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Pathogenesis of Fibrosis: A Comprehensive Review of Oxidative, Inflammatory, and Immune Mechanisms Underlying Tissue Damage in Multiple Organ Systems

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Abstract. *Fibrosis, oxidative stress, inflammation, and immunity are tightly coupled processes leading to tissue damage and disease progression. Oxidative stress, triggered by reactive oxygen species (ROS), favors inflammation through the activation of pro-inflammatory cytokines as well as immune cells, especially macrophages. Chronic inflammation impedes the mechanisms of repair in tissues, resulting in an excess deposition of extracellular matrix (ECM) leading to fibrosis. Immune dysregulation mediated through T cells, B cells, as well as innate immunity also propels the fibrotic pathway. In contrast, fibrotic tissue reinforces oxidative stress and inflammation, forming a vicious cycle that sustains tissue injury and remodeling. Emerging evidence indicates that various molecular pathways are involved in this complex interplay. Key signaling cascades such as transforming growth factor-beta (TGF-β), nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinases (MAPKs) play significant roles in amplifying oxidative and inflammatory responses. Dysregulation of antioxidant defense systems, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, further aggravates oxidative stress and enhances tissue vulnerability. Moreover, metabolic alterations within immune cells contribute to the persistence of a pro-fibrotic environment. Activated macrophages, for instance, secrete profibrotic cytokines like interleukin-13 (IL-13) and tumor necrosis factor-alpha (TNF-α), while T helper 17 (Th17) cells promote chronic inflammation and tissue remodeling. This intricate cellular cross-talk highlights the importance of immune-metabolic regulation in fibrosis progression. Understanding these interconnected mechanisms offers promising therapeutic opportunities. Targeting oxidative stress with antioxidants, modulating immune responses with biologics, and inhibiting fibrogenic pathways using TGF-β or tyrosine kinase inhibitors are currently being explored in both preclinical and clinical settings. Such interventions hold potential for breaking the vicious cycle of oxidative stress, inflammation, and immunity, ultimately preventing irreversible organ damage and improving clinical outcomes in fibrotic diseases.*

Keywords: *Fibrosis, Immunity, Inflammation, Oxidative stress, pathogenesis.*

1. INTRODUCTION

Another name for fibrosis is fibrotic scarring (Fibrosis ,2024). fibrosis is a pathological phenomenon responsible for scarring of tissues and organ impairment as a result of excessive deposition of extracellular matrix (ECM) Components, particularly Collagen. It occurs when the body repair mechanism is disrupted resulting in a disproportion in the production and degradation of extracellular matrix (ECM), similar in conditions like chronic inflammation, tissue injury, or unchecked wound healing. Various factors, such as tissue injury, autoimmune disorders, allergens, and recurrent infections, impact fibrogenesis within the various tissues and organs. (Antar et al., 2023), such as cirrhosis of the liver, pulmonary fibrosis of the lung, renal fibrosis of the kidney, and Scleroderma of the skin.

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Fibrosis is a leading Cause of morbidity and mortality globally and can lead to organ failure if untreated (Rockey et al., 2015; Martinez et al., 2017 Henderson et al, 2020).

The development of fibrosis is significantly influenced by oxidative Stress, inflammation, and immunological response.

2. OXIDATIVE STRESS AND FIBROSIS.

Since oxygen is necessary for numerous enzymatic steps during intermediate metabolism as well as xenobiotic biotransformation, oxygen-based life is dependent. Further, for the energy needs of cells, energy production is driven through oxygen usage within the electron transport chain in the mitochondria. However, with molecular oxygen usage as a consequence, free radical production results as a toxic product. Oxidative tension can be mediated through an imblance during between antioxidant strategies as well as when reactive oxygen species (ROS) production overwhelms intrinsic antioxidant defense in a cell (Rosa et al, 2022) .Adenosine triphosphate synthesis, cytochrome P450 Catalytic activities, nicotinamide adenine nucleotide phosphate oxidase (Noxs) cyclooxygenases and nitric oxide synthesis during drug Catabolism, phagocytosis, and acute inflammation all result in the production of oxygen free radicals (reactive oxygen species, or Ros) and nitrogen free radicals (Creactive nitrogen species, or RNS) by the mitochondria. Low levels of Ros and RNS produce redox signalings thate regulate numerous vital physiological activities under normal conditions. The oxidation and saturation of essential cellular Components, such as DNA, proteins and lipids results in oxidative stress, which in turn causes damage associated molecular patterm (DAMP(, which immune cells recognize as "non self".

