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Cell Biology in Rheumatoid Arthritis

Lukeshwari Sahu[1], S. Prakash Rao[2], Mahendra Verma[1]*, Akhilesh Kumar[1], Rajendra Sahu[1], Dhanesh Kumar[1], Chandrakant Yadav[3]

[1] Department of Pharmacology, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111 (Affiliated to Chhattisgarh Swami VivekanandaTechnology University (CSVTU)

[2] Department of Pharmacognogy, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111(Affiliated to Chhattisgarh Swami VivekanandaTechnology University (CSVTU)

[3] Department of Pharmaceutics, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111(Affiliated to Chhattisgarh Swami VivekanandaTechnology University (CSVTU)

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease, which affects about 0.33 to 2.65% of the population. In RA Synovium contain various type of immune cell. In which only one cell population cannot cause rheumatoid arthritis that requires more than one cell population. In normal condition, they act as a switch (active or inactive the cell signaling). It controls cell growth, proliferation or metastasizes. In an autoimmune disorder such as rheumatoid arthritis, the immune system mistakenly attacks and destroys the body's cells and tissues. Mostly cells are present in limited numbers in normal human synovium, but in rheumatoid arthritis and other inflammatory joint diseases, this population can expand to constitute 5-20% or more of all synovial cells. Recent investigations in a murine model have demonstrated that cells can have a critical role in the generation of inflammation within the joint.

Keyword: Cell Biology in rheumatic arthritis; Dendrite cell; T-cell; Mast cell; Fibroblastic cell; Macrophages cell.

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***Address for Correspondence:**

Mahendra Kuamr Verma, Columbia Institute of Pharmacy, Vill-Tekari, Near Vidhansabha, Raipur, Chhattisgarh, India

Introduction:

Rheumatoid arthritis (RA) is incurable aggressive autoimmune disorder symptoms generally included joint pain, swelling, stiffness, angiogenesis, and hyperplasia in affected joints [1]. It developed when their own immune system mistakenly attacks and destroys the body's cells and tissues [2]. The continuously progression of the disease may lead to lose functionality, decrease living standard and increase mortality and morbidity [3]. RA pathogenesis including immune complex interaction between genetic and environmental factors, inducing the aberrant activation of innate and adaptative immune system which cause the immune desregulation, auto antigen presentation with increasing the concentration and range of cytokines and chemokines lead to T and B cells activation [4]. The most known function of the innate immune system is the initial detection of microbial pathogens, primarily pathogens attacked with the surface or intracellular patterns recognition receptors of macrophages and dendritic cells. Thus they become activated, leading to the production of cytokines and chemokines. The deregulation of these events leads to synovitis, proliferation of synovial, cartilage and subchondral bone destruction appear in the affected joint. Effectors cells and molecules of the innate system are stored locally if pathogen cannot overcome alone than macrophages and DCs travel from local lymphoid tissue where processed antigens are recognized by histocompatibility complex molecule to the naive T cell. Thus the beginning of an adaptive response complete with lasting immunological memory. The anti-inflammatory mediator helps to clearance and destruction of the pathogen. In RA, It's proving that the innate immune system is continuously activated, as evidenced by the continual expression of macrophage-derived mediators [5]. Some of the common comorbidities associated with extra-articular organs, including skin, eye, lung, gastrointestinal system and cardiovascular system [6]. In the first stages of RA, the cellular components of the synovial membrane begin to invade the cartilage. But in the second stage, the synovial membrane converted into inflammatory tissue and due to this conversion of the synovial membrane becomes ruptured

adjacent bone and cartilage. The site between pannus and cartilage is occurred due to various cells such as activated dendrite cell, T-cell, B-cells, macrophages and synovial fibroblasts that manifested matrix metalloproteinase's [7].

Epidemiology:

Rheumatoid arthritis (RA) affects approximately 0.33 to 2.65% of the population, exhibit differences between countries and studies [8, 9]. As compared to other autoimmune diseases, RA is mostly found in women than men, this is due to hormonal differences [10]. RA is also largely occurred in the elderly patient with an immune system aging plays an important role in this disease [11, 12]. In case of RA, the patient mostly suffers from at least one or more comorbid conditions [13] and other commonly associated symptoms and diseases when you have arthritis. Some of the common comorbidities associated with RD are osteoporosis, anemia, bacterial infection, heart failure lymphoma, myocardial infarction, stroke, hypothyroidism, depression, gastrointestinal ulceration, fracture, and skin cancer [14].

