Review Article

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Bone Morphogenic Protein: A Short Reveiw

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Abstract

Bone morphogenic protein (BMP) was first observed by Marshall Urist. Bmp is effective in the process of osteoinduction. BMP belongs to transforming growth factor-b superfamily. BMP is expressed in various oral lesions like osteosarcoma, malignant fibrous histiocytoma and fibrous dysplasia. The BMP's play an important role in cell growth, its differentiation, apoptosis, preservation of joint integrity, vascular remodeling as well as commencement of fracture healing. The article is aimed at discussing various types of BMP's, their functions, molecular characteristics and their role in various oral lesions.

Keywords: Bone Morphogenic Protein; Molecular Characteristics; Oral Lesions.

Introduction and Historical Overview

In 1889, Senn observed that decalcified bone has ability to encourage the bony defects. He treated osteomyelitic bony defect by utilizing the decalcified remnants of ox-bone with use of iodoform. His main aim was to treat osteomyelitis by providing antiseptic coverage by using iodoform and decalcified ox-bone as a transporter for the iodoform. Unexpectedly, he observed that new bone was forming along with the infection control [1]. The BMP was first observed in the 1965 by Dr. Marshall Urist, an orthopedic surgeon. He observed that when devitalized bone were embedded into animal, a cellular reaction occurred which resulted in the development of fresh bone tissue [2,3,4]. In short, it was observed that BMP are naturally occurring proteins that exist in the demineralized bone matrix and are effective in process of osteoinduction [5].

BMP belongs to part of transforming growth factor-b superfamily. This family includes various proteins such as activins, inhibins, glial derived neurotrophic factors, growth differentiation factors, anti-mullerian hormones etc. [6]. Number of activity during early development are based on BMP signaling for the process of cell growth, differentiation as well as apoptosis [7,8,9,10]. It is also observed that BMP plays a principal supporting role in various processes such as preservation of joint integrity, vascular remodeling as well as commencement of fracture healing [11,12,13].

Functions of BMP

BMP-2 plays a remarkable role in epithelial-mesenchymal interaction of organogenesis. Also, BMP-2 plays important role in bone and cartilage morphogenesis, osteoblast differentiation and osteoinduction. Bmp-4 performs an important role during embryogenesis in ventral induction. Bmp-2 alongwith BMP-7 are considered to be powerful inducers of cartilage as well as bone formation. BMP-4 plays crucial role in teeth and bone morphogenesis. BMP-5 thought to play role in limb development alongwith bone morphogenesis.

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BMP-6, BMP-7, BMP-8 and BMP-9 have important role in bone and cartilage morphogenesis. BMP-12 was seen in ligament and tendon development. BMP-14 plays an important role in chondrogenesis and angiogenesis. BMP-3 are considered to be BMP inhibitor [14,15].

BMP receptors

The BMP receptors are formed from type 1 and type 2 serine/threonine kinase proteins. They consist of 10-12 cysteine residues, serine/threonine kinase, cytosolic domain and a transmembrane domain. BMP receptors are divided into 2 subfamilies i.e. type 1 and type 2. The BMP type-1 receptors include alk1, alk2, alk3, alk4 and alk6. There are three types of BMP type 2 receptors i.e. activin type ii receptor (actrii), activin type ii b receptor (actriib) and bmp type ii receptor (brii) [16]. BMP's have potential to bind type 1 receptor even in the absence of type 2 receptor. Although, their binding capability is raised when both receptors are present [17].

Carrier materials

Many types of carrier materials have been examined for their potential for delivering rhbmp's. Following the origin and chemical composition, carrier material can be classified into 4 main type's i.e. synthetic polymers, natural polymers, composites and inorganic materials (ceramics) [18].

Framework of various BMP

BMP-2: Bmp 2 expression can be noted in various structures like chorion cells and amniotic cells [19,20]. Bmp-2 expression can also be observed in apical ectodermal ridge, outer myocardial layer and in developing limbs [20,21,22,23].

