Role Of Wnt Signaling Pathway In The Pathogenesis Of Rheumatic Diseases

Essay
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Abbreviations:

$^{-}$ / $^{-}$	Double knockout
$^{+}$ / $^{-}$	Single knockout
ALP	Alkaline phosphatase
AP1	Activator Protein-1
APC	Adenomatous polyposis coli
AS	Ankylosis spondylitis
BCL9	B-cell lymphoma 9 protein
BMD	Bone mineral density
BMP	Bone morphogenetic protein
B-Trcp	Beta-transducin repeat containing E3 ubiquitin protein ligase
CamKII	Calicium/calmodulin- dependant kinase II
Cbfa1	core-binding factor subunit alpha-1
CBP	CREB-binding protein
Cby	Chibby
CDC42	Cell division control protein 42
CK1	Casien kinase 1
Col 2	Type II collagen
Col1A1	Collagen, type I, alpha 1
COX	Cyclooxygenase
CRD	Cysteine rich domain
CREB	cAMP response element binding protein
CSF	Colony stimulating factor
CtBp	C-terminal binding protein
Daam1	Dishevelled associated activator of morphogenesis 1
DAP12	DNAX activation protein of 12 kDa
DDD	Disc degenerative disease
DIP	Distal interphalangeal
DKK	Dickkopf
DKK1-AS	Dickkofp1 anti sense oligonuceotide
DKK-Ab	Dickkopf antibody
Dlx5	Distal less home box 5
Dn	Dominant negative
DVL	Dishevelled
EGF	Epidermal growth factor
EPHB	Ephrin type-B receptors.
ER	Endoplasmic reticulum

ERK	Extracellular signal regulated kinase
EZH2	Histone methyltrasferase enhancer of zeste homologue 2
FEVR	Famillial exudative vitreoretinophathy
FGFs	Fibroblast growth factors
FLS	Fibroblast-like synoviocytes
Frzb	frizzled-related protein
FZD	Frizzled protein
Gdf5	Growth/differentiation factor 5
GPCRs	G-protein coupled receptors
GSK3	Glycogen synthase kinase 3
H3K4	Trimethylation of histone H3 at lysine 4
HAT	Histone acetyltransferase
HBM	High bone mass
HDAC	Histone deacetylases
Hh	Hedgeohog pathway
HMG	High mobility group
HMT	Histone methyltransferase
HSCs	Hematopetic stem cells
HSPGs	Heparan sulfate proteoglycans
hTNFtg	Human TNF transgenic
IGF	Insulin like growth factors
Ihh	Indian hedgehog homolog signaling pathway
IL	Interleukin
Int	Integration
ITAM	Immunoreceptor tyrosin based activation motif
JNK	C-Jun N-terminal kinase
KLF4	Kruppel-like factor 4
KO	Knockout
Krm	Kremen
LEF	Lymphoid enhancer factor
LRP	Low density lipoprotein receptor-related protein
Mab	Monoclonal anti body
Macf1	Microtubule actin cross-linking factor 1
MAP	Mitogen-activated protein kinase
M-CSF	Macrophage-colony stimulating factor
miRNA	Micro RNA
MMP	matrix metalloproteinase
MMTV	Mouse mammary tumor virus
MSCs	Mesenchymal stem cells

MuSK	Muscle, skeletal receptor tyrosine kinase
NFAT	Nuclear factor of activated T-Cell
NLK	Nemo-like kinase
NLS	Nuclear localization signal
NRH1	Neurotrophin Receptor Homolog 1
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OP	Osteoporosis
OPG	Osteoprotegrin
OPPG	Osteoporosis pseudoglioma syndrome
OSCAR	Ostroclast associated receptor
PCP	Planar cell polarity (pathway)
PG	Prosta glandin
PI4KII	Phosphotidylinositol 4-kinase type II
PIP2	Phosphotidylinositol 4,5 biphosphonate
PIP5KI	Phosphotidylinositol-4-phosphate 5-kinase type I
PKA	Protein kinase A
PKC	Protein kinase C
PP1	protein phosphatase 1
PP2A	Protein phosphatase 2A
PPAR	Peroxisome proliferator-activated receptors
PsA	Psoriatic arthritis
PTH	Parathyroid hormone
PTK7	Tyrosine-protein kinase like 7
Pygo	Pygopus
RA	Rheumatoid arthritis
RanBP3	Ran binding protein 3
RANK	Receptor activator of nuclear factor-κB
RANKL	Receptor activator of nuclear factor-κB ligand
RF	Rheumatoid factor
RFZD	Rat frizzled
RGS	Regular of G-protein signaling
RHOA	Radigraphic hip osteoarthritis
ROCK	Rho-associated kinase
ROR	Receptor tyrosine kinase-like orphan receptor
Rspo	R-spondin
Runx2	Runt related transcription factor 2
RYK	RYK receptor-like tyrosine kinase
S/T	serine/ threonine

Scl-Ab	Sclerostin antibody
SDF	Stromal derived factor
SF	Synovial fibroblast
sFRP1	Secreted frizzled related protein 1
SI	Sacro iliac
siRNA	Small interfering RNA
SNP	Single nucleotide polymorphism
SOST	Sclerostin
SpA	Spondylo arthritis
TAK	TGF-β activated kinase
TBL1	Transducin B-like Protein
TCF	T-cell transcriptional factor
TERM2	Triggering receptor expressed in myloid cell 2
TGF	Tranforming growth factor
TLE	Tansducin like enhancer protein
TNF	Tumor necrosis factor
TSC2	Tuberous sclerosis protein 2
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
Wg	Wingless
WIF	Wnt inhibitory factor
WISP	Wnt inducible signaling pathway protein
Wnt	Wingless and integration
WRE	Wnt responsive element
WTX	Wilms tumor gene on the X-chromosome

INTRODUCTION AND AIM OF THE WORK

Introducion

The Wnt signaling pathway is a network of proteins that passes signals from receptors on the surface of the cell through the cytoplasm and ultimately to the cell's nucleus where the signaling cascade leads to the expression of target genes. It controls cell-cell communication in the embryo and adult (*ie*, cell proliferation and differentiation during development and healing) (***Logan and Nusse, 2004***).

