Bone Morphogenetic Protein-1 and Its Regulation - A Review

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Abstract

Bone morphogenetic protein 1, also referred to as BMP1, is a protein encoded by the BMP1 gene in humans. There are seven protein isoforms created through alternative splicing.It leaves the C-terminal propeptides of procollagen I, II and III. It induces cartilage and bone formation. It may participate in dorsoventral patterning during early development by cleaving chordin (CHRD). It is also responsible for the proteolytic activation of lysyl oxidase LOX.

Keywords: *BMP1, TGF β-1, lysyl oxidase, SpAN, bone, growth, cartilage*

Introduction

BMP1 is a member of the peptidase M12A family of bone morphogenetic proteins (BMPs). It causes the growth of bone and cartilage. It does not belong to the TGFβ superfamily, unlike other BMPs. It was initially discovered by inducing formation of bone and cartilage to function like other BMPs.[1] However, it is a metalloprotease that cleaves procollagen I, II and III at the C-terminus. It has an astacin-like protease domain. It has been shown to cleave laminin 5 and it is found in the bovine skin's epithelial layer. The locus of BMP1 encodes a protein that can cause in vivo cartilage formation.[1,2] Although other morphogenetic bone proteins belong to the superfamily of TGF-beta, BMP1 encodes a protein that is not closely related to other recognized growth factors. BMP1 protein and procollagen C proteinase (PCP), a secret metalloprotease that requires calcium and is essential for formation of cartilage and bone, are all similar. PCP or BMP1 protein cleaves procollagen I, II, and III C-terminal propeptides and increases their activity with the enhancer protein procollagen C-endopeptidase. The BMP1 gene is expressed as alternative spliced variants sharing an N-terminal protease domain but differing in their C-terminal region.[2]

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REGULATION OF BMP-1

The structure of BMP1 was determined through X-Ray diffraction using a resolution of 1.27 Å.Further crystallization experiments were performed by vapor diffusion at a pH value of 7.5. This is done because it is close to the pH of the human body, thus equilibrating the conditions, where BMP1 resides in vivo. BMP1 is 202 residues long. Its secondary structure is made up of 30% helices, or 10 helices, 61 residues long, and 15% beta sheets, or 11 strands, 32 residues long. It contains ligands of an acetyl group and a Zinc ion. A Ramachandran plot was constructed for BMP. This plot shows that BMP-1 most prefers Phi and Psi angles (Phi, Psi) of around (-60°,-45°) and (-60°, 140°). These preferred angles are an estimate of the most clustered data of the Ramachandran plot. The preferred region is much greater in range. 97% of the residues were in preferred regions and 100% of the residues were in the allowed region, with no outliers.[1-5]

The molecular functions of BMP1 include, calcium ion binding, cytokine activity, growth factor activity, identical protein binding, metalloendopeptidase activity, metallopeptidase activity, peptidase activity and zinc ion binding. The biological processes brought about by BMP1 include cartilage condensation, cell differentiation, extracellular matric disassembly, high density lipoprotein particle assembly, ossification, proteolysis, positive regulation of cartilage development and overall skeletal system development. The following

are the factors involved in the regulation of BMP1.

TGF β1

Transforming growth factor beta 1 (or TGF-β1) is a polypeptide member of the transforming growth factor beta superfamily of cytokines. It is a secreted protein that performs many cellular functions, such as cell growth, cell proliferation, cell differentiation and apoptosis. In humans, TGF-β1 is encoded by the *TGFB1* gene. [1,2] Transforming growth factor-1 (TGF-1) induces increased extracellular matrix deposition. Bone morphogenetic protein-1 (BMP-1) also plays key roles in regulating vertebrate matrix deposition. It is the procollagen C-proteinase (PCP) that processes procollagen types I±III, and it may also mediate biosynthetic processing of lysyl oxidase and laminin 5. [3] BMP-1 is itself up-regulated by TGF-1 and that secreted BMP-1, induced byTGF-1,is either processed to an active form or remains as unprocessed proenzyme, in a cell type-dependent manner. [4] Secreted BMP-1 and mTld, induced by TGF-1 in MG-63 and other fibrogenic cell cultures, were predominantly in forms in which pro regions had been removed to yield activated enzyme. Bone morphogenetic protein-1 (BMP-1) copurifies from osteogenic bone extracts with transforming growth factor(TGF-)-like proteins BMP-2 through -7. BMP-1, by structure an astacin-like protease, may function in morphogenesis by activating TGF-like molecules. [5] BMP-1 has a domain structure similar to, but shorter than, that of tolloid, a Drosophila protein that appears to act in patterning of embryos by potentiating the activity of decapentaplegic, a TGF-family member. [6] TGF-beta family proproteins are cleaved in the trans-Golgi between the N-terminal propeptide and the mature growth factor. For TGF-beta1, -beta2, -beta3, GDF-8, and GDF-11, the prodomain is secreted in association with the growth factor and maintains the growth factor in an inactive state. BMP-1 family of proteases regulate the activation of these latent complexes by several mechanisms. **BMP-1-related activation of latent TGF-beta family complexes occurs by three mechanisms.** First, BMP-1 cleaves latent TGF-beta-binding protein(LTBT) at two positions in a process required for efficient MMP-2-mediated liberation of TGF-beta from latency-associated peptide(LAP). Second,BMP-1 family proteases cleave at single positions within the GDF-8 and GDF-11 propeptides, releasing the active growth factor dimers. Third, activation of BMP in complex with chordin is mediated by BMP-1 proteolysis at two sites within chordin. [7]