This leads to inflammation which is mediated by nuclear factor kappa-B-inflammasmne, P38-C-JunN-terminal kinase, and Janus kinase-signaltransduser and activator of transcription pathways.

ROS and RNS rise excessively as a result of dysfunctional mitochondria, dysregulated Nox, and other free radical generation sources. Damaged and senescent Cells Continuously release DAMPS, which causes an inflammation that would otherwise be temporary to become systemic and persistent. This inflammation is the primary Cause of aging and age-associated disorders (AADS) (Sobhon et al 2023).

Oxidative stress generally occurs when free radicals (such Ros) and antioxidants are out of balance, causing tissue and Cell damage. The activation of profibrotic signaling, extracellular matrix (ECM) deposition, and Cellular damage are some of the routes via which oxidative Stress causes fibrosis.

Below are the key mechanisms:

A. Activation of profibratic signaling pathways: Oxidative stress activates key signaling pathways that promote fibrosis:

1. **TGF-B/Smad pathway:**

   Reactive oxygen species (Ros) enhance TGF-B1 production, a key profibrotic Cytokine, leading to fibroblast activation and Collagen formation.

3. **MAPK/ERK and NF-kB pathways:**

   ROS promote inflammation and fibrosis by activating nuclear factor kappa B (NF-kB) and mitogen-aptivated Protein kinase (MAPK) (Liu & Desai, 2015; piera-Velazquez and Jimenez, 2021)

B. Activation of Myofibroblasts and ECM Deposition

ROS induce fibroblast differentiation into myofibroblasts, which produce a surplus of extracellular matrix elements. (fibronectin, Collagen I/II). Inhibiting matrix metalloproteinases (MMPs) and increasing tissue inhibitors of metalloproteinases. (TIMPs), oxidative pressure also inhibits the degradation of extracellular matrix. (Hernandez-Gea & Friedman, 2011 :Rockey et al., 2015)

C. Epithelial-Mesenchymal Transition (EMT)

Ros Cause EMT, aprocess in which epithelial cells change into cells that resemble mesenchymal tissue and aid in the formation of fibroblasts. The Notch,Wnt/B-catenin, and TGF-B pathways mediate this (Kalluri and Weinberg, 2009, liu,2010)

D. Inflammatory Response and Fibrogenesis

ROS trigger the NLRP3 inflammasome, which in turn triggers the release of IL-1B and IL-18, which cause fibrosis. Fibrosis is made worse by macrophages that are polarized between Mo (pro-inflammatory) and M2 (pro fibratic) phenotypes under oxidative stress (Wynn and Barron, 2010; Ding and choi, 2015).

E. Mitochondrial Dysfunction and Apoptosis

Ros harm mitochondria, which causes Parenchyma cells (such as hepatocytes and alveolar cells) to undergo apoptosis and initiate fibrotie healing Damaged mitochondria release mtDNA and cytochrome C, further amplifying oxidative stress (Zhou et al., 2018, Meyer et al, 2018).

F. Hypoxia and oxidative stress Interaction

Oxidative stress stabilizes hyppoxia-inducible factors (HIF-1α), which stimulates the production of fibrogenic genes. (Tamanini et al, 2020; Copple et al, 2010).

G. Impaired Antioxidant Defenses.

Depletion of glutathione (GSH), Superoxide dismutase (SOD), and catalase exacerbates oxidative damage, creating apr-fibrotic microenvironment.

H. Senescence & SASP (Senescence-Associated secretory phenotype)

Oxidative stress induces Cellular Senescence leading to SAsp (secretion of IL-6, TGF-B), which promates. fibrosis. (NOX4 as a central mediator of TGF-B-induced fibrosis (Nat Commun. 2023) Nanoparticle - induced Ros in Silicosis (part Fibre Toxicol , 2024)

Oxidative stress drives fibrosis through TGF-B activation, myofibroblast differentiation, ECM deposition, chronic inflammation, mitochondrial dys function and hypoxia interactions.

Therapeutic strategies targeting Ros (e-g. Antioxidants, Nox inhibitors) are being explored to mitigate fibrosis.

3. INFLAMMATION AND FIBROSIS

The body uses inflammation as a quik defense mechanisms in reaction to damage infiction, or dangerous stimuli.