BMP-4: Bmp-4 is broadly expressed in embryo mainly in amnion and allantois [21,24]. An extreme bmp-4 expression is noted in neural tube area. As the development continues, bmp-4 transcripts is appreciable in various structures like myocardium, otic vesicles, developing eye, branchial arches etc. [22,24,25,26]

BMP-5: Bmp-5 shows their expression in developing lungs specially in mesenchymal cells. Various structures like meninges, ureter also shows Bmp-5 positivity [27].

BMP-6: Bmp-6 expression has been noted in various studies. Its expression is observed in visceral yolk sac and in branchial pouch [28,29]. Bmp-6 is expressed favorably in hypertrophic chondrocytes [30].

BMP-7: A large number of research has been conducted on bmp-7 expressions. The expression begins during the period of early gastrulation [19,21]. Bmp-7 seems to be strongly expressed in the ectoderm [19,22]. The Bmp-7 transcripts are noted in wolffian ducts. This wolffian duct is responsible for formation of ureteric buds. During the development of eye, Bmp-7 seems to be expressed in optic vessels as well as lens placode [31,32]. It is also noted that Bmp-7 expression is seen in atrial as well as ventricular chambers of heart [22].

Molecular characteristics of various BMP's

BMP-2: Bmp-2 is acidic glycoprotein having molecular weight 32kDa (kilodalton).it is composed of 114 amino acid residues and found to be rich in glutamate. With isoelectric point in between 4.8-5.1, they can be easily disintegrated into neutral salt solution. The Bmp-2 monomer foundation is based on 3 intra chain disulfide bonds which is formed by 6 cysteine residues. Bmp-2 proprotein consist of 4 glycosylation sites [33,34].

BMP-3: Bmp-3 contains 362 amino acid in prepropeptide alongwith 472 amino acid in precursor and in mature segment, It contains 110 amino acids. The weight of mature segment is approximately 13kDa. It contains disulfide linked homodimer [35]

BMP-3b/GDF-10: Human bmp-3b is also known as gdf 10 (growth differentiation factor 10). It contains 478 amino acid prepropolypeptide having molecular weight of 52kDa (approximately). The mature segment contains 110 amino acids having 7 cysteine alongwith 1 n-linked glycosylation position [36,37].

BMP-4: Bmp-4 is an acidic glycoprotein which is secretory and hydrophobic in nature. The bmp-4 consist of 116 amino acids having molecular weight of 30kDa (approximately) [38,39]. There are two types of arrangements of bmp-4. First type is seen in mature placenta and others are seen in osteosarcoma. The protein precursor of first and second types consists of 402 and 408 amino acids respectively [40].

BMP-5: Bmp-5 is arranged as 454 amino acid preproprotein. When divided, they produce 138 amino acid mature polypeptide, which consist of 7 cysteine with 3 n-linked glycosylation position [41].

BMP-6: Bmp-6 consists of 513 amino acid residues. It comprises of n-terminal peptide and a propeptide containing 23 amino acids residues and 490 amino acids residues respectively. Protease

hydrolyze the propeptide, which produces acidic glycoprotein having molecular weight of 15.6 kDa (approximately) and 139 amino acid residues. Bmp-6 carries 7 cysteine residues and 3 glycosylation sites [42].

BMP-7: Inside the cells, Bmp-7 is arranged in proprotein form. The proprotein form consists of 431 amino acid residues, which is composed of signal, leader and mature peptide [43]. The mature form of bmp-7 weighs 15.6 kDa (approximately) and comprises of 3 glycosylation sites. Bmp-7 can unite with other forms of bmp leading to formation of heterogenous dimmers like bmp-2/7, bmp-4/7. The biological happenings of heterogenous dimmers, when compared with homodimer, was found to be 2-20 folds higher [44,45].

