secretion of collagen.

For another antifibrotic mechanism, it is possible to look at the inhibition of the release of MMP-2 and MMP-13 metalloproteinases induced by TGF-β1 [16]. MMP-13 is one of the main collagenases responsible for the degradation of collagen, while MMP-2 hydrolyses the peptide bonds in collagen types I, II and III [45]. In asthma, metalloproteinases are involved in angiogenesis, and hyperplasia of the smooth muscle cells of the bronchus resulting from activation by TGF-β1; they also have an influence on inflammatory cell release and maintaining bronchial hyperresponsiveness [46]. Studies have demonstrated a constitutive lowering of BMP-7 levels in human mild asthma patients. After exposure to an allergen, a significant increase of protein expression was observed in the epithelium and in inflammatory cells [47]. This confirms that BMP-7 plays a role in EMT, but also suggests that it acts as a regulator in inflammation and tissue repair [48].

A similar increase of TGF-β1 expression was observed in both acute and chronic conditions in tests on mice immunised with ovoalbumin; however, only the chronic group demonstrated a fast increase of BMP-7 expression, which correlated positively with higher levels of collagen deposition. The mice were then subjected to specific BMP-7 therapy, which was found to be effective at inhibiting collagen type I induced by TGF-β1 [49]. The mouse studies offer promise for trials on the use of BMP proteins as markers of severe asthma associated with remodelling in humans.

The possibilities of clinical use of anti-fibrotic mechanism of BMP would be advantageous in patients with moderate and severe asthma. In patients with less advanced forms of asthma, the recombinant BMP proteins would be used

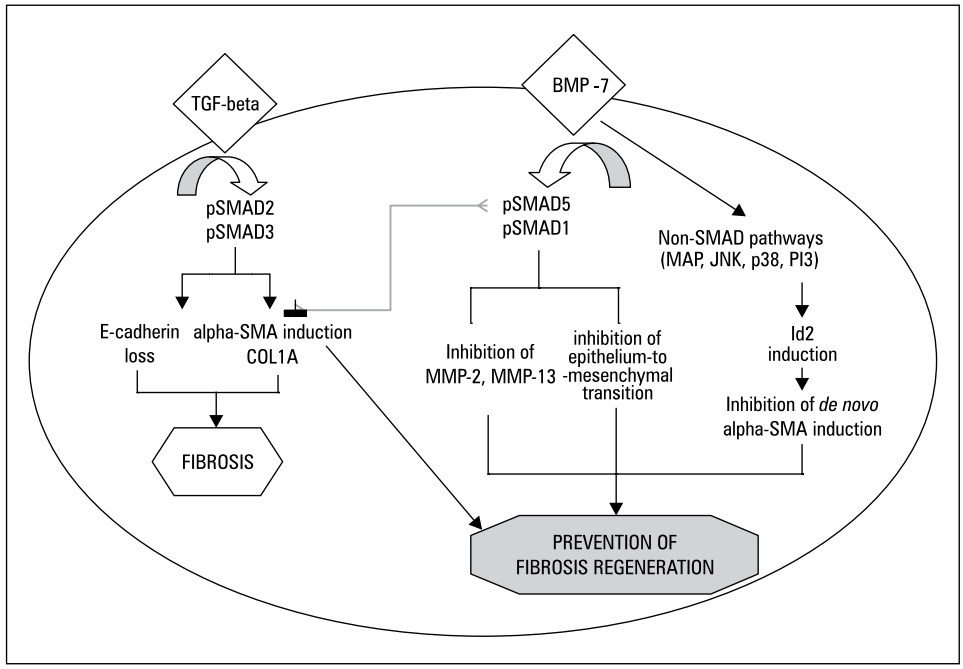

Figure 2. Potential regenerative and anti-fibrosis mechanism of BMP-7 based on [43], own modified template. BMP-7 inhibits the expression of collagen type I mRNA, A-Smooth Muscle Actin (A-SMA) and Tissue Inhibitor of Metalloproteinase Protein-2 (TIMP) by the induction of Id2. BMP-7 and Id2 reduce the secretion of collagen dependent on TGF-β1. The inhibition of fibrosis by reducing collagen secretion and the release of matrix metalloproteinases as well as by the inhibition of epithelial-to-mesenchymal transition results in a decrease in intensity of inflammation in the tissues and partial reversion of fibrosis effects