Blood vessels, immune cells and molecular mediators are all involved in removing the source of harm and starting tissue repair (Chavda et al., 2024).

Acute inflammation is a brief reaction (minutes to days) that is typified by Pain, swelling, heat, redness, and loss of function. Mediated by vasodilation, neutrophils, and cytokines (such as TNF-α and 1L-6). Prolonged response (weeks to years) involving macrophages, lymphocytes, and fibrosis is known as chronic inflammation. It is observed in autoimmune diseases (like rheumatoid arthritis) or chronic infections (Kumar et al., 2020; Medzhitov, 2008).

There is increasing evidence now to prove that inflammation-expecially chronic inflammation has a significant role in the onset as well as the advancement of coronary artery illnesses, diabetes, Cancer, renal disease, and is also highly associated with fibrosis (Liu et al, 2021).

Increased inflammation, tissue injury, and production of numerous inflammatory cytokines, including TGF-B1, tumor necrosis factor. alpha (TNF-alpha), monocyte chemoattractant protein (MCP-1), interleukin-6 (1L-6), and IL-8, are features of fibrosis. Consequently, tissue injury is made worse through a pro-inflammatory microenvironment (Elmahdy et al, 2021). EMT is the process by which differentiated epithelial cells give rise to

matrix-producing fibroblasts and myofibroblasts, and it is becoming recognized as a crucial element of tissue fibrogenesis after kidney injury.

EMT occurs in glomerular diseases and can lead to glomerulosclerosis, proteinuria, and podocyte dysfunction.

The fibroblasts are the mesenchymal cells responsible for developing renal disease. As depicted in Figure (8), renal disease leads to an accumulation of fibroblasts, either due to induction through different cytokines, particularly TGF-1, or due to the transformation into myofibroblasts.

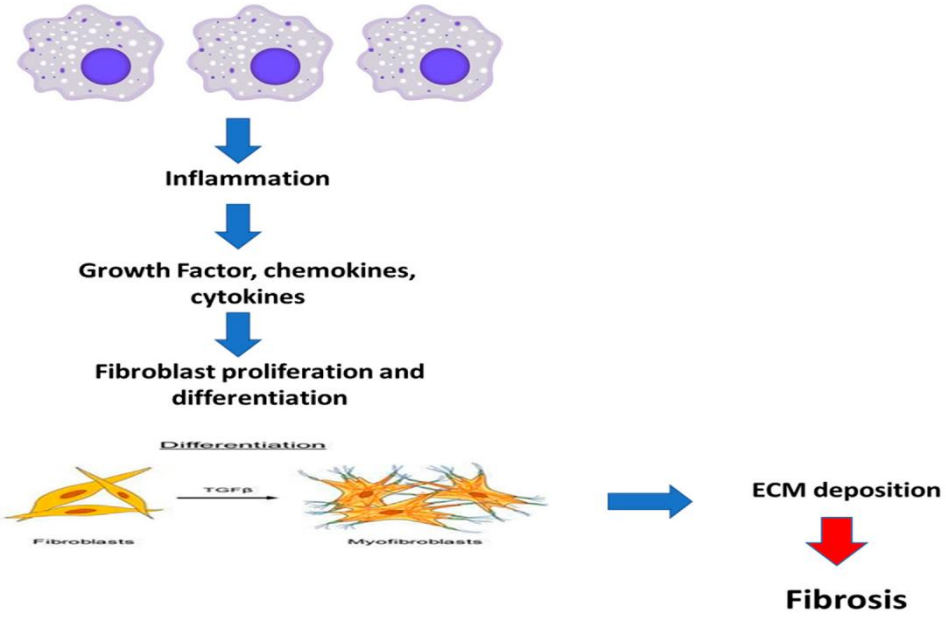

Figure 1. The schematic diagram illustrates how fibrosis is triggered by persistent inflammation. TFG-β; transforming growth factor. (Antar et al, 2023)

Role of TNF - & in Fibrosis

Depending on the situation tissue type, and stage of the disease the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) can either promote or inhibit fibrotic processes. A summary of its effects and mechanisms may be found below:r.

