Role of bone morphogenic protein in osteoarthritis

Essay

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Mohammed Makloph

List of figures

fig. No. title page No

List of abbreviations

Abb.	Full Term

ACLT……anterior cruciate ligament transaction

Act…… activin

AD MSC……....adult mesenchymal stem cell

AF…….. annulus fibrosus

Arg……....arginine

BMP…….....bone morphogenic protein

BMC……..bone marrow concentrate

CDMP……....cartilage derived morphogenic protein

cDNA ……cylic deoxy ribonucleic acid

Cys……. cysteine

ECM……extracellular matrix

EGF…….epidermal growth factor

FDA……food drug administration

FGF…… fibroblast growth factor

FOP…… fibrodysplasia ossificans progressive

GAGS……. Glycosaminoglycans

List of abbreviations (con. . . .)

Abb.	Full Term
GDF	growth differentiation factor
GS	glycine specific
HA	hyaluran hexachloride
IGF	insulin growth factor
IL	interleukins
Kg	kilogram
M	molecules
MMP	matrix metallo proteinase
O.A	osteoarthritis
OIF	osteo inductive factor
OP	osteogenic protein
NP	nucleus pulposus
PG	proteoglycan
PDGF	platelet derived growth factor
PLGA	poly lactic glycolic acid
PRP	platelet rich plasma

abstract

BMPs are members of the TGFb superfamily.The structure of more than sixteen different human BMPs has been identified with the aid of molecular biology techniques. BMPs induce the formation of both cartilage and bone. BMP2, 4, 6, 7, and 9 are commonly referred to as the osteogenic BMPs.

BMP-2 increased Extracellular matrix production and decreased expression of collagen type 1 When injected into murine knees, chondrophytes.Systemic administration of rhBMP-2 increases mesenchymal stem cell activity and reverses ovariectomy-induced and age-related bone loss in two different mouse models.

BMP7(OP-1) stimulates the synthesis of the majority of cartilage extracellular matrix proteins in adult articular chondrocytes derived from different species and of different age. OP-1 counteracts the degenerative effect of numerous catabolic mediators.BMP-7 has a strong anabolic effect on cartilage by stimulating synthesis of cartilage matrix components and increasing proteoglycan and collagen synthesis. Also there is reduction in the level of substance P. Recombinant bone morphogenctic protein

stimulates ingrowth of mesenchymal cells into the chondral defects which then transform into newly formed articular cartilage-like tissue. The regenerated cartilage was rich in proteoglycans and type II collagen.

Key word:

BMP,Chondrocyte, Mesynchmal stem cell, IL1,Proteoglycan, Collagen II, Fibronectin, Aggrecan, Noggin, Smad.

Introduction

Osteoarthritis (OA), the most common type of joint disease, is a degenerative disorder resulting from the breakdown of articular cartilage in synovial joint such as the knee , hip , and hands . The mechanisms of pathogenesis are not fully understood, but there appears to be a genetic component . There are many lines of treatment currently available for OA , ranging from the most conservative measures such as physical therapy and nonsteroidal antiinflammatory drugs to more surgical extremes , which range from arthroscopic procedures to total joint arthroplasty **(Buckwalter JA, Mankin HJ, 1998) .**

Although current lines of treatment target the symptoms of OA , they are not disease-modifying because they do not address the fundamental mechanism behind OA, which is the destruction of articular cartilage. A relatively new treatment is injection of hyaluronan, which improves joint lubrication and can decrease pain **(Puhl W,1993) .**

The activity of Bone Morphogenetic Proteins (BMPs) was first observed in the mid-1960s when it was

discovered that they could induce ectopic bone formation **(Urist MR, 1965).**

Many studies have since demonstrated the ability of BMPs to induce mesenchymal stem cells to differentiate into bone, confirming their role in bone and cartilage formation. BMPs are part of the Transforming Growth Factor-β superfamily proteins which includes TGF-βs, activins, inhibins, Growth Differentiation Factors (GDFs), Glial Derived Neurotrophic Factors (GDNFs), Nodal, Lefty, and anti-Müllerian hormone. Since their initial discovery, they have been shown to affect a wide variety of cell types and processes beyond bone and osteogenesis **(Badlani N et al ,2009)** . BMPs also play important roles in maintaining adult tissue homeostasis, such as the maintenance of joint integrity, the initiation of fracture repair, and vascular remodeling **(Bakker AC et al ,2001) .**

More than 15 known BMPs are structurally related and can be further categorized into subgroups based on amino acid or nucleotide similarity. In particular, BMP2/4, BMP5/6/7/8, BMP9/BMP10, and BMP12/13/14 (GDF5/6/7) are subgroups based on phylogenetic analysis **(Ellman MB et al,2008) .** Analysis with amino acid or nucleotide sequences of

BMPs yields similar clustering patterns. BMP1, while able to induce bone and cartilage development, is a metalloprotease that functions in collagen maturation as a procollagen C-proteinase and is not part of the TGF-β superfamily **(Ellsworth JL et al ,2002)** .