Table 1: Various co-morbidities and total Percentage [14, 15].

Co morbidities	Total percentage
Total co morbidities	45
Hypertension	24.3
Hypothyroidism	16.9
Diabetes mellitus	15.4
Interstitial lung disease	1.4
CAD	0.8
TB	0.6
Asthma	0.8
CKD	0.6
Nephritis	0.5
CNS involvement	0.3
Dyslipidemia	0.2
APD	0.1
Thalassemia	0.1
Nodular sclerosis of eye	0.1

Cell Biology of arthritis:

In RA Synovium contain various type of immune cell which are listed in table 1. In which only one cell population cannot cause rheumatoid arthritis that requires more than one cell population. Interaction between cell population in rheumatoid arthritis synovium can be divided into two classes: In the first class, interaction are mediated by secreted molecule such as cytokines and In the second type, cell-cell interaction requires direct contact between two different types of cell, which are listed into table 2 [16-17].

Table 2: Cellular components of synovial joint

Highly Abundant cell populations

Fibroblastic (type B) synoviocytes
Macrophage-like (type A) synoviocytes
T lymphocytes

Other cell populations

Mast cells
Dendritic cells
B lymphocytes
Plasma cells
Osteoclasts

Table 3: Cell-cell interaction that cause rheumatoid arthritis

Macrophage–fibroblast
B cell–fibroblast
T cell–antigen-presenting cell
T cell–fibroblast
Leukocyte–endothelial

The immune system and defense cell originate from the myeloid and lymphoid progenitor, this myeloid progenitor [Granulocytes, Monocytes (dendrites, macrophages, and mast cell)] and lymphoid progenitor [NK, T- cell and plasma cell] are the cell that crust up themselves and developed the cell-mediated immunity and also antibodies mediated of our body. In normal conditions, they activate or inactivate cell signaling as a switch. It controls the cellular pathway such as their growth, proliferation or metastasis [18]. In an autoimmune disorder such as rheumatoid arthritis, our immune system mistakenly attack and destroy the joint cells and tissues. These early auto antibodies are thought to first develop outside of the joints, environmental factor or other factors can modify our self-proteins making them targets for immune system one particular modification is called citral ination when the immune system recognizes these modified self-proteins it lead to a breach of self-tolerance and the production of autoreactive cells and autoantibodies [6, 19].

Individual role of immune cell for development of arthritis:

A) Dendrite cell:

Basic Biology: Dendrite cell is a granulocytic type of antigen-presenting immune cell that appears as a star. Their name is dendritic cell because of their long branches which are very similar to that of the dendrite of a neuron that's why their name is a dendritic cell. It is originated either from lymphoid progenitor or from the myeloid progenitor. Most of the dendritic cells occur in the tissues of the external site, such as skin, nose, lung and digestive tract [20, 21].

Function:

Dendritic cells play a very important role in the initiation of the immune response. They also create a bridge between innate and adaptive immunity [22]. Dendritic cells (DCs) are the most important antigen-presenting cells and they also maintain the immune homeostasis in the body. DCs (mDCs) mature cell are immunogenic. They can detect the antigen and bind them on their surface, and initiate the immune-related responses [23]. It is also able to present to T cell antigenic peptides in the concern of the MHC-II [24]. While in immature DCs (imDCs) have weak antigen-presenting then mature DCs and T cell activating abilities, hence they may induce T cell tolerance [25, 26]. It is thought that the tolerance potential of the dendritic cell is to release the immunosuppressive Cytokines such as TGF-β and IL-10 and also they having surface programmed death legends like PD-L1 and PD-L2 [27].

Dendrite cell in RA

CD4 T cell activation by DCs: Dendritic cells (DCs) are a major regulator of adaptive immune responses. Initially, CD4 T cells bind with synovial DCs; as a result, T cell activates. After activation of CD4 T cells, antigen-MHC-II complexes are formed on the surface of the APC and initiate co-stimulatory signals [28]. During continuously binding with APCs surface, CTLA-4 will fight with CD28 for CD80/CD86, and after competition of CTLA- 4 inhibition of T cell activation. T- Cell interact with other cell and involve in bone erosion, CTLA- 4

is the major site for drug therapy in case of rheumatoid arthritis [29].