BMP-8/BMP-8a/Op-2: Bmp-8, also known as op-2, contains 139 mature amino acid segments alongwith 244 amino acid in pro-region and 19 amino acid in signal sequence. Bmp-8 comprises of 8 cysteine. The mature bmp-8 polypeptide consist of 1 potential n-linked glycosylation [46].

BMP-9: Bmp 9, also called as gdf 2 (growth differentiation factor 2), contains 428 amino acids residues in proprotein [47].

BMP-10: Bmp-10 contains 309 amino acid proregion and 108 amino acid mature region. The mature region contains 7 cysteines [48].

BMP-11: Bmp-11 is also known as gdf-11 (growth differentiation factor 11). It consists of 407 amino acids prepropeptide and have 7 cysteine residues. In the mature area it contains 111 amino acids [49,50].

BMP expressions in various oral lesions

Osteosarcoma: In a study conducted by Yoshioka et al, they observed that a total of 17 cases out of 29 showed bmp immunoreactivity in the cytoplasm. Regarding the histologic subtypes of osteosarcoma, 8 cases of fibrohistiocytic osteosarcoma and 9 cases of osteoblastic sarcoma showed bmp positivity [51].

Another study conducted by Sulzbacher in 2002, where a total of 47 samples of osteosarcoma were examined immunohistochemically by using different bmp subtypes. They found that 28 cases expressed bmp-2/4 and 24 cases showed bmp-3 positivity. On the other hand, 41 samples showed bmp-5 positivity and 31 samples expressed positivity for bmp-6. They observed that high bmp-6 expressions were seen in areas having chondroid differentiation. Bmp-7 positivity was shown by 43 cases whereas bmp-8 immunoreactivity was shown by 42 cases. In a study conducted by Mehdi et al, they noted that 9 out of 11 cases of osteosarcoma showed positivity for bmp staining [53].

Malignant Fibrous Histiocytoma: Yoshioka et al. found that 11 cases of malignant fibrous histiocytoma showed the bmp immunoreactivity [51]. In another study conducted by Mehdi et al. in 2000, it was observed that 8 out of 10 cases of malignant fibrous histiocytoma showed bmp positivity [53].

Liposarcoma: Yoshioka et al in their study noticed that 5 cases of liposarcoma shows bmp positivity [51].

Fibrous dysplasia and Ossifying fibroma: A study had been conducted by Seta and Jabbar to check the bmp expression in samples of fibrous dysplasia and ossifying fibroma. In this study, they observed that 2 cases of fibrous dysplasia and 4 cases of ossifying fibroma showed positivity for bmp-7 [54].

Odontogenic tumors: A study had been conducted in 1997 by Gao et al. regarding expressions of bmp in odontogenic tumors. Different types of odontogenic tumor like ameloblastoma, adenomatoid odontogenic tumor, cementifying fibroma, dentinoma, compound odontoma, calcifying epithelial odontogenic tumor, benign cementoblastoma and odontogenic fibroma were included in the study. They observed that cementifying fibromas, dentinoma, odontogenic fibromas, benign cementoblastomas and compound odontomas showed positive bmp expression while ameloblastoma, calcifying epithelial odontogenic tumors and adenomatoid odontogenic tumors showed negative bmp expressions [55]. Another study were conducted by Nascimento et al. in 2017. In their study, they investigated the expression of bmp-2 and bmp-4 along with their receptors in solid ameloblastomas (30 cases), adenomatoid odontogenic tumors (30 cases) and unicystic ameloblastoma (10 cases). They noticed that all cases of solid ameloblastomas, adenomatoid odontogenic tumors and unicystic ameloblastomas showed bmp-2 and bmp-4 immunopositivity [56].

Conclusion

BMP has a very important role to play during the development as it is associated with development of various organs in the body. As the various BMP's are said to play an important role in different oral lesions, from the dental point of view it is important to do further research oriented studies on BMP.

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