These proteins activate various pathways in the cell that can be categorized into the canonical and noncanonical Wnt pathways (***Nusse, 2012***).

The canonical Wnt pathway begins with the binding of Wnt to a receptor of the Frizzled family and to co-receptors known as low density lipoprotein receptor-related protein 5 (LRP5) and low density lipoprotein receptor-related protein 6 (LRP6). This bond promotes signal transduction via cytoplasmic proteins (***Sen, 2005***).

There are various inhibitors of the canonical Wnt signaling, e.g., the proteins of the Dickkopf family and the secreted Fz-related proteins (collectively also known as frizzled-related proteins), which inhibit the Wnt–Fz interaction and attenuate Wnt signaling (***Sen, 2005***).

So,Wnt signaling is modulated by several different families of secreted negative regulators. Among those, dickkopf (DKK) is a family of cystein-rich proteins comprising at least four different forms (DKK-1, DKK-2, DKK-3 and DKK-4). The best studied of these is DKK-1, which functions as natural inhibitor of Wnt canonical signaling, which has a central role in bone formation and development (***Bafico et al., 2001***).

In the noncanonical Wnt pathway, theWnt-type MMTV integration site family, member 5A (Wnt5A)initiates the signaling cascade, most likely mediated by DVL1 [dishevelled, dsh homolog 1 (Drosophila)],resulting in the liberation of intracellular Ca+2 and in the activation of calcium/calmodulin-dependent protein kinase II alpha (CAMK2A) and of protein kinase C (PKC) (***Veeman et al., 2003***).

Another form of noncanonical pathway signaling can occur via the planar cell polarity pathway, which regulates the organization of the cytoskeleton (***Povelones et al., 2005***).

The proteins Rac and Rho, members of the small GTPase family, are activated by DVL1, stimulating the activation of mitogen-activated protein kinase 8, and Rho kinase, which are involved in cell differentiation and growth (***Habas et al., 2003***).

Sclerostin a secreted glycoprotein,which is the product of the SOST gene, located on chromosome 17, locus q11.2 in humans, was originally believed to be a non-classical Bone morphogenetic protein (BMP) antagonist. More recently Sclerostin has been identified as binding to LRP5/6 receptors and inhibiting the Wnt signalling pathway (***Krumlauf and Ellies, 2002***).

Sclerostin is produced by the osteocyte and has anti-anabolic effects on bone formation (***RefSeq, 2008***).

Affliction of joints is the hallmark of rheumatic disease. In addition to pain, both degenerative and inflammatory rheumatic diseases lead to a profound remodeling of the joint architecture, that causes functional disability and progressive crippling (***Firestein, 2003***).

There are two major patterns of joint pathology in rheumatic diseases. One of these is progressive bone and joint destruction leading to joint instability. This pattern is the hallmark of rheumatoid arthritis(RA) and results in progressive joint deformity (***Walsh et al., 2005***).

In contrast, diseases such as ankylosing spondylitis and psoriatic arthritis are very different from rheumatoid arthritis and represent the second pattern of joint pathology, which is characterized by new bone formation. After initial destructive changes,joints ‘respond’ by forming osteophytes, which are bony appositions originating from the juxta-articular periosteal lining (***Klippel, 2001***).

The activation of Wnt signaling contributes to osteophyte formation and might be related to the anabolic model in joint remodeling observed in patients with ankylosing spondylitis, whereas the blockade of Wnt signaling facilitates bone erosion and might contribute to the catabolic model in the bone remodeling observed in patients with RA (***Schett et al., 2008***).

The activation of the Wnt/beta-catenin signaling in the chondrocytes induces cartilage matrix degradation similar to that which occurs in osteoarthritis and RA (***Yuasa and Iwamoto, 2006***).

It is hypothesised that inflammatory cytokines promote the imbalance between bone resorption and formation by affecting regulatory molecules of the Wnt pathway such as sclerostin. Targeting a pathway able to counter-regulate this imbalance of bone turnover may therefore be a key strategy in preventing structural damage in arthritis (***Wehmeyer et al., 2010***).

DKK-1 is a regulator of bone mass and joint remodeling. It may be a promising therapeutic target in osteoporosis; monoclonal antibody-based inhibition of Dkk-1 is already under development for osteoporosis treatment. Its role as a regulator of joint remodeling in animal models requires further exploration in human (***Daoussis and Andonopoulos, 2011***).

Therapeutic approaches to block or suppress canonical Wnt-β-catenin signaling may protect cartilage damage in end-stage OA. There are many naturally occurring Wnt-β-catenin signaling antagonists, including dickkopf 1 (DKK1), secreted frizzledrelated proteins (sFRPs), and sclerostin (SOST) (***Chan and Little, 2012***).

In patients with Ankylosing spondylitis, circulating bone formation–promoting factors functionally prevail. This can be at least partially attributed to decreased Dkk-1–mediated inhibition (***Daoussis et al., 2010***).

Aim of the work

The aim of this study is

1- To review the role of Wnt signaling pathway in the pathogenesis of rheumatic diseases.

2- To review the role of Wnt signaling pathway-dependant therapy as a treatment of rheumatic diseases.