ROLE OF ANTI-INFLAMMATORY AND IMMUNOMODULATORY AGENTS IN RHEUMATOID ARTHRITIS.

BY

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Abstract:

This review is an attempt to illustrate the co-relation between inflammatory cytokines (such as IL-6, TNF alpha and IL-1), angiogenic markers (such as VEGF and TGFβ), apoptotic markers (such as Bax and caspase-3) and their relation to bone protection (OPG and RANKL). It also shows the role of each in rheumatoid arthritis (RA) progression. As the pathogenesis of RA depends on massive inflammation and neovascularization.

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune inflammatory disease associated with irreversible joint destruction which leads to permanent motor disability and compromised quality of life. It carries essential or real burden on the patient or individual and the society. The patient burden comes from joints destruction and deficits that lead to decline in daily physical function, comorbidities risks and finally quality of life. While, the economic burden on the society results from medical costs and decreased work capacity due to disability **(McInnes and Schett, 2011).**

The incidence of rheumatoid arthritis is 0.5 – 1 %. This incidence may be differ from rural and urban areas. It also may decrease from north to south. According to the World Health Organization (WHO), RA predominantly strikes during the most productive years of adulthood and within 10 years of its onset, more than half of RA patients in developed countries lose their full-time jobs **(Briggs *et al.*, 2016).**

The main cause of RA is unknown till now, although a lot of factors could be involved in its occurrence or trigger its mechanism of development such as susceptibility genes, environmental factors (smoking, low socioeconomic status and low educational attainment) in addition to alcohol consumption. Moreover, microbiomes (microbial populations in oral, salivary and GIT sites) are associated with CRP level and may be involved in triggering of RA **(Barton and Worthington, 2009; Carlens *et al.*, 2010).**

Rheumatoid arthritis affects the joints mainly the synovium of joint. Cartilage destruction and bone erosion develop during late stages of RA after occurrence of synovitis, synovial hyperplasia, pannus formation, stiffness and joint swelling (Kotake *et al.*, 1996; Maeno *et al.*, 2004; McInnes and Schett, 2011; Briggs *et al.*, 2016). In conjunction with its articular manifestations, RA patients usually suffer from coexisting autoimmune hepatitis and splenomegaly. RA also affects other organs as lung, skeletal muscles and heart **(Marra, 2006; Turesson and Matteson, 2006).**

Although the precise etiology of RA remains obscure, heightened immune response is thought to play a vital role in provoking joint inflammation and bone erosion **(Garnero *et al.*, 2010; Kremer *et al.*, 2011) (Fig. 1)**.

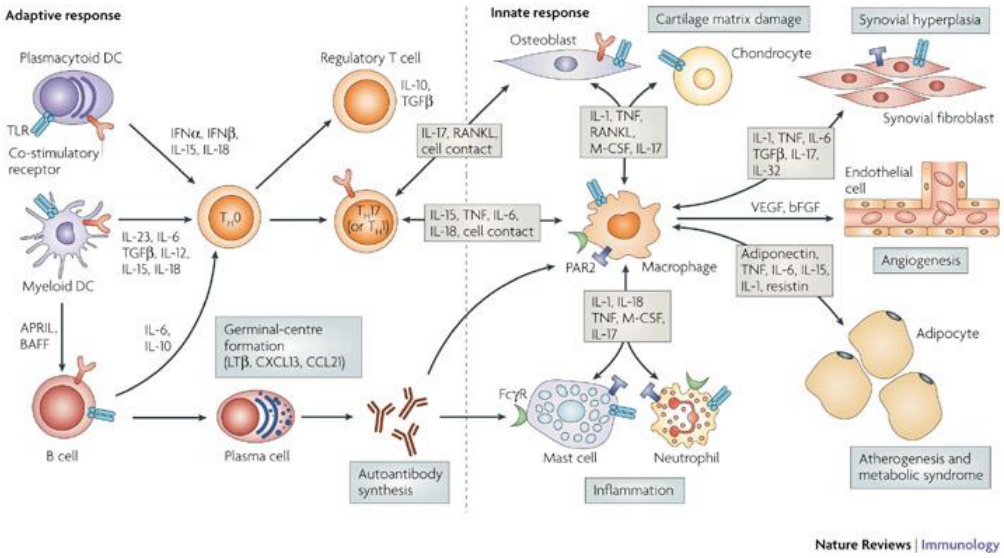

Fig.1. Pathogenesis of RA (McInnes and Schett, 2007).