BMP-7, a member of the transforming growth factor-β superfamily, is best known for its osteogenic properties **(Cook SD, 1999).**

Studies have shown that BMP-7 has many major benefits on cartilage tissue in vitro. It has a strong anabolic effect on cartilage by stimulating synthesis of cartilage matrix components and increasing proteoglycan and collagen synthesis . More over it has been known to protect cartilage and inhibit degradation in models of OA by antagonizing catabolic mediators of cartilage, leading to a possible protective effect **(Chubinskaya S, Kuettner KE, 2003) .** Interleukin (IL)-1 cause downregulation of proteoglycan which is a mean component of cartilage . It was found that Treatment of human articular chondrocytes with BMP-7 blocked down regulation of proteoglycan synthesis, Thus prevent the occurrence of OA **(Huch K ,1997) .** BMP-7 also blocked the cartilage damaged caused by fibronectin by preventing proteoglycan degradation

Introduction

(Koepp HE ,1999). BMP also reduce matrix metalloproteinase (MMP)-13 expression in chondrocytes, which normally plays a pathologic role in the cartilage destruction **(Im HJ,2003) .**

Flechtenmacher J et al found that Recombinant human BMP-7 known as Osteogenic protein one(OP-1) markedly stimulate synthesis of proteoglycans (mostly aggrecan) and collagens (predominantly type II) by all chondrocyte preparations. and was associated with continued expression of the chondrocyte phenotype **(Flechtenmacher J et al,1996)**

Although the name implies that all members are inducers of bone, some BMPs can act as inhibitors of bone formation. For example, BMP3 is a negative regulator of bone density, and BMP13 is a strong inhibitor of bone formation **(Elshaier AM et al ,2009) .** BMP2, 4, 6, 7, and 9 are commonly referred to as the osteogenic BMPs, based on their potent bone-inducing activity **(Fan H et al,2010) .** For instance, BMP2 is indispensable for endochondral bone formation.It is considered a main player during endochondral bone development for chondrocyte proliferation and maturation **(Fan J, et al,2010) .**

Introduction

BMP2 contributes to both chondrocyte hypertrophy and cartilage degradation **(Papathanasiou I et al,2012) .** This dual role of BMPs in OA has been discussed and explains why both increased cartilage anabolism and catabolism are observed in the same time **(Nakase T et al, 2003) .** Elevated serum BMP2 and BMP4 is evidence of advanced OA , hence it has been proposed as indicators for disease severity and joint arthroplasty**(Albilia JB et al ,2013)** . An association between two polymorphisms in intron I of the *BMP5* gene and OA has been demonstrated, and suggests that variability in gene expression of BMP5 is a susceptibility factor for the disease **(Southam L et al, 2004)** .

Aim of the work:

The aim of this study is to explore the effectivness of Bone morphogenic protein(BMP) as a therapy for preexisting OA and to begin to elucidate a mechanism behind its potential protective effect on articular cartilage.

Chapter (1)

Osteoarthritis(O.A)

Full-thickness chondral defects and early osteoarthritis continue to present major challenges for the patient and the orthopaedic surgeon as a result of the limited healing potential of articular cartilage. The use of bioactive growth factors is under consideration as a potential therapy to enhance healing of chondral injuries and modify the arthritic disease process **(Lisa AF,et al, 2011) .**

Osteoarthritis (OA) is a progressive, debilitating disease of the joints characterized by the erosion of articular cartilage of Synovial joints **(Ginette T,et al,2004).** Synovial joints account for most of the body articulations they are characterized by wide range of frictionless movement. The articulating bony surfaces have a thin plate of hyaline articular cartilage serves as the bearing and gliding surface tightly adherent to the bony end plate.The joint cavity is a space containing a few milliliters of synovial fluid ,between the articular surface surrounded by joint capsule **(Bulckwalter and Mankin,1998).**

Osteoarthritis(O.A)

The articular cartilages are avascular they receive their nutrition through double diffusion system. It has lamellar organization consisting of successive zone, Superficial(gliding)zone, Transition(middle) zone, and radial(deep) zone **(jasin,1995)** . It is formed of cells(chondrocytes) and matrix(water and macromolecules), the occurence of O.A through the decreased proteoglycan content of the matrix by degradation through mettalloproteases in association with damaged collagen structure leading to loss of physiological properties of the aricular cartilage matrix **(Bulckwalter and Mankin,1998).**

Although much is known about the expression and regulation of genes associated with OA (e.g., metalloprotease, tissue inhibitor of metalloproteases, inflammatory cytokines, and extracellular matrix proteins such as collagens and proteoglycans), it is likely that the expression of many other genes is also affected during this pathologic process, and more is yet to be learned in order to gain a comprehensive understanding of this disease **(Ginette T,et al,2004).**

The earliest finding in O.A a disruption of the surface which instead of being smooth , It shows