International Core Journal of Engineering Volume 8 Issue 1, 2022
ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

Research Progress of Osteogenesis Induced Jointly by BMP and BGN

Yue Ma[1, a], Wenjuan Bi[2, *]

[1] School of Stomatology, North China University of Technology, Tangshan, China

2 Key Laboratory of Oral Tissue Repair and Reconstruction of Tangshan City, Tangshan, China

[a]792065501@qq.com, [*]bixiaobi2003@163.com

Abstract

The extensive critical bone defect is still a clinical problem; cytokine treatment has become one of the hot contents in bone tissue engineering research due to its high safety and low side effects. This paper reviewed the research progress of osteogenesis induced by bone morphogenetic proteins (BMPs) and biglycan (BGN) two cytokines, respectively, and discussed the osteogenesis mechanism of the joint application of BMP heterodimer and BGN.

Keywords

Bone Morphogenetic Protein, Biglycan, Bone Tissue Engineering, Osteogenic Differentiation.

1. Introduction

The cytokine treatment which applies bone morphogenetic proteins BMPs) and other osteogenic induction factors has become one of the research hotspots in the treatment field of extensive and extreme bone defects. Studies show that bone morphogenetic proteins can significantly promote stem cell differentiation and bone tissue regeneration in vivo and in vitro [1-4]. According to research, it was found that the osteogenic performance of BMP heterodimer is better than that of homodimer. In recent years, studies have found that the position of biglycan (BGN) can be fixed in many bones, which is involved in the regulation of bone and blood vessel generation. This paper reviewed the related studies of BMPs and BGN in osteogenesis, and discussed the osteogenic mechanism of the joint application of BMP heterodimer and BGN.

2. Research Progress of Osteogenesis Induced by BMPs

Bone morphogenetic protein is the member of the transforming growth factor-β (TGF-β) superfamily, BMPs are formed by connecting two peptide chains via disulfide bond, which can form homodimer and heterodimer. The homodimer is formed when two peptide chains are the same, and the heterodimer is formed when two peptide chains are different [5-6]. The osteogenic ability of the formed dimer is not only related to the osteogenic ability of the monomer itself, but also related to the homology among the monomers [7-9], the lower the homology of the two peptide chains, the stronger the osteogenic induction ability. The osteogenic induction effect of homodimer is lower than that of heterodimer whose two peptide chains come from the same subclass, the osteogenic induction effect of heterodimer whose two peptide chains come from the same subclass is lower than that of heterodimer whose two peptide chains come from different subclasses [10]. In vitro experiments also confirmed that BMP2/7, BMP2/6 and BMP4/7 heterodimers show stronger osteogenic activity than their homodimers [11].

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

BMPs form the ligand-receptor complex by binding serine/threonine receptors on the cell surface, thus activating the signaling pathway of BMPs to play a role. BMP mainly interacts with 3 types of I receptors (Alk-2 (ActR-IA), Alk-3 (BMPR-IA), Alk-6 (BMPR-IB)) and 3 types of II receptors (BMPR-II, ActR-IIA, ActR-IIB) [12]. By interacting with different receptors, BMPs have different activation degrees for signaling pathway and different gene expression strengths. However, the two receptors are indispensable during signal transduction. After BMPs as ligands bind receptors, they activate a series of signaling pathways including Smad-dependent signal transduction pathways (such as Smad1/5/8) and Smad-independent MAPK signal transduction pathways (such as ERK, p38, JNK, etc.). Both Smad and MAPK pathways can directly or indirectly promote the transcription of target genes in the nucleus. The Smad pathway generally occurs in osteoblasts, chondroblasts and their precursor cells, and is strictly regulated in these cells.