LYSYL OXIDASE

Lysyl oxidases (LOX) are a family of copper-dependent amino oxidases for which important roles in cancer and vascular and fibrotic diseases have been proposed. [7] Five different LOX enzymes have been identified in mammals (LOX, and LOX-like 1 to 4), showing a high degree of homology in the catalytic carboxy terminal end and more divergence in the rest of the sequence. [8] Lysyl oxidase catalyzes the final enzymatic step required for collagen and elastin cross-linking in extracellular matrix biosynthesis. Pro-lysyl oxidase is processed by procollagen C-proteinase activity, which also removes the C-propeptides of procollagens I-III. [9,10] The Bmp1 gene encodes two procollagen C-proteinases: bone morphogenetic protein 1 (BMP-1) and mammalian Tolloid (mTLD). Mammalian Tolloid-like (mTLL)-1 and -2 are two genetically distinct BMP-1-related proteinases, and mTLL-1 has been shown to have procollagen C-proteinase activity. [11]

SpAN

SpAN is a sea urchin metalloprotease in the astacin family containing BMP1 and tolloid. [12] Embryos expressing SpAN initiated gastrulation on a time scale indistinguishable from controls, but invagination of the vegetal pole was subsequently delayed by several hours. At tailbud stages the most severely affected embryos were completely ventralized, lacking all dorsal structures. [12] Molecular analysis of injected embryos, using probes for both dorsal (xgsc and xnot) and ventral (xhox3 and xwnt8) mesoderm, indicates that SpAN ventralizes dorsal mesoderm during gastrula stages. [13] These results mirror those previously obtained with BMP4, suggesting that SpAN may enhance the activity of this ventralizing factor. [14] Consistent with this suggestion, it has been shown that SpAN blocks the dorsalizing activity of noggin and chordin, two inhibitory binding proteins for BMP4, but not that of a dominant-negative receptor for BMP4. [15] In contrast, a dominant-negative SpAN, in which the metalloprotease domain has been deleted, dorsalizes ventral mesoderm, a phenotype that can be rescued by coexpressing either SpAN or XBMP1. This suggests that SpAN is mimicking a Xenopus

metalloprotease responsible for regulating the activity of Xenopus BMPs during gastrulation. [16]

DIMERIZATION

Refolding and dimerization of BMP are extremely slow under all conditions and could be described by consecutive first-order reactions involving at least one long-lived intermediate. [17] The rate constants vary from ~ 0.2 × 10(-5) to ~ 3.5 × 10(-5) s(-1). It is strongly dependent on temperature, redox conditions, and the presence of stabilizing or destabilizing ions. [18,19] In particular, the combined impact of ionic strength and redox conditions on the rates indicates that electrostatic interactions control thiol-disulfide exchange reactions on the path from the unfolded and reduced monomers to the disulfide-connected growth factor in a rate-determining way. [20,21,22]

Conclusion

By controlling cellular lineage engagement, morphogenesis, differentiation, proliferation, and apoptosis of different types of cells in the body, the bone morphogenetic protein (BMP) ligand family plays an important role in a multitude of processes throughout embryonic development and adult homeostasis. BMP1 belongs to a family of bone morphogenetic proteins (BMPs) called peptidase M12A. It causes the growth of bone and cartilage. It is different from other BMPs in that it does not belong to the TGFβ superfamily. It is important to understand the regulation of BMP1 and the important roles it plays.

Ethical Clearance – Not required since it is a review article

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Conflict of Interest – Nil

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