B) T- CELL:

Basic Biology: T-cells are also known as lymphocytic cells generated from bone marrow and mature in the thymus gland and play a major role in immune response in our body. They are mostly divided into T- helper cell and T- NK cells. T cell is showed the dynamic shape and also having about 8-10 micron in diameter. T cell possesses a large nucleus and contains few mitochondria, ribosomes, and lysosomes. The cytoplasmic component is larger when antigens are attached to the cell [30, 31].

Function: The main function of T-cell is to produced cell-mediated immune response various type of cell-cell interaction occurs between the t-cells and another cell, for example, the interaction between a macrophage and a T cell for a phagocytic response, the interaction between T cell and B cell for humoral response and interaction between a T cell and another T cell which release IL2, IL4, IL5, interferon-gamma, macrophages inhibitor factor, and macrophage activation factors this are very important cytokines and they play a very important role within the immune system. Hence T cell can arise two types of functions one in which is effecter function and another one is regulating function. They expressed CD4, CD8, CD44, CD25 receptor. The T cell receptor consists of the protein complex and actually, they are comprised of two separate peptide chains [32, 33]. CD4 T-Cell could play an important role in the development of the chronic inflammation occurring in RA. These cells are a major regulator of the immune response producing pro-inflammatory cytokine and operating with B- Cells for secreting antibodies CACPA or rheumatoid factor, while not in the other patient [34].

CD4 T cell in rheumatoid arthritis:

CD4 T cell activation and function in synovitis: CD4 T-Cell is expending in overall synovium, where they establish communication between cell to cell and play a vital role in the pathological immune response to joint damage [35].

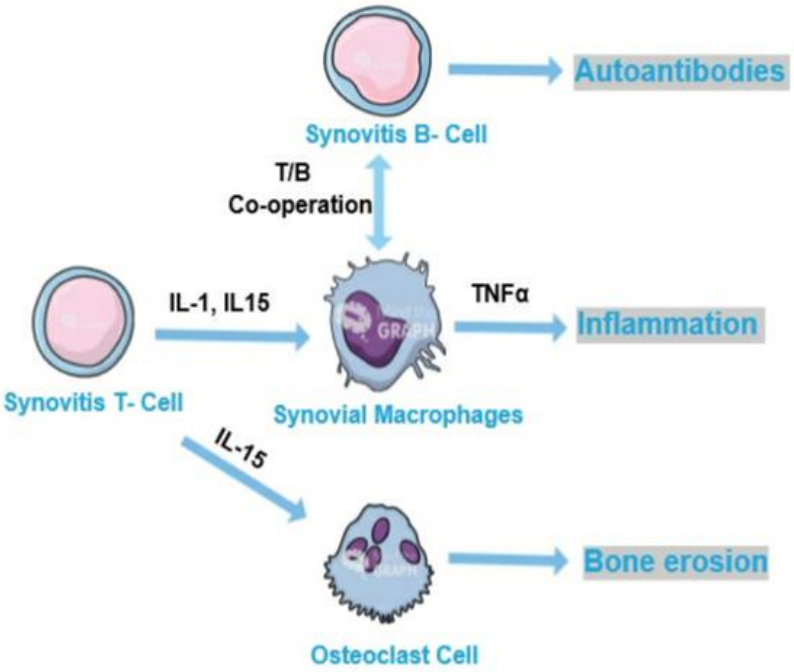

Fig:-1 T-cell regulation in Synovitis

Regulation of FLSs by CD4 T cells:

FLSs play a critical role in joint architecture. In a normal joint, this is the component that forms synovial lining and secretes synovial fluid. FLSs are an aggressive phenotype in RA, which causes hyperplasia in synovitis. This hyperplasia in synovitis creates a hypoxic environment where angiogenesis and elevation of inflammation is developed. Also, Rheumatic arthritis FLSs secreted large amounts of collagen proteases in synovial fluid, as a result of bone erosion, cartilage destruction, and trigger pro-inflammatory cytokines. The regulation of FLSs is altered by CD4 T cells by the help of pro-inflammatory cytokines TNF-α, IL-15, and IL-18 [36]. FLSs Collagen synthesis also altered by CD4 T cells, this process is carried out by TNF-α, IFN-γ, and IL-1α [37].