A. pro-Fibrotic Role of TNF-α

TNF- α can promote fibrosis through multiple pathways:

1) Activation of fibroblasts and Myofibroblasts:

TNF- α promotes the growth and differentiation of fibroblasts into myofibroblasts, which are important cells in fibrosis that generate an excess of extracellular matrix (ECM) proteins, such as Collagen. It increases the synthesis of various fibrogenic mediators and TGF-B, a key profibrotic Cytokine.

2) Induction of inflammation

a. Prolonged TNF- alpha signaling maintains inflammation, which damages tissue and Causes fibrotic repair.

b. Attracts immune cells that release more pro-fibrotic factors, such as neutrophils and macrophages:

3) Extracellular Matrix Remodeling

a. TNF alpha disrupts normal ECM turnover by upregulating matrix metalloproteinases (MMPs) and inhibiting tissue inhibitors of metalloproteinases (TIMPs)

b. It is encouraged through the excessive deposition of Collagen.

4) Anti- Fibrotic Role of TNF-alpha

In some situations - TNF alpha might paradoxically also prevent fibrosis

a. Induction of Apoptosis in myofibroblasts

Elevated TNF- α levels can cause active myofibroblasts to undergo apoptosis, which lowers the synthesis of extracellular matrix.

b. Suppression of TGF-B signaling

TNF- α can sometimes reverse TGF-B induced fibrosis via modifying Smadsignaling.

c. promotion of ECM Degradation

TNF- α can increase MMP activity, which promotes the breakdown of ECM.

(Chen et al, 2020, Wang et al, 2021, Sethi and Hotamisligil,2021).

d. Role of NF-kB in Fibrosis

Through its regulation of inflammation, fibroblast activation, and extracellular matrix Synthesis the NF-kB (Nuclear Factor kappa B) pathway is essential to the onset and advancement of fibrosis.

A transcription factor Called NF-kB regulates the expression of genes implicated in:

1) Inflammation-promotes the release of pro inflammatory cytokines (TNF-α-1L-1B, IL-6) that drive fibrotic responses.
2) Fibroblast Activation-induces the differentiation of fibroblasts into myofibroblasts (key ECM producing cells).
3) ECM Remodeling - upregulates matrix Metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPS), Contributing to fibrosis.
4) Apoptosis Resistance - protects myofibroblasts from apoptosis, perpetuating fibrosis.

Mechanistic perspectives:

1) An avicious cycle can be created when TGF-B, akey profibrotic cytokine, activates NF-KB, which in turn enhances TGF-B Signaling.
2) In response to damage-associated molecular patterns (DAMPs) toll-like receptors (TLRs) activate NF-kB, which promotes fibrosis.
3) The activation of NF-kB by reactive oxygen species (ROS) can exacerbate fibrotic responses. (Capece et al, 2022; Domino et al, 2020; Zou et al., 2021)

Role of JunN - Terminal kinase (JNK) in Fibrosis

Cellular stimuli (e.g., cytokines, uv radiation, oxidative Stress) may activate the serine/threonine kinase Jun N-terminal kinase (JNK), a member of the mitogen-activated protein kinase (MAPK) family.

JNK promotes fibrogenesis via a number of methods:

1) Activation of pro - Fibrotic Transcriptional pathways.
2) Myofibroblast Activation
3) Inflammation and Apoptosis (Antar et al,2022, Nikolie - Paterson et al, 2021 Mu et al 2018).

Role of Wnt pathway in fibrosis.

The WNT signaling pathway is a Collection of signal transduction pathways composed of proteins that transmit signals into cells via cell surface receptors. It is highly conserved across different species. Fibroblast activation and collagen release in fibrosis are significantly influenced by the classical WNT pathway.

WNT signaling increased the release of extracellular matrix components, promoted the differentiation of resting fibroblasts into myofibroblasts, and caused fibrosis. (Frenquelli and Tonon, 2020; Griffin et al ,2022).

Immunity and its role in Fibrosis.

The immune system reacts to an injury by repairing the damaged tissue. However, occasionally this healing process goes awry, resulting in fibrosis rather than typical tissue restoration. Therefore, the immune response to persistent inflammation may be related to the immune system's role in both healing tissue and battling infections. Long-term immune system activation, such as in autoimmune disorders or chronic infections, may result in excessive tissue repair and fibrosis due to the constant release of inflammatory signals. Fibroblasts, which create collagen and other extracellular matrix components, are the cells that cause fibrosis. However, how do fibroblasts and immune cells interact? (Huang et al, 2020). Both innate and adaptive immunity Contribute to fibrogenesis (Lara - Reyna et al, 2020)

Innate Immune Cells in the pathogenesis of Fibrosis

persistent activation of innate immune cells release substances that encourage Collagen deposition and fibroblasts activation.

