Role of Bone Morphogenetic Protein-2 in Primary Osteoarthritis

Thesis

Submitted for partial fulfillment of Master Degree in Physical medicine, Rheumatology and Rehabilitation

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2014

Acknowledgement

First and foremost I would like to express my sincere gratitude to ***Prof. Dr. Nadia Abdel Salam EL Kadery,*** *Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her continuous support, patience, motivation and immense knowledge.*

My sincere thanks also goes to ***Prof. Dr. Henaz Farouk Khaled,*** *Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her excellent guidance, caring, valuable advice and insight throughout my work.*

I owe my deepest appreciation to ***Assist Prof. Dr. Abeer Ahmed Kadry Elzoheiry,*** *Assistant Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her kind assistance, support, encouragement and providing coherent answers to my questions.*

Last but not the least; I would like to thank my ***Family*** *for supporting and encouraging me always with their best wishes.*

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List of Abbreviations

Abbrev.	Meaning
ABC	: Avidin-Biotin-Peroxidase Complex
ACR	: American college of rheumatology
ActR	: Activin receptor
ADAMTS	: A disintegrin and metalloproteinase with thrombospondin motifs
ALK	: Activin receptor–like kinase
ALP	: Alkaline phosphatase
ALT	: Alanine transaminase
Ang	: Angiopoietin
AST	: Aspartate Aminotransferase
AUC	: Area under the curve
BMI	: Body mass index
BMPR	: Bone morphogenetic protein receptor
BMPs	: Bone morphogenetic proteins
BUN	: Blood urea nitrogen
C Smad	: Common partner Smads
CBC	: Complete blood count
Cbfa1	**:** Corebinding factor-1
CDMP	: Cartilage-derived morphogenetic protein
COMP	: Cartilage oligomeric matrix protein
CRP	: C-reactive protein
CSF1	: Colony-syimulating factor-1
CT	: Computed tomography
DDR2	: Discoidin domain receptor 2
DKK	: Dickkopf factors
DM	: Diabetes Mellitus
ECM	: Extracellular matrix
EDTA	: Ethylenediaminetetraacetic acid
EGF	: Epidermal growth factor

List of Abbreviations *(Cont...)*

Abbrev.	Meaning
ELISA	: Enzyme-linked immunosorbent assay
ER	: Endoplasmic reticulum
ERK	: Extracellular signal-regulated kinase
ESR	: Erythrocyte sedimentation rate
EULAR	: European League Against Rheumatism
FBS	: Fasting blood sugar
FGF	: Fibroblast growth factor
FKBP12	: FK-binding protein 12
FN	: False negative
FP	: False positive
FZD	: Frizzled receptors
GDF	: Growth differentiation factor
GDNF	: Glial cell line derived neurotrophic factor
GPI	: Glycosylphosphatidylinositol
GRO α	: Growth regulated oncogene α
GS	: Glycine-Serine
GTPase	: Guanosinetriphosphatase
Hg	: Haemoglobin
HGF	: Hepatocyte growth factor
HIF	: Hypoxic inducible factor
HISS	: Hepatic insulin-sensitizing substance
HMG	: High mobility group
HS	: Highly significant
IGF	: Insulin-like growth factor
IL	: Interleukin
I-Smad	: Inhibitory Smad
JNK	: Jun N-terminal kinase
K-L	: Kellgren and Lawrence scoring system
KOOS	: Knee injury and osteoarthritis outcome score