BMP homodimer has different affinities with different types of receptors. BMP2 has a high affinity with type I receptor and has a relatively weak affinity with type II receptor, BMP7 has a higher affinity with type II receptor and has a relatively weak affinity with type I receptors. Compared to BMP2 or BMP7, BMP2/7 heterodimer has stronger affinity with type I and type II receptors, so the ligand-receptor complex can be formed more quickly and stably to activate BMPs signaling pathway [13-14]. Koh et al. found that both BMP2 and BMP7 could slightly promote the phosphorylation level of Smad1/5/8, but did not increase the contents of Smad. BMP2/7 could not only significantly increase the phosphorylation level of Smad1/5/8, but also increased the contents of Smad, and its activity to stimulate osteoblast differentiation is also enhanced [7]. Miao et al. proved that BMP can make bone marrow mesenchymal stemcells (BMSC) of rats have obvious osteogenic effect by regulating the ERK signaling pathway [15]. Zhang et al. found that there was difference in the osteogenic effects of different cells induced by BMP2/7 heterodimer, this situation may depend on the different expression levels of the ERK signaling pathway of BMP2/7 in different cells [16].

In addition, the expression of BMPs is affected by Noggin, CIZ and other negative feedback regulator elements. Zhu et al. found through research that compared with BMP2 homodimer, BMP2/7 heterodimer not only significantly reduces the inductive formation ability of Noggin, but also may be due to the asymmetry of the heterodimer structure, as a result, the binding ability of BMP2/7 and Noggin is also significantly weaker than its corresponding homodimer [17]. As the negative feedback inhibitor of the signaling pathway of BMPs, CIZ has a weaker negative feedback inhibitory effect on the osteogenic signaling pathway induced by BMP2/7 than its homodimer, so the osteogenic effect of heterodimer is higher than that of homodimer [18].

BMPs can also indirectly promote the differentiation and activity of osteoclast by regulating RANKL and OPG [19], this view has also been verified in animal models [20]. Studies found that BMP2/7 heterodimer promotes osteoclast differentiation and activity induced by RANKL, and has concentration dependence [21].

3. Research Progress of Osteogenesis Induced by BGN

Biglycan(BGN) is a member of the leucine-rich small proteoglycan (SLRP) family in the extracellular matrix (ECM), is involved in the regulation of bone formation and bone matrix mineralization. It is 150kDa molecule composed of a~45kDa core protein and two glycosaminoglycan (GAG) chains. BGN was first discovered in bone matrix by L W Fisher et al. in 1983 [22], with the progress of research, BGN can be positioned in many bone areas, including articular cartilage, epiphyseal cartilage, subchondral area, and periosteum. It also exists in non-skeletal tissues and participates in the regulation of various biological processes, such as innate immunity, chemotaxis, angiogenesis, and growth factor regulation [23-25].

The osteoporotic phenotype occurs in BGN-deficient mice, and the role of BGN in osteogenesis attracted attention for the first time. Xu et al. found that BGN targeted knockout mice did not show obvious skeletal abnormality at birth, but as they get older, lack of BGN will lead to the decrease of growth rate and bone mass of mice. The concrete representation is multiple metabolic defects exist

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

in bone marrow stromal cells, including increase of apoptosis, the decrease of the number of colony forming unit of fibroblastoid cells(CFU-F), and the decrease of collagen production. Research results suggest that BGN has a key role in bone development [26]. CHEN et al. further carried out bone marrow ablation experiments, found that mice lacking BGN cancellous bone formation decreased and are lower in bone deposition than normal mice. Osteogenesis defects of juvenile mice are regulated by BGN and have nothing to do with change and apoptosis of the number of stem cells. BGN plays an important role in the process of osteogenesis after bone marrow ablation, this view is further confirmed [27].

According to research, it was found that BGN and FMOD in the SLRP family members had rich expression and position in the articular cartilage of the mandibular condyle [28], the injection of BMP2 accelerated the recovery of the osteogenic matrix in the condyle in the disturbance syndrome of temporomandibular joint model of BGN and FMOD knockout mice, although BGN and FMOD did not dominate this process, they played a significant regulation and promotion role in this process [29].

In addition, Berendsen et al. tested the fracture healing condition of BGN knockout mice, and found that the cartilage, woven bone, and other bone tissues formed in the BGN-deficient mice were significantly lower than the control group. Moreover, the gene expression of vascular endothelial growth factor A (VEGF) in BGN-deficient mice was significantly reduced, it shows that BGN has a regulatory effect on osteogenesis process during fracture healing, and its influence on angiogenesis may be its molecular basis [23]. BGN is needed to promote angiogenesis during fracture healing, and the mechanism of BGN to regulate angiogenesis is related to the expression and function by inhibiting the anti-angiogenic protein-endostatin [30].