In this context, infiltrating synovial tissue/joints with immune cells and synoviocytes produce proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (ILs) including IL-1b, IL-6, IL-17 and IL-18 that regulate synovial cell proliferation **(Firestein, 2003; Sebba, 2008) (Fig. 2)**.

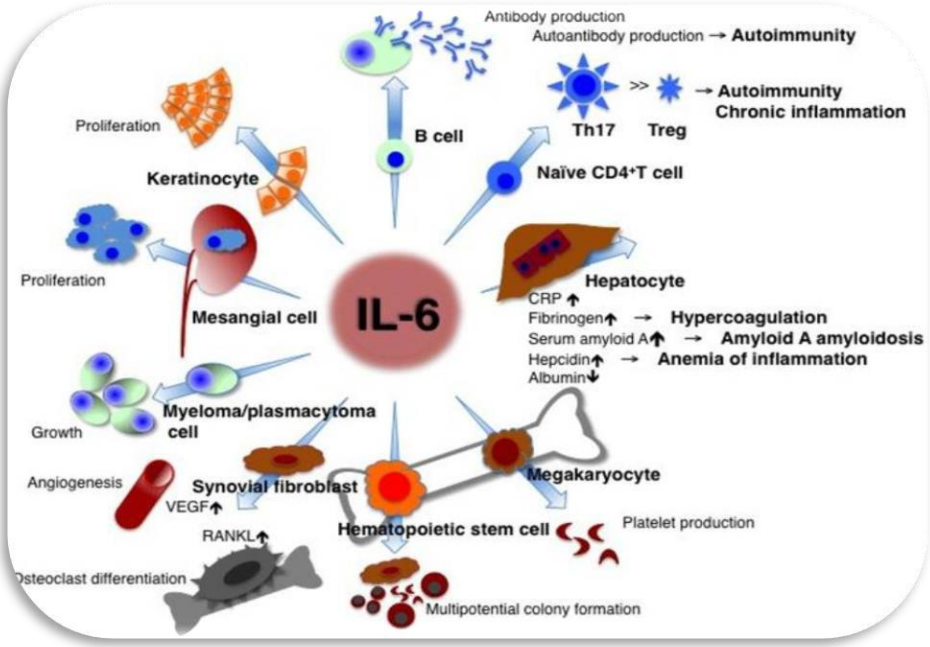

Fig.2. Pleiotropic activity of IL-6 (Tanaka and Kishimoto, 2012)

However, several pro-inflammatory cytokines are involved in RA development, IL-6 is the key inflammatory mediator in RA **(2012; Tanaka *et al.*, 2012)**. IL-6 is a pro-inflammatory cytokine with a pleiotropic activity. IL-6 is produced from different/various immune cells like/such as synovocytes (synovial fibroblastic cells) in response to synovocytes stimulation/activation by different/ various cytokines like TNF, IL-17 and IL-1 or (others) in response to infection, trauma and immunological challenges (Kotake *et al.*, 1996; Palmqvist *et al.*, 2002; Hashizume and Mihara, 2011). IL-6 has multiple/ many functions depending on its signaling pathway where it binds with two types of receptors: membrane bound Il-6 receptor (mIL-6R) and soluble IL-6 receptor (sIL-6R) which lacks/ loses its intracytoplasmic portion of mIL-6R **(Kishimoto *et al.*, 1992; Narazaki *et al.*, 1993; Rose-John and Neurath, 2004; Mihara *et al.*, 2005).**