List of Abbreviations *(Cont...)*

Abbrev.	Meaning
LRP5/6	: Lipoprotein receptor-related protein 5/6
MAP	: Mitogen activated protein
MCP1	: Monocyte chemotactic protein 1
M-CSF	: Macrophage colony-stimulating factor
MIP	: Macrophage inflammatoey protein
MISR	: Mullerian inhibiting substance receptor
MMPs	: Matrix metalloproteinases
MRI	: Magnetic resonance imaging
MSC	: Mesenchymal stem cells
NGF	: Nerve growth factor
NO	: Nitric oxide
NPRS	: Numeric pain rating scale
NS	: Non significant
OA	*:* Osteoarthritis
OP-1	: Osteogenic protein-1
OPG	: Osteoprotegrin
PDGF	: Platelet-derived growth factor
PGs	: Prostaglandins
PLT	: Platelets
PTH	: Parathyroid hormone
R -Smad	: Regulated Smad
RA	: Rheumatoid arthritis
RANK-L	: Receptor activator of NF-k B ligand
RANTES	: Regulated and normal T-cell expressed and secreted
RF	: Rheumatoid factor
RGM	: Repulsive guidance molecule
rhBMPs	**:** Recombinant human Bone morphogenetic protein
ROC	: Receiver operating characteristic
R-Smad	: Regulated Smad

List of Abbreviations *(Cont...)*

Abbrev.	Meaning
RUNX2	: Runt-related transcription factor 2
S	: Significant
SD	: Standard deviation
sFRPs	: Secreted frizzled related proteins
SGOT	: Serum glutamic oxaloacetic transaminase
SGPT	: Serum glutamic-pyruvic transaminase
SLE	: Systemic lupus erythematosus
SMAD	: Small mother against decapentaplegic
SOX-9	: SRY-related high-mobility-group box transranscription factor 9
SpA	: Spondyloarthropathy
SPSS	: Statistical package for Social Science
TGF-β	: Transforming growth factor β
TLR	: Toll-like receptor
TMB	: Tetramethylbenzidine
TN	: True negative
TNF	: Tumor necrosis factor
TP	: True positive
Tsg	: Twisted gastrulation
USAG-1	: Uterine sensitization-associated gene-1
VEGF	: vascular endothelial growth factor
WBC	: White blood cells
Wifs	: Wnt inhibitory factors
Wnt	: Wingless proteins
WOMAC	: Western Ontario and McMaster university osteoarthritis index

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Introduction

Osteoarthritis (O.A), also known as 'osteoarthrosis' is the most prevalent complex, degenerative chronic disease. It is a disorder of the hyaline joints characterized by wear, softening and thinning of the articular cartilage and diminished compliance of the sub-chondral bone ***(Bijlsma et al., 2011).***

These pathological changes progressively lead to severe limitation of physical activity and great impairment of quality of life, which can ultimately lead to articular prosthetic substitution ***(Loeser, 2010).***

O.A affects nearly half the elderly population worldwide. The patterns of O.A incidence and prevalence shows that it occurs in the hip, knee, foot, hand, wrist and spine and is rarely to occur in the ankle, elbow and shoulder ***(Lories and Luyten, 2011).***

Many different factors contribute to the onset and progression of OA, these include genetics, age, sex, obesity and joint instability.

For the purpose of this thesis, these factors will be mentioned in brief, we will focus on the molecular pathways involved in cartilage and bone changes in OA. In particular, major factors involved such as bone morphogenetic proteins, will be discussed in details.

Multiple genetic factors can contribute to the incidence and severity of O.A and these may differ according to specific joint (hand, hip, knee, or spine), sex, and race. Generalized nodal O.A was twice as likely to occur in first degree relatives. Also, there is a significantly higher concordance for O.A between monozygotic twins than between dizygotic twins, and that the hereditable component of O.A may be in the order of 50% to 65% ***(Valdes et al., 2008).***

Several candidate genes encoding proteins of the extracellular matrix of the articular cartilage have been associated with early onset O.A. In addition to point mutations in type II collagen, inherited forms of O.A may be caused by mutations in several other genes that are expressed in cartilage, including those encoding types IV, V, and VI collagens, as well as cartilage oligomeric matrix protein (COMP). Other non structural proteins such as the secreted frizzled related protein 3 and von Willebrand factor genes have also been identified ***(Miyamoto et al., 2008).***