Regulation of macrophages/monocytes by CD4 T cells:

Macrophages cells are the most abundant monocyte in the synovial joint. Where they directly interact with synovial cells and secrete pro-inflammatory mediators like TNF-α cytokine. CD4 T- Cells also regulate macrophage-like synoviocytes. T- Cell having homologous behavior in RA patients [38]. Where TNF-α is also produced by IL15 stimulated NK Cell [39]. Neutralizing therapy used for minimizing the TNF-α in the progression of RA [40]. Macrophages are progenitors of osteoclasts that degraded bone in the case of RA. In normal conditions, osteoclast and osteoclast maintain the homeostasis and skeletal integrity [41, 42].

C) Mast Cell

Basic Biology: Mast cells are present in mucosae and Connective tissue, normally aggregated at blood vessels, around nerves and epithelial surfaces [43]. They are originated from bone marrow and known as CD34+ progenitor cells after entered inside the tissue they are known as mature mast cells [44, 45]. Which are intensely heterogeneous, and largely variable in cytokine production, granule contents, and receptor expression. The major role of mast cell has antigen presentation, intracellular killing, and phagocytosis, [46, 47]. They are found in blood vessels, synovial cavity peritoneum, and pleural space. This existence indicates as a guard for detecting antigens and inflammatory response [48]. Thereafter, mast cells clustered in chronically inflamed cartilage tissue.

Function of Mast cell:

IgE-Activation: Mast cells are having high-affinity toward IgE receptor FcεR1, The receptor is tetrameric structure made up of α, β and 2γ subunit [49]. When the FcεR1 receptor bind with antigen, the immunoreceptor tyrosine-based activation motifs (ITAMs) are phosphorylated on the β and γ chain subunit and this turn activates a signaling cascade, as a result, three distinct pathways are initiated *de novo* synthesis of cytokines, eicosanoids pathway, and chemokines pathway. Within second to minute the granules present in the cytoplasm of the mast cell are ruptured to each other and release from intracellular to extracellular spaces due to the IgE cross-linking. The granules are released on the basis matured mast cell, the chemical mediator of mast cell such as histamine, neutral proteases, and heparin, broadly divided into three group carboxypeptidases, chymases, and tryptases. Histamine enhances vascular permeability; proteoglycans provide a stage where granules of proteases are packaging and the neutral proteases are rupture proteins from complex and plasma therewith to activating propeptides interleukin-1β and angiotensin II [50]. Tumor necrosis factor (TNF) is also stored in the granules which are used for the development of airway hyperreactivity (AHR) [51]. The activation of the IgE receptor which turns initiates the arachidonic acid pathway and produces eicosanoids [52].

Table 4: Selected mediators of mast cell and their roles in arthritis:

Mediator	Some relevant functions
Histamine	Leukocyte recruitment, Vascular permeability, fibroblast activation
Heparin	Angiogenesis and osteoclast activation
Neutral proteases	Matrix degradation, leukocyte recruitment, fibroblast activation
TNF	Leukocyte recruitment, fibroblast activation
PGD2	Vascular permeability, Neutrophils recruitment
LTB4	Vascular permeability, leukocyte activation
Cysteinyl leukotrienes	Vascular permeability, immunomodulatory (LTC4)
IL-1	Leukocyte recruitment, fibroblast, angiogenesis differentiation and activation
IL-2	Lymphocyte stimulation
IL-3	Leukocyte growth factor
IL-4	Immunomodulatory, profibrotic
IL-6	leukocytes and fibroblasts activation
IL-8	Neutrophil recruitment
IL-10	Immunomodulatory
IL-13	Immunomodulatory, B cell stimulation
IL-18	Angiogenesis, lymphocyte stimulation
TNF	Leukocyte recruitment, fibroblast/chondrocyte activation, angiogenesis
IFN-γ	Activation of synovial macrophages
TGF-β	Immunomodulatory, fibroblast mitogen, angiogenesis
PDGF	Fibroblast mitogen
VEGF	Fibroblast mitogen, angiogenesis
Bfgf	Fibroblast mitogen
NGF	Fibroblast mitogen
MCP-1	Leukocyte recruitment
MIP-1α, MIP-1β	Leukocyte recruitment, osteoclast differentiation
RANTES	Leukocyte recruitment

Mast cells in inflammatory arthritis:

Rheumatic arthritis (RA) is a synovial inflamed tissue in which the amount of mast cells is increased in the synovial joint (Fig. 2). In the normal condition, the synovium joint made up of a thin layer of macrophages ('Type A' cells) and fibroblasts ('Type B' cells) which are enclosed in the sub-lining of highly vascular matrix connective tissue and adipose tissue. In the normal condition, mast cell is found around the vessels and nerve as a clustered form and covering up to 3% of all cells inside the synovium [53]. In normal condition; mast cell remains a defense system against bacterial peritonitis infection. In the case of RA patient, the synovial lining is expended from 1–4 cells to 10 cells and the T cells, B cells, macrophages, and neutrophils are infiltrated with sub lining. The number of clustered mast cells depends upon the patient [54, 55, 56]. Mast cells are present around the synovial sub-lining, where they have formed a cluster in an abnormal layer of pannus which is present near joint cartilage and begins bone erosion [57]. The phagocytosis nature of mast cells may also play critical roles for the stimulation of inflammatory mediators due to the profibrotic effects of IL-4 and T and B lymphocytes stimulation by IL-6 [58].

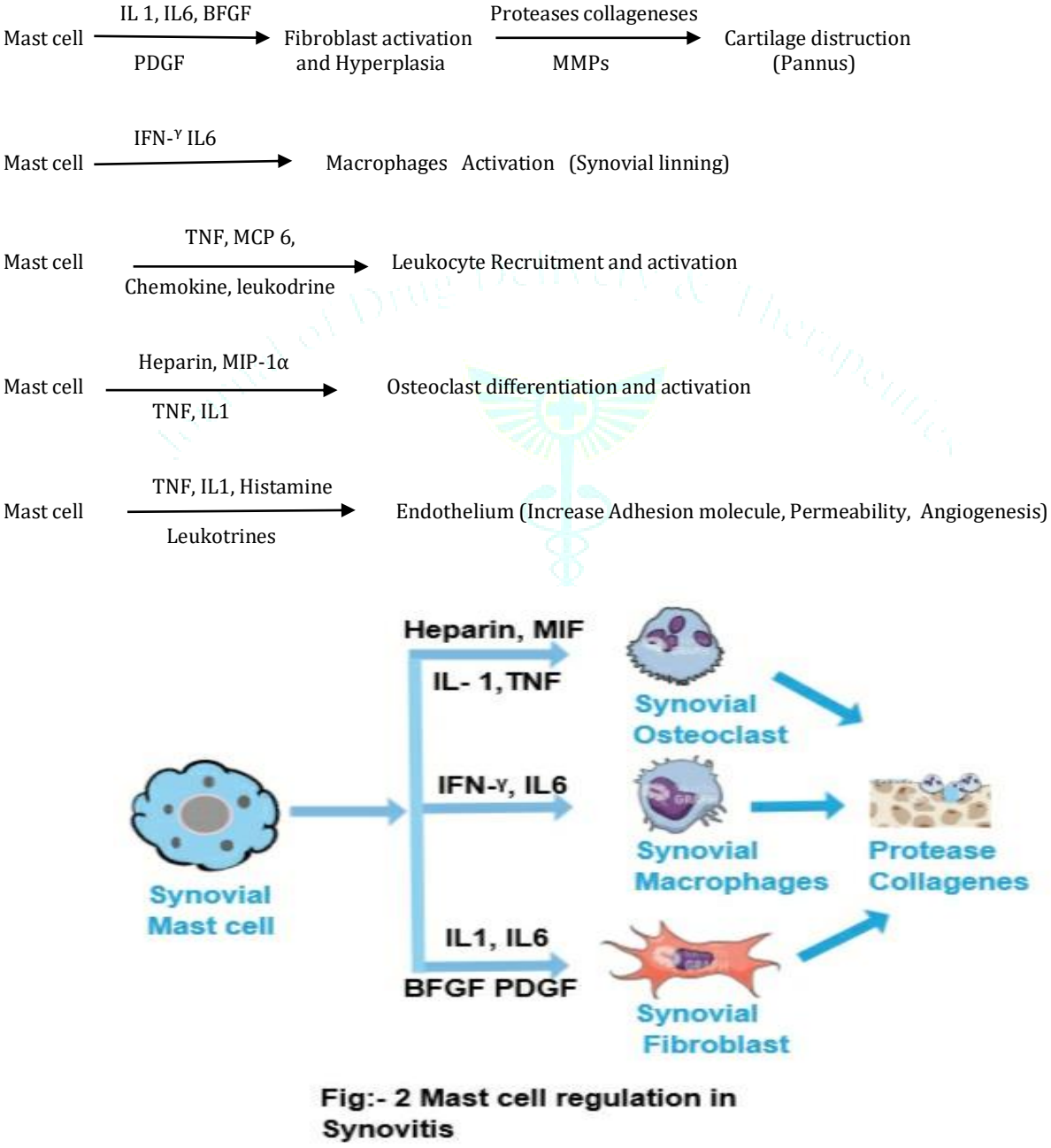

Fig:- 2 Mast cell regulation in Synovitis

Fig 2: - Cell mediator and Cell-Cell interaction of mast cell in rheumatoid arthritis of synovitis including Synovial Osteoclast, Synovial fibroblast, and macrophages recruitment and activation causes cartilage and bone destruction. Once mast cell is enhancing in synovitis they lead to increase vascular permeability, molecular interaction, and angiogenesis. Mast cells may cause cartilage and bone destruction by matrix metalloproteinases (MMPs) through fibroblasts and chondrocytes in the pannus site and lead to direct and indirect differentiation and activation of osteoclast.

D) Synovial Fibroblast:

Basic Biology: Fibroblast cells are mostly found in the connective tissue which connects, binds and supports other tissues and organs. These cells derived from mesenchymal stem cells, stem cells that are adequate for differentiation as they are needed. Fibroblast is usually 10-15 micron in size. The lifetime of fibroblast is about 57 days measured in chick embryos. Fibroblast cells use endocytosis as their transport mechanism. They play a major role in the propagation of inflammation and bone erosion [59]. In normal condition, synovial tissue comprises two layers the first one is the intima layer or synovial lining and the second one is an underlying layer or subintima layer. The first one is directly attached to the intra-articular cavity which is present inside the joint capsule and this synovial cavity is filled with synovial fluid. The main job of the intima