After IL-6 binding with its receptors, it forms a complex which will be associated/ linked with a signal transducer glycoprotein 130 (gp130) that is expressed on different/various immune cells unlike/ in contrast to mIL-6R which is expressed only on limited/certain immune cells such as/like hepatocytes and certain types of leukocytes **(Kishimoto, 2006)**. After that signals transduction occurs/happens via several mediators of Janus-activated kinase-signal transducer and activator of transcription (JAK/STAT) pathway which finally leads to gene transcription **(Heinrich *et al.*, 1998)**. This signal transduction pathway is called trans-signaling pathway. IL-6 has two different features/characters that based/depend on its signaling pathway including; (A) pro-inflammatory features/characters that are correlated to trans-signaling mechanism and (B) its anti-inflammatory features/characters that are secondary to classic signaling mechanism **(Calabrese and Rose-John, 2014)**. IL-6 contributes to/involves in RA development through various/different actions/mechanisms such as differentiation of activated B-cells into plasma cells (antibody producing cells), and naïve (lymphocyte T-helper 1 cell) Th-1 (synergically with transforming growth factor beta (TGFβ)) into (lymphocyte T-helper 17 cell) Th-17 which involved in RA progression and production of other inflammatory cytokines **(Iwanami *et al.*, 2008)**. Furthermore, IL-6 is involved in joint/cartilage destruction via/through osteoclastogenesis that is responsible for focal bone erosion, proliferation of synovocytes and differentiation of osteoclast through/via receptor activator of NF-Kappa B ligand (RANKL) expression. Interleukin-6 (IL-6) is also participated with IL-1 in production of matrix metalloproteinases (MMPs) from synovial cells that involved in cartilage destruction and bone erosion **(FUJIKAWA *et al.*, 1996; Mohamed, 2008; Suzuki *et al.*, 2010).**

Beside alongside its effect/action on osteoclast, IL-6 enhances/improves angiogenesis (formation of new blood vessels from existing ones) and vascular permeability of synovial tissue through/via inducting/inducing production of vascular endothelial growth factor (VEGF) from synovial fibroblast **(Nakahara *et al.*, 2003)**. VEGF is also produced secondary to/in response to simulation/ activation by TGFβ **(Frater-Schroder *et al.*, 1987**). Synovial angiogenesis contributes to/ participates in maintenance of inflammation and progression of RA (Maruotti *et al.*, 2006). VEGF that is produced from

different/various inflammatory cells such as/ like macrophages, fibroblasts, vascular smooth muscles cells and synovial lining cells **(Ballara *et al.*, 2001; De Bandt *et al.*, 2003)** is the most important and powerful angiogenic factor/marker in RA development/progression that contributes/correlates to or participates in pannus formation **(Nakahara *et al.*, 2003; Hashizume *et al.*, 2009)**.

Similar to Il-6, VEGF produces/appears at early stage and it is maintained throughout RA disease course **(Ballara *et al.*, 2001)**. Serum and synovial levels of IL-6 and VEGF are correlated with/ linked to disease activity **(Hirano *et al.*, 1988; Houssiau *et al.*, 1988; Guerne *et al.*, 1989; Madhok *et al.*, 1993)**. Serum concentrations of VEGF also correlate with serum levels of C-reactive protein (CRP) that is considered as an inflammatory biomarker/factor in RA and produced from hepatocytes secondary to/ in response to stimulation/activation by IL-6, so it is produced at the early stage of the disease and its concentrations correlate with severity of the RA **(Paleolog and Miotla, 1998)**. Moreover, VEGF contributes/relates to the proliferation of synovial tissues. Neovascularization/angiogenesis permits/allows infiltration of more and more inflammatory cells that worse the disease state **(Maruotti *et al.*, 2006).**

On the other hand, Apoptosis has a role in most auto-immune disease. Apoptosis is a programmed cell death type I (PCD). It is involved in both physiological and pathological process. It participates in normal cell turnover, proper development and functioning of immune system. Inadequate or Inappropriate apoptosis is correlated to several diseases/pathologies such as neurodegenerative disease and autoimmune disorders. Apoptosis occurs normally during growth/development and aging. It also has homeostatic role/mechanism to maintain/preserve cell populations in tissues. Sometimes It occurs as a defense mechanism in secondary to/ response to immune response/ immunological reactions or cellular destruction caused/induced by disease or harmful agents **(Norbury and Hickson, 2001).**

Apoptosis composed/consists of two pathways, one of both is intrinsic pathway and other is extrinsic pathway **(Fig. 3).**