as the causal treatment to prevent fibrosis and irreversible rebuilding. We believe that the prevention of the remodelling would keep the disease under control (evaluated by ACQ- asthma control questionnaire), prolong the patient's life and improve its quality (AQLQ- asthma quality of life questionnaire). The inhibition of fibrosis by reducing collagen secretion and the release of matrix metalloproteinases, as well as by the inhibition of epithelial-to-mesenchymal transition results in a decrease in intensity of inflammation in the tissues and partial reversion of fibrosis effects. Partial rebuilding of the tissues would be clinically manifested by lessening the obstruction, improving the spirometry results and better response to treatment. One of the reasons for the ineffectiveness of bronchodilators in severe asthma is irreversible obstruction. The use of the causal treatment of specific biological therapy and recombinant factor inhibiting inflammation and fibrosis in combination with conventional anti-inflammatory and bronchodilator therapy would probably improve the control over the disease and prevent its distant effects. For this reason, further study of bone morphogenetic proteins, especially BMP-4 and BMP-7 in terms of their ability to inhibit or reverse fibrosis appears to be justified.

It is important to note that in 2001, the FDA (Food and Drug Administration) opened clinical trials of the osteoinductive potential for recombined rh-BMP7 (Eptotermin-A), which actively recruits mesenchymal stem cells from the tissue surrounding the bones and initiates a cascade of bone formation [50]. Although rhBMP-7 has only been used to a limited degree, this result offers hope that other molecules of recombinant BMP-7 could be used in the prevention, control and treatment of the symptoms of severe asthma associated with remodelling.

Either overexpression or the lack of expression of any BMPR receptors results in disturbances in intracellular signalling along the BMPR-SMAD pathways. In illnesses with impaired BMPR-SMAD transduction like Primary Pulmonary Hypertension (PPH) or Non-Small Cell Lung Cancer (NSCLC), the lack of BMP-regulated signalling promotes the expression of other growth factors [51]. Patients with a mild course of asthma demonstrate lower constitutive expression of BMPR-I, BMPR-II, ALK-2 and ALK-6 receptors, compared to a control group. This suggests that the 'down-regulation' of signalling pathways in patients with mild disease may contribute to an increase in the activity of remodelling processes after the transition to symptomatic asthma. Following exposure to allergen, patients with mild asthma demonstrated restitution of the BMPR receptors and fast activation of the

ligand-activated signalling pathway, which was maintained for the following seven days; this may be associated with the initiation of the cascade of anti-inflammatory and antifibrotic processes [47].

Summary

Studies have indicated the role played by subtypes of bone morphogenetic protein (BMP) in the pathogenesis of respiratory diseases accompanied by fibrosis. BMP signalling pathways are active in the respiratory tract and form an integral part of the physiological response to damage to the tissue and smooth muscle of the respiratory tract. The sources given in this study highlight the role of BMP-4 and BMP-7 in the degradation and remodelling of the extracellular matrix, which is one of the elements involved in the reconstruction of the structure of the bronchi in severe forms of asthma. The BMP-4 and BMP-7 subtypes exhibit antifibrotic effects which act antagonistically to TGF-β1, the main cytokine increasing the risk of fibrogenesis.

The effects of BMP are numerous and varied: they modulate the activity of lung fibroblasts, myofibroblasts and elements of the extracellular matrix. Study results which have been obtained so far encourage to conduct *in vivo* and *in vitro* experiments with the use of animal models. Bronchial asthma has been found to be associated with dysregulation of BMP protein and BMPR receptor expression, and the constitutive level of these receptors and the changes in their expression may be used in diagnostics as predictive markers of severe asthma. In addition, disorders at this level can be targets for the creation of new small molecule ligands of the BMPR receptor with the use of molecular biology techniques. The antifibrotic activities of BMP represent a promising field for therapeutic intervention. The possibility of even a partial reversal of the effects of airway remodelling can significantly translate into control of asthma symptoms, reducing the chronic effects of the prolonged disease process, extending life expectancy and improving the quality of life. Further detailed studies of the expression and regulation of BMP proteins, their mechanisms of activation and intracellular signalling seem to be significant from the point of view of diagnostics, reflecting the development of the fields of biology and molecular biology, and the growth of gene therapy.

Conflict of interest

The authors declare no conflict of interest.

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