Although older age is the greatest risk factor for O.A, O.A is not an inevitable consequence of growing old ***(Shane Anderson and Loeser, 2010).*** The mechanisms for the link between aging and O.A are incompletely understood. Cell stress and oxidative damage contribute to chronic inflammation that promotes age related diseases. This, results in senescence associated secretory phenotype, which has many of the characteristics of an osteoarthritic chondrocyte in terms of the cytokines, chemokines, and proteases produced ***(Loeser, 2011).***

There is a marked increase in prevalence among women after the age of 40 years and the cause of this increase has been ascribed to estrogen insufficiency. Articular chondrocytes possess functional estrogen receptors, and there is evidence that estrogen can upregulate proteoglycan synthesis. In support of a role for estrogens in O.A, there are human studies indicating that estrogen replacement therapy reduces the incidence of O.A ***(Sniekers et al., 2008).***

Obesity is another important risk factor for O.A. An increase in mechanical forces across weight-bearing joints is probably the primary factor leading to joint degeneration. The majority of obese patients exhibit varus knee deformities, which result in increased joint reactive forces in the medial compartment of the knee, thereby accelerating the degenerative process ***(Anderson and Felson, 1988).***

Emerging data implicate a crucial role for adipocytes in regulation of cells present in bone, cartilage, and other tissues of the joint. Protein such as leptin may have important involvement in the onset and progression of O.A. In addition, adipocyte derived factors such as interleukin (IL)-6 and C reactive protein (CRP) appear to be procatabolic for chondrocytes ***(Dumond et al., 2003).***

Whether joint malalignment leads to the development of O.A is a matter of debate. However, the evidence does indicate that varus or valgus deformities are associated with risk for progression of knee O.A ***(Sharma, 2006).*** As regards their mechanisms, altered joint geometry may interfere with nutrition of the cartilage, or it

may alter load distribution, either of which may result in altered biochemical composition of the cartilage ***(Hunter et al., 2007).***

The first consideration with respect to exercise is whether wear and tear resulting from repetitive use of articular cartilage leads to progressive O.A. However, exercise in the absence of injury, has not been found to increase one's risk of developing O.A, on the contrary it helps O.A of the knee by strengthening the muscles surrounding the joint providing better support and also act as shock absorbers ***(Bosomworth, 2009).***

In contrast with degradation occurring in O.A, a remodelling process is initiated as a response to injury, resulting in osteophytes at the joint margins. The bone morphogentic proteins (BMPs) are involved in protection against cartilage destruction and in new bone and cartilage formation. They stimulate production of extracellular matrix (ECM) components by chondrocytes and have the ability to counteract catabolic cytokines like interleukin 1 (IL-1) ***(Matsubara et al., 2008).***

The bone morphogentic proteins are subset of the (TGF- ß) superfamily. Although other growth factors such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) can be found in bone and have various effects on bone and cartilage cells in vitro, only BMPs have been demonstrated to induce either cartilage or bone formation in vivo ***(Issa et al.,2006).***

Bone morphogentic proteins are produced by mesenchymal cells, osteoblasts and chondrocytes. Different BMPs as-2,-4and-7 function independently or in collaboration with each other, as well as with other members of the TGFβ superfamily, to trigger a cascade of events that promote the formation of cartilage and bone. Cellular processes stimulated include chemotaxis, mesenchymal cell proliferation and differentiation, angiogenesis and synthesis of extracellular matrix ***(Reddi et al., 2001).***

It has been proposed that BMP-2 may be one of the most potent inducers of mesenchymal cell differentiation to osteoblasts, while the remaining BMPs promote the maturation of committed osteoblasts ***(Cheng et al., 2003).*** Moreover, BMP-2 controls the expression of several other BMPs and when its activity is blocked, marrow stromal stem cells fail to differentiate into osteoblasts ***(Edgar et al., 2007).***

Although BMP-2 is able to induce cartilage formation, it was found that its expression in healthy cartilage was low but that its expression was elevated in areas surrounding cartilage lesions and in OA cartilage. This could indicate that BMP-2 is upregulated as a reparative response but could also indicate that BMP-2 is merely upregulated as a pathological side effect, thereby further stimulating injury ***(Dell'Accio., 2006).***