Role of Survivin, a member of the apoptosis inhibiting protein family, in Rheumatoid Arthritis

Thesis
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Abstract

Rheumatoid arthritis (RA) is a highly heterogeneous disease with respect to its joint destructivity. Deficient apoptosis in rheumatoid synovial tissue has recently been demonstrated. Survivin is a 142-amino-acid protein that belongs to the IAP family, It can downregulate, directly or indirectly, both death-receptor-mediated and mitochondria mediated pathways of apoptosis. survivin was assessed by an ELISA in blood samples collected from 35 RA patients. Results were related to joint erosivity at the time of sampling. Survivin levels were significantly higher in patients with destructive disease as compared with in RA patients displaying a non-erosive disease.

Key words

Erosive RA.
Apoptosis.
Caspase.
IAPs family.
Survivin.

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List Of Abbreviations

Abbreviation	Full Name
ACR	American college of rheumatology.
AIF	Apoptosis-inducing factor.
ANA	Antinuclear antibody.
Apaf-1	Apoptosis protease-activating factor 1.
BAD	Bcl- XL /Bcl-2-associated death promoter.
Bak	Bcl-2 homologous antagonist/killer.
Bax	Bcl-2 -associated x protein.
Bcl-2	B cell leukaemia-2.
BH	Bcl-2 homology.
BIR	Baculoviral inhibitory repeat.
bp	Base pair.
C. Elegans	Caenorhabditis elegans.
CAD	Caspase-activated DNase.
cAMP	Cyclic adenosine 3',5'-monophosphate.
CARD	Caspase activation and recruitment domain.
CBC	Complete blood count.
CRP	C reactive protein.
DD	Death domain.
DED	Death effector domain.
DIP	Distal inter phalangeal.
DISC	Death-inducing signaling complex.
DNA	Deoxy ribonucleic acid.
ELISA	Enzyme linked immune-sorbent assay.

ESR	Erythrocyte sedimentation rate.
FADD	Fas-associated death domain.
FasL	Fas ligand.
FasR	Fas receptor.
FLICE	Fas ligand-interacting cell effector.
FLIP	FLICE-inhibitory protein.
FLS	Fibroblast like synoviocytes.
HLA	Human leucocytic antigen.
IAP	Inhibitor of apoptosis.
IL	Interleukin.
kb	Kilobase.
kDa	Kilodalton.
M.W	Molecular weight.
MCP	Meta-carpo-phalangeal.
MHC	Major histocompatability complex.
ML	Milliliter.
MRI	Magnetic resonance imaging.
mRNA	Messenger ribonucleic acid.
MTP	Meta-tarso-palangeal.
NF-κ B	Nuclear factor κ B.
No	Number.
P value	Probability value.
PCR	Polymerase Chain Reaction.
PIP	Proximal inter phalangeal.
RA	Rheumatoid arthritis.

RAI	Ritchie articular index.
RBCs	Red blood corpuscles.
RF	Rheumatoid factor.
RNA	Ribonucleic acid.
ROS	Reactive oxygen species.
SD	Standard deviation.
Smac	Second mitochondria-derived activator of caspases.
TGF-β	Transforming growth factor-beta.
TNF	Tumor necrosis factor.
TNFR	Tumor necrosis factor receptor.
TNF-α	Tumor necrosis factor-α.
TRAIL	TNF-related apoptosis inducing ligand.
XIAP	X chromosome-linked inhibitor of apoptosis.

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INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory joint disease characterized by hyperplasia of synovial tissue and pannus formation growing invasively into the cartilage, followed by cartilage and bone destruction. Analyses of hyperplastic synovial tissues of patients with RA reveal features of transformed long-living cells such as the presence of somatic mutations, expression of oncogenes, and resistance to apoptosis ***(Chou et al., 2001)***

Apoptosis is a tightly regulated process of elimination of aged cells without disrupting cellular integrity. Apoptosis may be initiated by extracellular stimuli through activation of death receptors on the cell surface, and intracellularly by the release of mitochondrial cytochrome c into the cytoplasm. Both pathways induce expression of apoptosis genes and activation of the caspase cascade, resulting in DNA fragmentation. The apoptosis signals are abrogated by the family of apoptosis-inhibiting proteins (IAPs) ***(Kim et al., 2002).*** A number of disturbances in the apoptosis machinery have been pointed out in RA patients ***(Hussein et al., 2004).***

Survivin is a 142-amino-acid protein that belongs to the IAP family, and it inhibits the activity of caspase 3, caspase 7, and caspase 9, but not of the upstream initiator protease caspase 8. Survivin can thereby

downregulate, directly or indirectly, both death-receptor-mediated and mitochondria-mediated pathways of apoptosis ***(Li F., 2003).***

survivin regulates the inflammatory and destructive process inside the joints of patients with RA, high levels of extracellular survivin are associated with chronic erosive arthritis, indicating poor prognosis ***(Bokarewa et al., 2005).***

AIM OF THE WORK

This study is designed to determine whether serum survivin has a role in the pathogenesis of Rheumatoid arthritis and if it has a role in the presence of erosion as well as evaluation of the possible influence of the ongoing treatment on the level of serum survivin.