4. Research Progress of Osteogenesis Induced Jointly by BMP and BGN

Another effective mechanism of BGN to promote osteogenesis is the ability to regulate the expression of key factors such as BMP, transforming growth factor-β (TGF-β) and Wnt [31-34]. According to reports, BGN promotes osteogenic differentiation of cells by regulating two important ways: extracellular signal-regulated kinase (Erk) and Smad signaling pathway.

Prapaporn et al. synthesized various recombinant and synthetic peptides corresponding to various domains of BGN, carried out in vitro studies, and found that the leucine rich repeat 2-3 domain (LRR2-3) of BGN significantly enhanced the Smad1/5/8/9 phosphorylation, osteogenic gene expression and alkaline phosphatase activity of muscle-derived C2C12 cell induced by BMP2, and significantly promote the in vitro mineralization of MC3T3-E1 cell. It follows that BGN can enhance the osteogenic ability of BMP2 and promote bone tissue regeneration [35]. The research of Mochida et al. showed that BGN core protein can bind BMP2 and activin receptor-like kinase 6 (ALK6), thereby maintaining the binding of BMP2 and ALK6, and promote osteoblast differentiation induced by BMP2 through its specific binding. The BMP2/BGN/ALK6 complex can promote Smad1/5/8 phosphorylation and downstream signal transduction related to osteogenesis [31].

SONG et al. found that after BGN stimulated the normal valve cells of heart, the expression of bone morphogenetic protein-2 (BMP-2) and alkaline phosphatase (ALP) in cartilage/osteogenesis markers increased, and promoted calcium deposition. BGN can induce phosphorylation of ERK1/2, p38MAPK and NF-κB, and inhibiting ERK1/2 can significantly reduce the up-regulation effect of BGN on BMP2 and ALP expression, while the effect of inhibiting p38MAPK and NF-κB is weaker [36]. CHEN et al. found in BGN knockout gene mice experiments that the lack of BGN reduced the sensitivity of bone marrow stromal cells to transforming growth factor-β (TGF-β), resulting in the decrease of BMP4 binding, thereby reducing the sensitivity of bone cells to BMP-4 stimulation. The loss of sensitivity results in the decrease of Cbfa1 expression, which ultimately leads to defects of osteoblast differentiation [33]. Mauricio et al. found that BGN can regulate BMP4 signaling pathway by binding BMP4 and BMP4 antagonist Chordin [37]. BGN enhances the transcriptional activity of Runx2 by activating the Erk signaling pathway, in which glycosaminoglycans (GAGs) chains play

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

an important role. The research of YE et al. showed that the mutant BGN which lacks the GAG chain reduced BGN-assisted BMP-4 signal transduction and osteoblast differentiation, and the expression of this mutant BGN in BGN knockout skull osteoblasts could not save its differentiation defects as effectively as wild-type (WT) BGN. These results strongly suggest that the GAG chain of BGN promotes the function of BGN to assist BMP4.

5. Prospect

To sum up, BGN promotes the conduction and expression of BMP by regulating Smad and Erk signaling pathways, and induces osteogenic differentiation of cells. After applying BMP homodimer transfection in the BGN gene knockout experiment, it shows obvious advantages of osteogenic induction. In addition, BGN show promoting and regulating effects on BMP homodimer in chondrogenesis and osteogenesis. BMP heterodimer has lower effective concentration, better osteogenesis effect, and small side effects, and other advantages in comparison with BMP homodimer. At present, there is no report on the joint application of BMP heterodimer and BGN in the existing literatures at home and abroad. Whether the joint application of BMP heterodimer and BGN can produce the synergistic and promotion effect in inducing osteogenesis is still unclear, its internal mechanism still needs to be explored.

Acknowledgments

Foundation Programs: National Youth Science Fund Project (81600844), Hebei Youth Science and Technology Project (20191103), Hebei Youth Science and Technology Project (20180738), Science Research Funds of North China University of Science and Technology (Z201732).

References

[1] PING L, CECILIA Y. Long-term expansion and enhanced osteogenic potential of Macaca MSCs via BMP signaling modulation [J]. Tissue and Cell, 2020, 67(prepublish).

