Cytokine & Growth Factor Reviews 27 (2016) 81–92

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Mechanisms of action of bone morphogenetic proteins in cancer

Hayley Davis[a], Erna Raja[b], Kohei Miyazono[b], Yutaro Tsubakihara[c,d], Aristidis Moustakas[d,e,*]

[a] Gastrointestinal Stem Cell Biology Laboratory, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
[b] Department of Molecular Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[c] Department of Molecular Medicine for Pathogenesis, Ehime University Graduate School of Medicine, Ehime, Japan
[d] Ludwig Institute for Cancer Research, Science for Life Laboratory, Box 595, Biomedical Center, Uppsala University, 75124 Uppsala, Sweden
[e] Department of Medical Biochemistry and Microbiology, Science for Life Laboratory, Box 582, Biomedical Center, Uppsala University, 75123 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 31 August 2015
Accepted 13 November 2015
Available online 24 November 2015

Keywords:
BMP
Cancer
EMT
Metastasis
TGF-β

ABSTRACT

The bone morphogenetic proteins (BMPs) play fundamental roles in embryonic development and control differentiation of a diverse set of cell types. It is therefore of no surprise that the BMPs also contribute to the process of tumourigenesis and regulate cancer progression through various stages. We summarise here key roles of BMP ligands, receptors, their signalling mediators, mainly focusing on proteins of the Smad family, and extracellular antagonists, that contribute to the onset of tumourigenesis and to cancer progression in diverse tissues. Overall, the BMP pathways seem to act as tumour suppressors that maintain physiological tissue homeostasis and which are perturbed in cancer either via genetic mutation or via epigenetic misregulation of key gene components. BMPs also control the self-renewal and fate choices made by stem cells in several tissues. By promoting cell differentiation, including inhibition of the process of epithelial-mesenchymal transition, BMPs contribute to the malignant progression of cancer at advanced stages. It is therefore reasonable that pharmaceutical industries continuously develop biological agents and chemical modulators of BMP signalling with the aim to improve therapeutic regimes against several types of cancer.

1. BMP ligands and antagonists

1.1. BMP ligands

Bone morphogenetic proteins (BMPs), a subfamily of the transforming growth factor (TGF)-β family, are glycosylated extracellular matrix-associated molecules that act as ligands for specific receptors on target cells (Fig. 1). BMPs were identified through a pivotal role in bone formation; subsequent work has demonstrated that BMP signalling is an evolutionary conserved pathway with a diverse range of functions in different tissue types including embryonic patterning, homeostasis, cell proliferation, apoptosis, differentiation control, bone metabolism, vascular homeostasis and iron deposition in the liver, amongst many others. It has been proposed that the term "Body Morphogenetic Protein" may be more apt in light of our current knowledge [1].

The BMP signalling pathway is an intricate system with more than 20 ligands and these can be further categorised based on their nucleotide or amino acid similarities. Ligands are synthesised in a wide number of cells but often act trans-compartmentally. Different tissues have variable ligand–receptor–antagonist relationships, which generates a complex, tissue context-dependent control network. BMP ligands can form both hetero- and homodimers which have differing potencies adding a further level of complexity [2].

BMPs are secreted proteins that form cystine knots which are involved in tertiary and quaternary folding. BMPs are generated as large pre-proteins composed of signal peptide, prodomain and a carboxyl-terminal domain containing the highly conserved cysteine residues [2]. After the synthesis and elimination of the signal peptide, the pro-BMPs undergo dimerisation and are cleaved by specific proteolytic enzymes in the trans Golgi network to generate the mature ligand which is secreted into the extracellular space.

1.2. BMP antagonists

Regulation of BMP signalling is performed at many levels, one of which is by secretion of antagonist molecules otherwise known as

* Corresponding author at: Department of Medical Biochemistry and Microbiology, Science for Life Laboratory, Box 582 Biomedical Center, Uppsala University, 5123 Uppsala, Sweden.
E-mail address: aris.moustakas@imbim.uu.se (A. Moustakas).