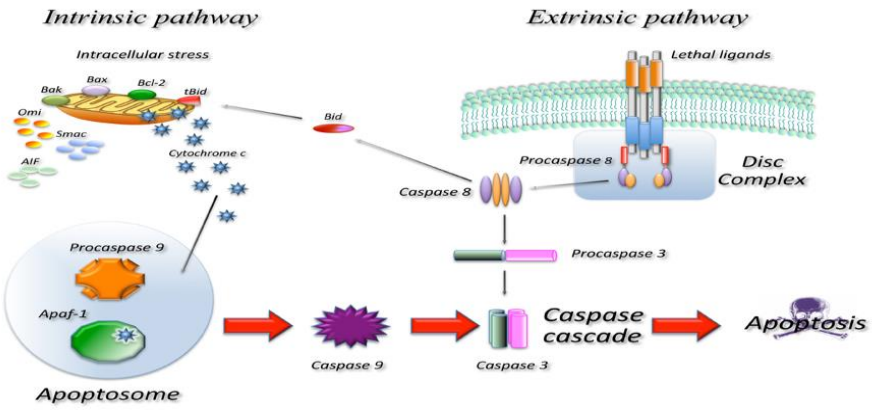

Fig.3. Pathways of apoptosis (Favaloro *et al.*, 2012).

The extrinsic pathway of apoptosis initiates or starts apoptosis via transmembrane receptor- mediated interactions **(Fig. 3)**. These include or involve death receptors which are considered members of the tumor necrosis factor (TNF) receptor gene superfamily **(Locksley *et al.*, 2001)**. These death receptors have a cytoplasmic domain of about 80 amino acids called the "death domain" **(Ashkenazi and Dixit, 1998)**. This death domain plays a vital or critical role in transmitting the death signal from the cell surface into the cell (intracellular signaling pathways). To date, the best-characterized ligands and corresponding death receptors include FasL/FasR, TNF-α/TNFR1 **(Elmore, 2007; Nangia-Makker *et al.*, 2007).**The sequence of events that define this pathway are best characterized with those models. There is grouping of receptors that binding with ligand. Upon ligand binding, cytplasmic adapter proteins (ex, FADD adaptor proteins) which exhibit corresponding death domains that bind with the receptors are recruited. The binding of Fas ligand to Fas receptor results in the binding of the adapter protein FADD and the binding of TNF ligand to TNF receptor results in the binding of the adapter protein TRADD with recruitment of FADD and RIP **(Wajant, 2002)**. After that FADD binds with procaspase-8 through or via dimerization of the death effector domain (DED). Finally, a death-inducing signaling complex (DISC) is formed and procaspase-8 is activated. Once caspase-8 is activated, the execution phase of apoptosis is triggered. Death receptor mediated apoptosis can be inhibited by a protein called c-FLIP which will bind to FADD and caspase-8, rendering them ineffective **(Kischkel *et al.*, 1995; Scaffidi *et al.*, 1999).**

On the other hand, the intrinsic pathway mainly depends on cytochrome c which released from intermembrane space of mitochondria into cytoplasm of the cell after Bax and Bak aggregation on the mitochondrial membrane and forming BH123 channel that allows/ permits release of cytochrome c **(Saelens *et al.*, 2004)**. In this pathway cytochrome c is triggering apoptosis via/through activation of caspases (caspase cascade reaction). Caspases are widely expressed in form of an inactive proenzyme in majority of cells. After that it can activate other procaspases which lead to amplification of the apoptotic signaling pathway and finally leading to rapid cell death. Aggregation of Bax/Bak that cause changing in permeability of mitochondrial membrane. This process can be controlled and regulated by the Bcl-2 family of proteins **(Cory and Adams, 2002)**. The Bcl-2 family can be either pro-apoptotic such as Bax or anti-apoptotic such as Bcl-2, Bcl-X, and Bcl-Xs.