is to secret the components of the synovial fluid are within this intima and this layer is about 20–40 Am thick, one to three cells deep, loosely organized, avascular, and not supported by a basement membrane. The lower layer is known as the subintima of the synovial membrane [60]. In the normal intima and subintima, two types of cells face into the synovial fluid, first one is known as macrophage-like (type A) synoviocytes (MLS) [61,62], and the second one is FLS (type B synoviocytes). FLS membrane is bipolar, spindle-shaped cells with prominent secretary hyaluronic acid machinery, including endoplasmic reticulum, higher ribosomal arrays, and well-developed Golgi apparatus. Their nuclei are pale. In contrast to FLS, MLS and lack HLA class II antigens, having endocytosis ability, and are CD68 negative [63].

FLS Function: The major function of Fibroblastic-like synovial cells (FLS) is to maintain the structural and functional integrity of the connective tissue by continuously releasing extracellular proteins like collagen, glycoproteins, and glycosaminoglycans. Fibroblast cells maintain homeostasis by keeping a normal pH 7.4-7.7. FLS plays a critical role in normal joint homeostasis. The Mature intimal FLS produces an increasing amount of long-chain polymeric hyaluronan into the synovial cavity, which has provided lubricating and immunomodulatory properties. Intimal FLSs also secrete the glycoprotein lubricin, as well as plasminogen activator. Lubricin imparts viscosity at synovial space. Plasminogen activator may inhibit fibrous adhesions in the joint, promoting joint bone movement [64]. The major job of FLS is to control synovial fluid volume. When synovial fluid volumes are increased due to mechanical stress on intimal FLS appeared, lowering hyaluronan production leads to decreasing oncotic pressure in the joint. In contrast, joint destruction in arthritis represents due to disturbance of synovial fluid volume control, with friction forces provoking excess hyaluronan production, and accumulation of plasma dialysate in the synovial cavity. FLS may also involve in inflammatory responses as well as its co-receptor CD97, DAF modulates tissue responses can also alter on the cell surface [65]. FLS also involve in leukocyte trafficking, via their interaction with leukocytes. Intimal FLS act as a ligand like and VCAM-1 CD44, ICAM-1 and integrins, this ligand bind with other cells. Thus, intimal FLS may inhibit mononuclear cells such as monocytes and lymphocytic cells in the synovium while entering neutrophil into the joint space, through which the amount of leukocyte is controlled via two compartments while the amount of leukocyte is to be reduced in the synovial cavity. Finally, we can say that FLS maintains the maintenance of joint capsules in case of the joint disorder [66].