http://dx.doi.org/10.1016/j.cytogfr.2015.11.009
1359-6101/

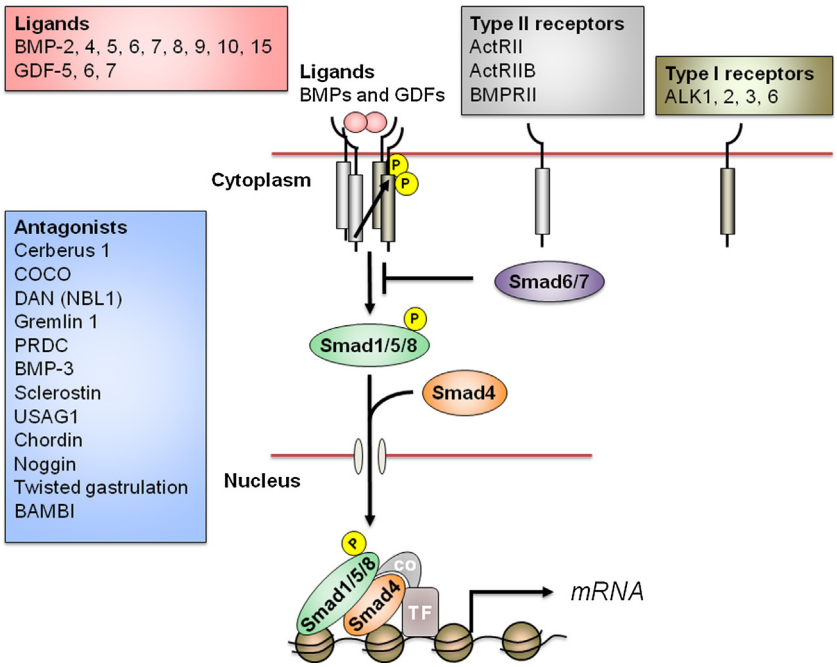

Fig. 1. BMP signalling pathway: ligands, receptors and antagonists. Various growth factors of the BMP and GDF families are listed and are shown to bind to their plasma membrane receptor complexes. The two groups of cell surface receptors are listed as type II and type I receptor groups and each type II receptor forms a homodimeric complex in association with the corresponding homodimeric type I receptor, leading to a hetero–tetrameric receptor complex bound to ligand. This scheme provides great flexibility for the generation of many ligand–receptor combinations. The ligand-bound type II receptor kinase phosphorylates the type I receptor (arrow leading to (P)) and then the type I receptor phosphorylates the C-terminal sequence of Smad1, Smad5 or Smad8, which form complexes with Smad4 and accumulate in the nucleus. The nuclear Smad complex binds to chromatin together with various transcription factors (TF) and co-transcriptional factors (co), i.e. co-activators or co-repressors, which lead to regulation of mRNA synthesis. The BMP pathway can be negatively regulated by Smad6 and Smad7 that block the activity of the type I receptor and by a long series of antagonists, most of which are secreted extracellular proteins and one, which is a membrane-bound pseudoreceptor (BAMBI).

ligand traps (Fig. 1). These antagonists attach to and sequester ligands, preventing them from binding receptors by blocking their binding sites. Some BMP antagonists have similar structure to BMPs, including cysteine-rich domains which form the cystine knot. BMP antagonists can be categorised into different groups depending on the location of their cysteine residues, have been extensively reviewed elsewhere [3,4] and are summarised in Table 1.

Different antagonists function in different tissues, for example there is much greater physiological expression of both Gremlin1 and Gremlin2 than Noggin in human intestinal stroma [5] whereas the association of germline inactivating Noggin mutations with skeletal conditions correspondingly reflects the greater significance of Noggin's role in bone development than in intestinal homeostasis [6]. Antagonists that act on other TGF-β ligands as well as BMPs, such as Follistatin, should also be recognised. The role of cooperation between differing BMP antagonists has recently been discovered, as well as the counterbalance between BMP and TGF-β signalling whereby both pathways can have a dampening effect on each other [3].

2. BMP signalling

The extracellular, dimeric BMPs recognise cell surface dual specificity kinase receptors (that exhibit high kinase activity towards serine and threonine and weaker towards tyrosine) [2,7]. These receptors are grouped into two distinct sub-families, the type II and type I receptors (Fig. 1). When the ligands bind to the homodimeric type I receptors and the homodimeric type II receptors co-assemble in a sequential pattern, forming a tetrameric receptor, then the type II receptor kinase phosphorylates specific serine residues in the type I receptor juxtamembrane domain, causing their catalytic activation based on conformational changes and on release of chaperone proteins that mask the activity of the type I receptors [7]. The BMPs utilise three type II receptors, BMPRII, ActRIIA and ActRIIB, and four type I receptors, also known

Table 1
BMP extracellular antagonists.

BMP antagonist group	Protein size	BMPs antagonised
Noggin	64-kDa glycosylated protein, homodimer	BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-13, BMP-14
Chordin	120-kDa homodimer	BMP-2, BMP-4, BMP-7
Tsg (twisted gastrulation)	23-kDa secreted glycoprotein	BMP-2,BMP-4
DAN (differential screening-selected gene aberrant in neuroblastoma)		
Including:		
Gremlin1	21-kDa	BMP-2, BMP-4, BMP-7
Sclerostin	23-kDa	BMP-2, BMP-4, BMP-6, BMP-7
Dan	19-kDa	BMP-2, BMP-4, BMP-14