1. **Macrophages**

   Macrophages have a key role in controlling fibrosis and tissue healing. M_1 (pro-inflammatory) and M_2 (anti-inflammatory) are their distinct activation states. M_1 macrophages remove germs and debris from acute injuries. M_2 macrophages take over tissue healing if the damage has healed. However, M_2 macrophages may Continue to release pro- fibrotic cytokines such as TGF-B in the presence of chronic damage. Fibroblasts are activated by TGF-B to form myofibroblasts, which generate large amounts of collagen. Therefore, macrophages particularly M_2 - are most likely important In this situation (Jiang et al, 2024 wynn and Vannella 2016).

2. **Neutrophils**

   The release of profibrotic cytokines (TNF- α, TGF-B, and IL-17), the generation of reactive oxygen species (Ros) and proteases that cause tissue damage and extracellular matrix remodeling, the formation of neutrophil extracellular traps (NETS) that perpetuate inflammation, interactions with other immune cells (macrophages ,Tcells) that promote a profibrotic environment, and dysregulation of the normal. resolution processes that result in chronic injury are some of the potential mechanisms that link neutrophils to fibrosis (Growley et al, 2024)

3. **Mast cells**

   Mast cells play a role in both fibrosis and allergic responses They emit mediators such as histamine, tryptans, and others that can recruit additional immune cells and promote vascular permeability. They may have direct interactions with fibroblasts, encouraging Collagen production and proliferation.

   Systemic sclerosis and other fibrotic diseases have been linked in certain studies to the quantity of mast cells.

   In addition to secreting cytokines (1L- 4, 1L-13, and IL-33) that stimulate Th2 polarized immune responses, which in turn drive fibrosis by inducing collagen production and fibroblast activation, mast cells also secrete vascular endothelial growth factor (VEGF), which promotes angiogenesis and supplies fibrotic tissues with nutrients and oxygen, thus maintaining remodeling (Hügel, 2014).

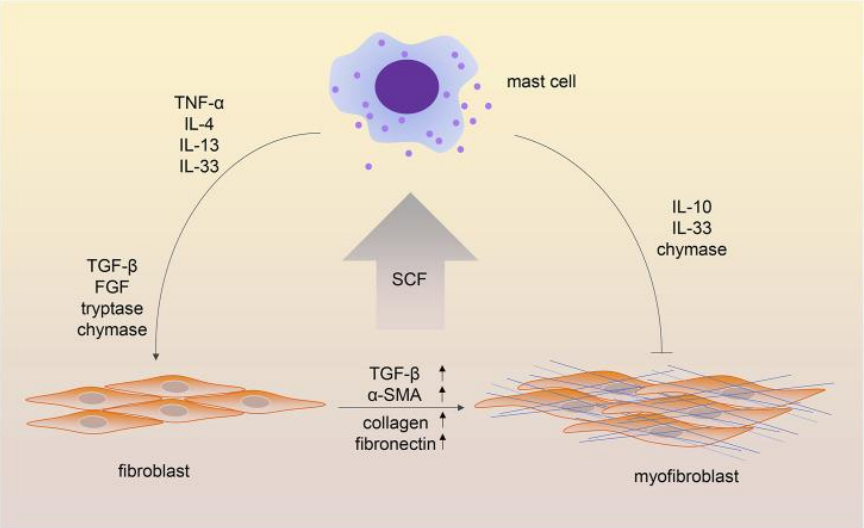

Figure 2. Crosstalk between mast cells and fibroblasts in fibrotic processes. The cell–cell adhesion between mast cells and fibroblasts depends on the stem cell factor-Kit (SCF-KIT) interaction. In addition, mast cell-derived cytokines and chemokines contribute to the transition of fibroblasts into myofibroblasts. Interestingly, some mast cell mediators have been shown to have both profibrotic and antifibrotic functions. (Wang et al, 2024).

4. **Dendritic cells**

As specialized antigen - presenting cells, dendritic cells (DCs) have a greater role in fibrosis, a pathological condition marked by tissue scarring and excessive extracellular matrix deposition. Their role is complex affecting both pro- fibrotic and anti-fibrotic pathways based on disease stage, subset diversity, and Context (Lu, 2012; Carvalheiro et al, 2020).