RHEUMATOID ARTHRITIS

Historical data

Rheumatoid Arthritis appeared in Europe as late as 300 years ago only. It wasn't until 1859 that the disease earned a proper name, when Sir Alfred Garrod, the London physician, coined the clinical term “Rheumatoid Arthritis” ***(Rothschild and Woods, 1990).*** The name is derived from the Greek word, *rheumatos,* meaning "flowing", the suffix *-oid* meaning "in the shape of, *arthr* meaning "joint" and the suffix *-itis,* a "condition involving inflammation'' ***(O'Dell, 2004).***

The auto-immune theory to explain RA pathogenesis was first formulated in 1939. In 1941, RA, became official, as the American Rheumatism Association officially recognized RA as a distinct disorder and in 1946, the American Committee to Control Rheumatism is founded in Philadelphia, officially announced the modern American field of rheumatology. The Arthritis Foundation came shortly after, established in 1948 ***(Dequeker and Rico, 1992).*** 1948 also brought us two important discoveries, the therapeutic anti-inflammatory effects of steroid hormones and the antibody known as the rheumatoid factor is isolated in the blood of patients with RA ***(Rothschild, 2001).***

Epidemiology:

RA is the most common inflammatory arthritis. It affects approximately 1% of the population worldwide (more prevalent in western world than in black African population). However, these figures may be underestimated

since patients with mild disease may never present for a medical opinion. The peak incidence usually occurs between 30 and 50 years of age ***(Firestein, 2005).***

Females are 2-3 times more likely to develop RA than males. Perhaps due to the stimulatory effects of estrogen on the immune system ***(Harris, 2005).***

Aetiology and pathogenesis of RA

Despite the explosion of information on the pathogenesis of RA over the past two decades, the exact aetiology is not fully understood. However, the current hypothesis favours the notion that interplay among genetic and environmental factors initiates an autoimmune disease mechanism that culminates in a disease with inflammatory and destructive features ***(Edwards and Cooper, 2006).***

Genetic susceptibility:

Genetic makeup plays a critical role in susceptibility to RA. Identical twins show 30% to 50% concordance for the disease; first-degree relatives of patients with RA have about a twofold to threefold increased incidence ***(MacGregor et al., 2000 and Oliver et al., 2006).***

Environmental factors:

It now appears that an unknown antigen(s) initiates the autoimmune response in a genetically susceptible host. The potential antigen incriminated in the development of immune response in RA may be an exogenous (Foreign) or endogenous(Auto) antigen ***(Firestein, 2005).***

A) Autoantigens:

1-Type II Collagen:

Hyaline articular cartilage contains type II, IX, X and XI collagen. Type II collagen is the most abundant fibrillar protein and constitutes 80-85% of the total cartilage collagen. Type II collagen is an MHC-restricted, T cell-dependent antigen ***(Li et al, 2002). Crook et al (2004)*** reported that antibodies against intact type II collagen are a feature of RA, but they have limited diagnostic value. Extensive studies of the animal model show that cartilage collagens can induce an erosive polyarthritis similar to RA ***(Bajtner et al., 2005).***

2-Immune complexes:

Immune complexes have been detected in both the serum and synovial fluid of RA patients by a variety of techniques and can be present in high levels ***(Elkon, 1984).*** In RA this leads to a series of pathological events giving rise to joint damage and destruction. It is believed by some that small IgG-RF self-associating immune complexes may be significant in the immunopathogensis of RA ***(Edward and Cambridge, 1998).***

(B) Foreign antigens:

Over the years, a number of potential infective agents have been suggested but as yet no single organism has ever been demonstrated for RA. The proposed infective agents in RA may include viruses (Epstein - Barr virus (EBV), rubella, cytomegalovirus, hepatitis B and others) and bacteria (Mycobacteria, Escherichia coli and Proteus mirabilis) ***(Maini and Feldmann., 2004***). The process by which an infectious agent might cause RA remains a subject of debate. The mechanisms may be:

- Persistent infection of articular structures.
- Retention of microbial products within the synovium.