The FLS in RA

Hyperproliferation of FLS: RA FLS are hyperproliferative [67], and several in vitro studies, it has been finding that the rheumatoid arthritis FLS makes more division than normal cell [68]. In the rheumatoid arthritis condition several growth factors which overexpress the FLS mitosis in the synovial joint [69].

Inflammation and autoimmunity: When FLS are activated they them self produce inflammatory mediators including IL1, IIL4, IL6, IL8, IL10, IL12, IL13, IL17, IL18, IL21, TNF-a, TGF-h, and cyclooxygenase-2, prostaglandin E2 [70, 71]. IL15 is a pro-inflammatory cytokine, which also activates t-cell, neutrophils and macrophages. In the case of a rheumatoid arthritis patient, this cell is overexpressed by FLS [72]. Therefore, FLS is the most important driver in rheumatoid arthritis inflammation. RA FLS also secret several types of proangiogenic factor including FGF [73], VEGF [74], and IL-18 [75], it is also involved in blood vessels growth, require arthritis process and pannus formative. Angiopoietins are responsible for inflammation in rheumatoid arthritis with the help of angiogenesis and leukocyte [76, 77] production, direct contact between T cells and RA FLS leading to T cell activation, enhancing the production of cytokines as well as T cell proliferation [78, 79, 80]. Thus, Rheumatoid arthritis FLS may play a major role in multiplication, inflammation, and autoimmunity. Conversely, resting FLS activated by T cells [81].

FLS and tissue destruction: Fibroblast-Like Synoviocyte (FLS) produced an HK2 enzyme that is very important for tissue destruction in rheumatoid arthritis. They also produce matrix metalloproteases which responsible for cartilage destruction. This is commonly observed in tandem, laboratory and clinical evidence suggests that these processes are distinct [82, 83]. Radiographic joint damage evaluated in RA is joint space destruction, enlargement of synovial lining cell, pannus formation, marginal cartilage erosions, and bone erosions.

Fibroblast —(IL 6 / chemokines)→ Macrophages

Fibroblast —(Protease collagens / IFN- β, MHC- 2)→ Chondrocytes

Fibroblast —(CXCL 12, CCL21)→ T lymphocyte recruitment and retention

Fibroblast —(VLA- 4 / CXCL 13, CXCL 12)→ B- lymphocyte

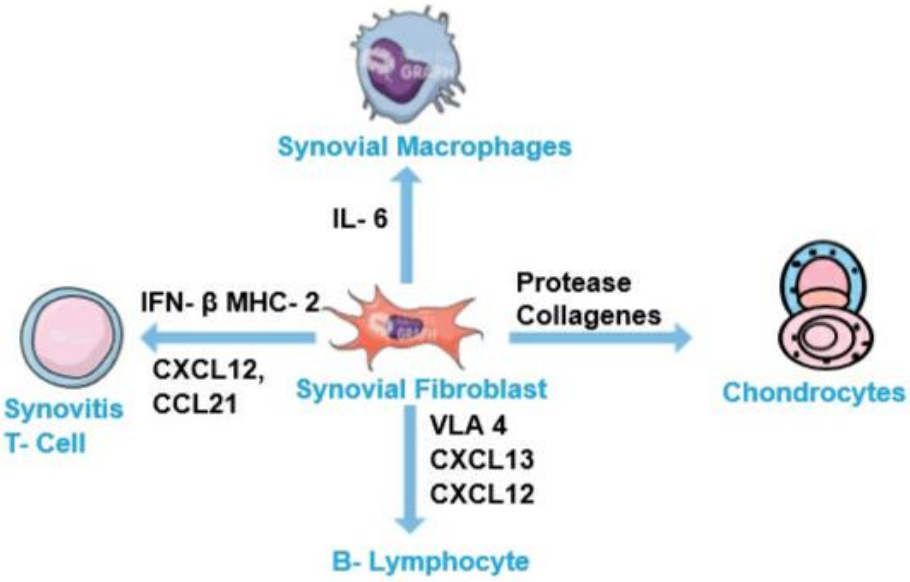

Fig:- 3 Fibroblast regulation in synovitis

Fig 3: Cellular components and cell-cell interaction of Fibroblasts like cell in proinflammatory function and rheumatoid arthritis in synovitis. Synovial fibroblast cell interacts with different cell including macrophages, T- lymphocyte, B- lymphocyte and other in the presence of soluble factors like IL6, IFN- β, MHC 2, CXCL- 12, CXCL 13, CCL21, VLA-4 to maintain synovial lining by their recruitment, retention, activation, and differentiation.