5. **Y&T cells**

Depending on the situation, gamma delta T cells can either stimulate or prevent fibrosis by producing Cytokines, interacting with fibroblasts, and modifing other immune cells. Because of their multiple roles, they are a challenging yet intriguing therapeutic target (Segawa et al., 2016).

6. **NK cells**

By eliminating activated fibroblasts and stellate cells and secreting anti-fibrotic Cytokines like IFN-Y, NK cells largely play an anti-fibrotic role. Factors such as TGF-B Can support their action in chronic fibrosis (Jin et al., 2017).

Adaptive Immune cells in the pathogenesis of Fibrosis

1. Th_1 cells in Fibrosis

The cells, which are a subset of CD4+ Thelper cells. generate TNF- α and IFN – Y, which often have anti- fibrotic properties.

Inhibiting fibroblast activation, Collagen synthesis, and myofibroblast development, they neutralize Th2 cell's pro-fibrotic activities (which induce fibrosis via IL-4, IL-13, and TGF-B). However, by maintaining inflammation, persistent Th1 responses in chronic inflammation might indirectly promote fibrosis by causing tissue damage. Therefore, even while Th1 cytokines normally inhibit fibrosis, in some situations, their extended activation may exacerbate fibrotic consequences (Fielding et al, 2014; Nevers et al, 2017)

2. Th_2 cells in Fibrosis

A subset of CD4+ T cells known as Th2 (T-helper 2) cells release cytokines such as 1L-4, 1L-5, 1L-13 and IL -31, which encourage fibrosis via:

a) Activation of Fibroblasts

Fibroblasts are stimulated by 1L-13 and IL-4 to create extracellular matrix (ECM) proteins, including Collagen.

b) Alternative Macrophage Activation (M2)

Macrophages with the apro - fibrotic M2 phenotype, which secretes TGF-B, a crucial fibrotic mediator, are driven by Th2 cytokines.

c) Tissue Remodeling

IL-13 disrupts the natural balance of extracellular matrix by inducing matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (Kokubo et al, 2022).