In RA, there is a relationship between angiogenic cytokines, bone erosion markers and apoptosis process. So, apoptosis (apoptotic process) participates in RA pathophysiology. TGFβ increases apoptosis in the synovium **(Firestein *et al.*, 1995)**. Furthermore, RANKL induces apoptosis of osteoblasts **(Goldring, 2003)**. Heightened and lessened activity of apoptotic machinery have been both reported **(Catrina *et al.*, 2002**). During early stage of RA, apoptosis is inhibited resulting in rapid cell proliferation along with increasing cellular influx from blood into the synovium **(Firestein *et al.*, 1995)**. This increases cytokines production and inflammation resulting in hyperplasia, the prominent feature of RA. In contrast, later stage of RA is characterized by intensified apoptosis secondary to increased expression of p53, a critical regulator of synovial fibroblast like cell proliferation, apoptosis and invasiveness **(Tak *et al.*, 2000a; Tak *et al.*, 2000b; Dhaouadi *et al.*, 2007).** Remarkably, p53 overexpression was observed in cultured fibroblast like synovocytes derived from RA patients. Western blot analysis and immunoprecipitation

studies also confirmed the high levels of p53 protein in RA synovium compared with forms of arthritis. Another study showed that characteristic DNA ladders were found in DNA isolated from whole RA synovial tissues, suggesting that apoptosis occurs in inflamed synovium **(Tak *et al.*, 2000a)**. Apoptosis also correlated with RA severity **(Catrina *et al.*, 2002).** This is in accordance with Paul et al**., (Tak *et al.*, 2000a)** who has reported that apoptosis was increased in late stage RA adjuvant induced arthritis model. Furthermore, it has been shown that T-cells in rheumatoid synovial expressed low Bcl-2, high Bax and High Fas, a phenotype that suggests increased susceptibility of T-cells to apoptosis.

While using, apoptosis inducing agents may be useful in early stage of RA to overcome the rapid proliferation of cells and inhibit recruitment of inflammatory cells in RA synovium, the continuous apoptotic effect and/or further apoptosis induction aggravate bone erosion. Accordingly, the use of anti-apoptotic therapeutic agent or apoptosis inducing agent must be linked with the disease stage.

Conclusion:

There is a strong correlation between inflammatory, angiogenesis, apoptotic markers and their relation with bone protection/erosion **(Fig. 4)**

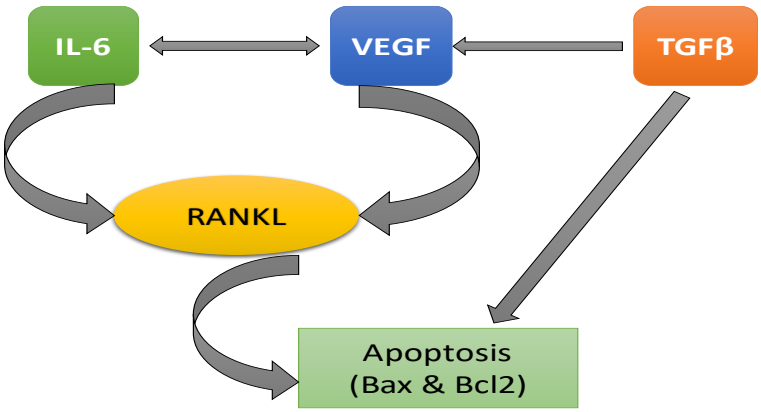

Fig.4. Sketch diagram showing crosstalk between inflammatory, angiogenesis, apoptotic markers and their relation with bone protection.

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دور المواد المضادة للإلتهاب والمعدلة للمناعة فى التهاب المفاصل الروماتيدى

للسادة الدكاتره

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توضح هذه الدراسة العلاقة بين علامات أو دلالات الإلتهاب (مثل الانترولكين 6, وعامل نخر الورم ألفا والانترولكين 1) , والعلامات الوعائية (مثل نمو بطانة الأوعية الدموية , وتحويل عامل النمو بيتا), وعلامات موت الخلايا المبرمج (الباكس و كاسباس 3) مع حماية العظام ودور كل منها فى طريقة تطور التهاب المفاصل الروماتيدى. حيث أن الفيزويولوجيا المرضية لإلتهاب المفاص تعتمد على الإلتهاب الشديد وتكون العديد من الأوعية الدموية الجديدة.