[2] Wang Liu, Song Dongzhe, Huang Dingming. Bone morphogenetic protein 9 regulates stem cell differentiation and bone regeneration [J]. Chinese Journal of Tissue Engineering Research, 2021, 25(19): 3064-70.

[3] Chen Ruiqi, Huang Sicong. Effect of Bone Morphogenetic Protein 2 Concentration on the Growth of Rabbit Bone Marrow Mesenchymal Stem Cells [J]. The Journal of Medical Theory and Practice, 2020, 33(22): 3693-6.

[4] Di Yuntao, Wang Cunyang, Zhu Huixue, et al. Experimental study on repairing rabbit skull defect with bone morphogenetic protein 2 peptide/functionalized carbon nanotube composite [J]. Chinese Journal of Reparative and Reconstructive Surgery, 2021, 35(03): 286-94.

[5] BRAGDON B, MOSEYCHUK O, SALDANHA S, et al. Bone morphogenetic proteins: a critical review [J]. Cellular signalling, 2011, 23(4): 609-20.

[6] KUZNETSOVA V S, VASILYEV A V, BUHAROVA T B, et al. [Safety and efficacy of BMP-2 and BMP-7 use in dentistry] [J]. Stomatologiia, 2019, 98(1): 64-9.

[7] GUO J, WU G. The signaling and functions of heterodimeric bone morphogenetic proteins [J]. Cytokine & growth factor reviews, 2012, 23(1-2): 61-7.

[8] ISRAEL D I, NOVE J, KERNS K M, et al. Heterodimeric bone morphogenetic proteins show enhanced activity in vitro and in vivo [J]. Growth factors (Chur, Switzerland), 1996, 13(3-4): 291-300.

[9] ZHAO M, ZHAO Z, KOH J-T, et al. Combinatorial gene therapy for bone regeneration: cooperative interactions between adenovirus vectors expressing bone morphogenetic proteins 2, 4, and 7 [J]. Journal of cellular biochemistry, 2005, 95(1): 1-16.

[10] Zhou Jian, Tu Yeying, Zhao Zimu, et al. New progress in osteogenesis induced by heterodimer of bone morphogenetic protein [J]. Stomatology, 2020, 40(11): 1054-60.

[11] LOWERY J W, ROSEN V. The BMP Pathway and Its Inhibitors in the Skeleton [J]. Physiological reviews, 2018, 98(4): 2431-52.

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

[12] KATAGIRI T, WATABE T. Bone Morphogenetic Proteins [J]. Cold Spring Harbor perspectives in biology, 2016, 8(6).

[13] BUIJS J T, HORST G V D, HOOGEN C V D, et al. The BMP2/7 heterodimer inhibits the human breast cancer stem cell subpopulation and bone metastases formation [J]. Oncogene, 2012, 31(17): 2164-74.

[14] LITTLE S C, MULLINS M C. Bone morphogenetic protein heterodimers assemble heteromeric type I receptor complexes to pattern the dorsoventral axis [J]. Nature cell biology, 2009, 11(5): 637-43.

[15] MIAO C, QIN D, CAO P, et al. BMP2/7 heterodimer enhances osteogenic differentiation of rat BMSCs via ERK signaling compared with respective homodimers [J]. Journal of cellular biochemistry, 2018.

[16] ZHANG X, CHEN S, LIU Y, et al. Heterodimeric BMP-2/7 exhibits different osteoinductive effects in human and murine cells [J]. Growth factors (Chur, Switzerland), 2018, 36(3-4): 141-52.

[17] ZHU W, KIM J, CHENG C, et al. Noggin regulation of bone morphogenetic protein (BMP) 2/7 heterodimer activity in vitro [J]. Bone, 2006, 39(1): 61-71.

[18] Pan Qiuhui, Yang Songhai, Dong Qunwei, et al. Relationship Between the Bioactivity of BMP2/7 Heterodimers and Its Regulation of CIZ Expression [J]. China Biotechnology, 2007, (09): 14-8.

[19] HUNTLEY R, JENSEN E, GOPALAKRISHNAN R, et al. Bone morphogenetic proteins: Their role in regulating osteoclast differentiation [J]. Bone reports, 2019, 10: 100207.