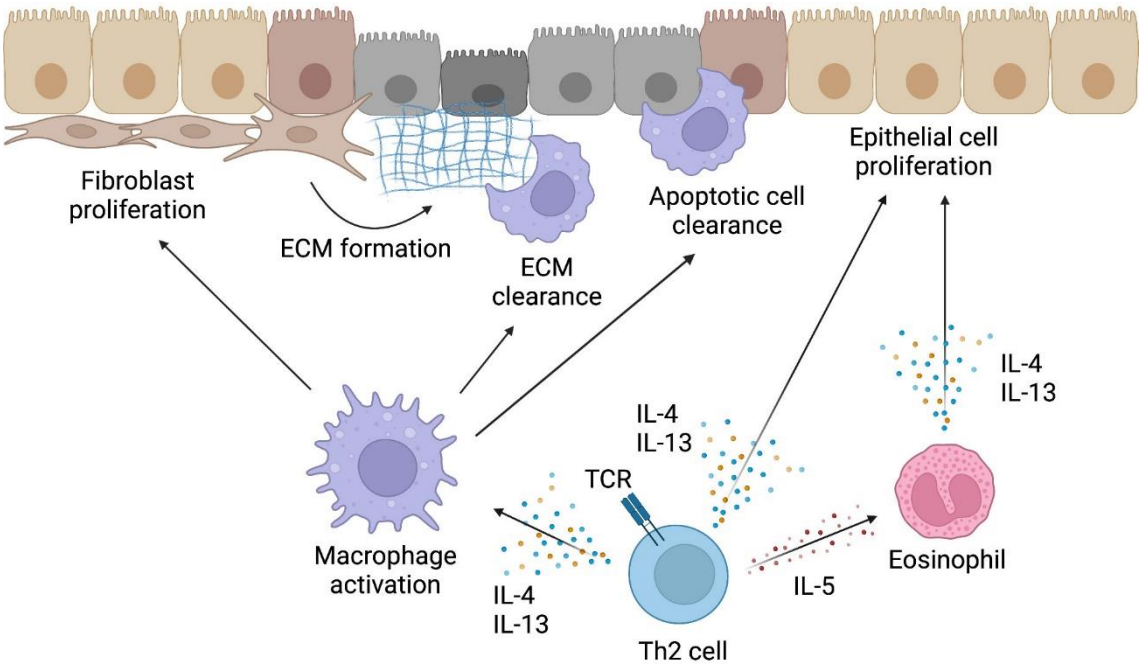

Figure 3. Mechanism of tissue repair by Th2 cells. Type 2 cytokines produced by Th2 cells not only induce type 2 inflammatory responses but also contribute to the repair of injured tissues. The activation of macrophages by IL-4 and IL-13 is important for the resolution of the type 2 inflammatory response and initiation of tissue repair. Activated macrophages induce fibroblast proliferation, remove extracellular matrix (ECM) formed by fibroblasts and other cells, and clear apoptotic cells in injured tissues. IL-4 and IL-13 produced by Th2 cells can also directly induce the proliferation of epithelial cells and contribute to the reconstruction of injured tissues. Furthermore, eosinophils, which are recruited to inflammatory sites by IL-5 produced by Th2 cells, can also produce IL-4 and IL-13. Thus, Th2 cells induce tissue repair both directly and indirectly. This figure was created with BioRender.com. (Kokubo et al, 2022).

3. Th_{17} cells in Fibrosis

Through their promotion of tissue searring and chronic inflammation, Th17 cells a subpopulation of CD4+ T helper cells, significantly contribute to fibrosis. They secrete pro-inflammatory cytokines like 1L-17A; 1L-17F, 1L-21, and IL-22,

Which:

a) Stimulate fibroblasts

Increase the production of Collagen and the deposition of extracellular matrix (ECM)

b) Recruit neutrophils & Macrophages

Amplify inflammation and fibrogenic responses.

c) Synergize with TGF-B

An important profibrotic cytokine that exacerbates fibrosis in the skin,liver, and lungs (Liang et al, 2014 Zhang et al. 2017).

4. Regulatory T cells

Depending on the tissue and ailment, regulatory T cells (Tregs), a subset of CD4+ T cells that express Foxp3 have two roles in fibrosis:

a) Anti-fibrotic Role

By inhibiting pro-fibrotic immune cells. (Th17, macrophages) and lowering TGF-B and IL-13 Signaling, Tregs reduce excessive inflammation. By secreting anti-inflammatory cytokines (IL-10, TGF-B) in regulated quantities, they aid in tissue repair.

b) pro- fibrotic Role

By releasing TGF-B, stimulating fibroblasts, and encouraging Collagen deposition Tregs may be a contributing factor to fibrosis in some chronic diseases (MacDonald et al, 2015; Moye et al: 2020, Takei et al., 2020).

5. Follicular Helper T cells in Fibrosis

Are a specific fraction of CD4+T cells that are essential for splenic and lymph node germinal center (GC) reactions. Their main functions include:

a) B cell Help:

Tfh cells give B Cells Cues (Via surface markers like CD40L and cytokines like IL-21) that encourage B cell activation, proliferation, and differentiation into memory B cells and antibody- producing plasma cells.

b) Germinal Center Formation:

As B cells go through somatic hyper- mutation and affinity maturation to create high-affinity antibodies, they aid in the establishment and upkeep of germinal centers.

c) Antibody class Switching

For efficient immune responses, Tfh cells direct B cells to change antibody classes (for example, from IgM to IgG, IgA, or IgE). Immunodeficiency, allergies, and auto - immunity are all associated with Tfh cell dysregulation. They are necessary for both long- term humoral immunity and vaccination. responses (Sahinoglu et al, 2024; Asai et al., 2019).

6. B cells

By generating pro- fibrotic antibodies and cytokines (such as TGF-Band 1L-6), Stimulating fibroblasts, and encouraging Chronic inflammation, B cells Contribute to fibrosis. Additionally, they promote the deposition of extracellular matrix (ECM) via supporting macrophages and T cells. B lymphocytes may occasionally play regulatory roles that prevent fibrosis. The tissue and illness setting determines their precise function. (Manganelli et al, 2020; Fillatreau et al., 2021).

Apart from antibody secretion and the supposed activation of pathogenic T cells, B lymphocytes have five primary roles, which are as follows:

1. They cause myofibroblast precursors to undergo the epithelial to mesenchymal transition. and activated fibroblasts to produce more Collagen.
2. They secrete collagenous proteins, which directly contribute to tissue fibrosis.
3. They Control the rigidity of the extracellular matrix.
4. They release chemotactic factors for M2 macrophages and potential fibro genie CD4+ CTLS.
5. They increase the recruitment of inflammatory cells by stimulating fibroblasts (Della Torre et al, 2020).