E) Synovial Macrophages:

Basic Biology: A macrophage is a granulocyte of white blood cell (WBC), which performs the process of phagocytosis. A macrophage is a cell generated from the monocyte progenitor and release in blood. They are found in different tissue according to their performance such as in the liver they are called kuffer cells, in lung alveolar macrophage cell and in joint it is known as synovial macrophages. The size of macrophages is about 15-18 µm in diameter [84, 85].

MLS Function: Macrophages are caused by inflammation and elevate the body temperature while pathogens entered in our body. It acts as a messenger for the hypothalamus to increase body temperature. Macrophages are phagocytic [86]. There is two pathogen killing mechanism first one is oxygen dependent and second one is oxygen-independent. In oxygen-dependent, they produce ROS and RNS, which is causing damage to the pathogen and another one is an oxygen-independent mechanism that firstly engulfs the bacteria and digests them through a lysosomal antimicrobial peptide, after digestion, they removed from the body [87]. Macrophages have secreted some molecule like cytokine, IL1, which are inflammation producing molecule this molecule alarm other macrophages around the body and other immune cells come and fight the pathogen [88].

The MLS in RA: The type A (the macrophage) interlocked with the type B cell (the fibroblast) in the synovial joint. In the normal condition, the type B-cell is found largely in synovium as compared to Type A-cell, while in RA condition type A-cell will be found greatly [89]. They also involved in bone resorption [90]. Rheumatoid arthritis most common caused by macrophages. When the number of macrophages is increased in synovium they cause radiological damage [91], joint pain and inflammation [92]. Synovitis degeneration with rheumatoid arthritis can be seen in almost 50% of the patient without cellular congestion. Chemical mediator which responsible for macrophages activation in rheumatoid arthritis-like growth factors and cytokines, including TNF-a, GM-CSF, IL-1, 6, 8, 10, 13, 15, 18, migration inhibitory factor (MIF) and chemokines [93, 94]. Macrophages are produced several types of proteases including leukocyte elastase, MMP-1, MMP-3 and MMP-9, and matrix metalloproteinases (MMPs) in case of articular destruction [95].

Macrophages —TNF, IL-1→ Fibroblast activation —Protease collagenes→ MMPs and cathepsin

Macrophages → T lymphocyte activation —RANKL→ Osteoclast

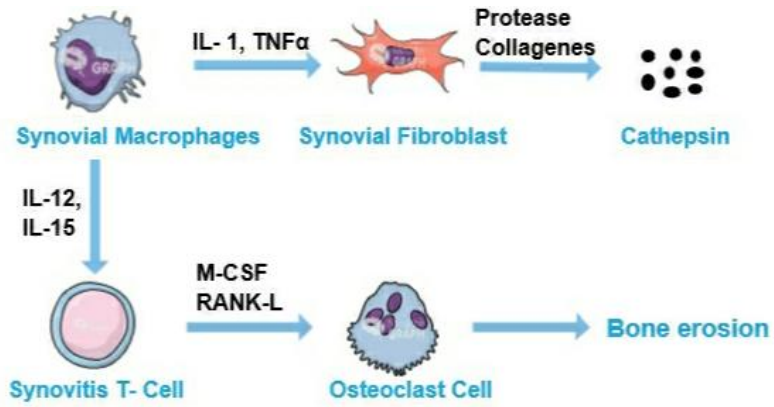

Fig:- 4 Macrophages regulation in synovitis

Fig 4:- Synovial lining consists of both activated macrophages and fibroblastic synoviocytes, which actively degraded cartilage and bone by producing protease collagens, RANKL, TNF, and IL-1 of which formed MMPs, cathepsin, and osteoclast which responsible for bone erosion.

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