[20] Chen Xiang, Wang Pingping. Mechanism of the bone morphogenetic protein 2 inducing osteoclast activation in the mouse model [J]. Journal of Bengbu Medical College, 2020, 45(01): 18-23.

[21] BI W, LIU Y, GUO J, et al. All-trans retinoic-acid inhibits heterodimeric bone morphogenetic protein 2/7-stimulated osteoclastogenesis, and resorption activity [J]. Cell & bioscience, 2018, 8: 48.

[22] FISHER L W, TERMINE J D, DEJTER S W, et al. Proteoglycans of developing bone [J]. The Journal of biological chemistry, 1983, 258(10): 6588-94.

[23] BERENDSEN A D, PINNOW EL, MAEDA A, et al. Biglycan modulates angiogenesis and bone formation during fracture healing [J]. Matrix biology: journal of the International Society for Matrix Biology, 2014, 35: 223-31.

[24] MORETH K, IOZZO R V, SCHAEFER L. Small leucine-rich proteoglycans orchestrate receptor crosstalk during inflammation [J]. Cell cycle (Georgetown, Tex), 2012, 11(11): 2084-91.

[25] NASTASE M V, IOZZO R V, SCHAEFER L. Key roles for the small leucine-rich proteoglycans in renal and pulmonary pathophysiology [J]. Biochimica et biophysica acta, 2014, 1840(8): 2460-70.

[26] XU T, BIANCO P, FISHER L W, et al. Targeted disruption of the biglycan gene leads to an osteoporosis-like phenotype in mice [J]. Nature genetics, 1998, 20(1): 78-82.

[27] CHEN X-D, ALLEN M R, BLOOMFIELD S, et al. Biglycan-deficient mice have delayed osteogenesis after marrow ablation [J]. Calcified tissue international, 2003, 72(5): 577-82.

[28] WADHWA S, EMBREE M C, KILTS T, et al. Accelerated osteoarthritis in the temporomandibular joint of biglycan/fibromodulin double-deficient mice [J]. Osteoarthritis and cartilage, 2005, 13(9): 817-27.

[29] SHIRAKURA M, KRAM V, ROBINSON J, et al. Extracellular Matrix Mediates BMP-2 in a Model of Temporomandibular Joint Osteoarthritis [J]. Cells, tissues, organs, 2017, 204(2): 84-92.

[30] MYREN M, KIRBY DJ, NOONAN ML, et al. Biglycan potentially regulates angiogenesis during fracture repair by altering expression and function of endostatin [J]. Matrix biology: journal of the International Society for Matrix Biology, 2016, 52-54: 141-50.

[31] MOCHIDA Y, PARISUTHIMAN D, YAMAUCHI M. Biglycan is a positive modulator of BMP-2 induced osteoblast differentiation [J]. Advances in experimental medicine and biology, 2006, 585: 101-13.

[32] BERENDSEN AD, FISHER LW, KILTS TM, et al. Modulation of canonical Wnt signaling by the extracellular matrix component biglycan [J]. Proceedings of the National Academy of Sciences of the United States of America, 2011, 108(41): 17022-7.

[33] CHEN XD, FISHER LW, ROBEY PG, et al. The small leucine-rich proteoglycan biglycan modulates BMP-4-induced osteoblast differentiation [J]. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 2004, 18(9): 948-58.

[34] BI Y, STUELTEN C H, KILTS T, et al. Extracellular matrix proteoglycans control the fate of bone marrow stromal cells [J]. The Journal of biological chemistry, 2005, 280(34): 30481-9.

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0060

[35] JONGWATTANAPISAN P, TERAJIMA M, MIGUEZ P A, et al. Identification of the effector domain of biglycan that facilitates BMP-2 osteogenic function [J]. Scientific reports, 2018, 8(1): 7022.

[36] SONG R, ZENG Q, AO L, et al. Biglycan induces the expression of osteogenic factors in human aortic valve interstitial cells via Toll-like receptor-2 [J]. Arteriosclerosis, thrombosis, and vascular biology, 2012, 32 (11): 2711-20.

[37] MORENO M, MUñOZ R, AROCA F, et al. Biglycan is a new extracellular component of the Chordin-BMP4 signaling pathway [J]. The EMBO journal, 2005, 24(7): 1397-405.