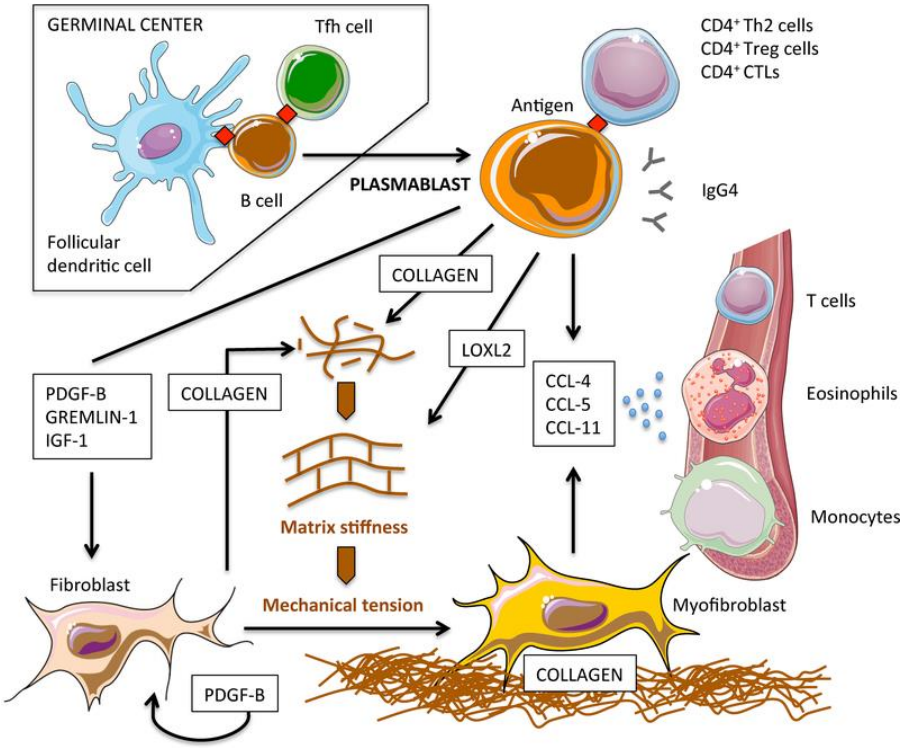

Figure 4. Updated pathogenetic model of IgG4-RD pathogenesis: B-cell involvement in tissue fibrosis. After germinal centre activation, antigen contacted naïve B cells differentiated into class-switched plasmablasts and entered inflamed

tissues where they participate in tissue fibrosis through various mechanisms. Plasmablasts induce fibroblast commitment towards myofibroblasts through soluble mediators triggering transcriptional programmes involved in mesenchymal transition. Plasmablasts also induce fibroblasts to produce collagen and PDGF-B, thereby increasing fibroblast activation within an auto/paracrine loop. Plasmablasts also form collagenous proteins, directly participating in the fibrosis. Plasmablasts modulate extracellular matrix stiffness through production of collagen molecule crosslinking enzymes like LOXL2. Enhanced extracellular matrix stiffness activates fibroblast mechanoceptors, thereby promoting their complete commitment towards myofibroblasts. Plasmablasts recruit inflammatory cells with added fibrotic capability like CD4+ CTLs, eosinophils, and M2 macrophages, by production of CCL-4, CCL-5, CCL-11, through a paracrine action, and through inducing fibroblasts towards production of these very much identical chemokines. Pathogenic role of IgG4 antibodies, as well as of T-cell populations likely supported by cognate antigen specific plasmablasts, yet needs clarification. (Della Torre et al, 2020).

4. CONCLUSION

1. Oxidative stress generates reactive oxygen species (ROS), damaging cells and triggering inflammation.
2. Inflammation activates immune cells (e.g., macrophages, T-cells), releasing pro-fibrotic cytokines (e.g., TGF-B).
3. Dysregulated immunity (chronic activation or failure to resolve inflammation) Promotes persistent fibroblast activation.
4. Fibrosis results from excessive extracellular matrix (ECM) deposition, further sustaining oxidative stress and inflammation.

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