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Histological Remodeling of Tissues During Chronic Inflammation: The Role of Immune-Mediated Fibrosis.

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Abstract :

Chronic inflammation is a prolonged immune response that causes structural and functional changes in tissues. It is characterized by continuous immune cell infiltration, persistent cytokine production, and progressive tissue damage. One critical outcome is fibrosis, driven by immune-mediated mechanisms, which disrupts normal tissue architecture and impairs organ function. Chronic inflammation leads to tissue remodeling, loss of parenchymal cells, expansion of fibrous tissue, and angiogenesis, with activated macrophages, lymphocytes, and fibroblasts playing central roles in this process. Chronic inflammation-induced fibrosis is a condition characterized by the accumulation of fibrotic tissue. This process is triggered by mediators that stimulate fibroblast proliferation and transformation into myofibroblasts, key effectors in ECM production. Prolonged inflammation disrupts the balance between ECM synthesis and degradation, leading to various chronic inflammatory diseases. Understanding the histological progression and immune mechanisms can help identify potential therapeutic targets for the disease.

Key words: Chronic inflammation, Immune-mediated fibrosis, Tissue remodeling, Extracellular matrix, Myofibroblasts, Pro-fibrotic cytokines.

إعادة تشكيل الأنسجة على المستوى النسجي أثناء الالتهاب المزمن: دور التليف المناعي/ مراجعة مقال

نور محمد جعفر حمودي ، مروة خليل إبراهيم ، رنا علاء العامري
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مستخلص:

الالتهاب المزمن هو استجابة مناعية طويلة الأمد تسبب تغييرات تركيبية ووظيفية في الأنسجة. يتميز بتسلل مستمر لخلايا المناعة، وإنتاج مستمر للحركيات الخلوية، وتلف تدريجي للأنسجة. واحدة من النتائج الحرجة هي التليف، الذي يدفعه آليات متعلقة بالمناعة، مما يعطل التركيب الطبيعي للأنسجة ويؤثر على وظيفة الأعضاء. يؤدي الالتهاب المزمن إلى إعادة تشكيل الأنسجة، وفقدان الخلايا الحشوية، وتوسع الأنسجة الليفية، وتكون الأوعية الدموية، مع تفعيل البلاعم الكبيرة والخلايا اللمفاوية والاورومات الليفية التي تؤدي أدوارًا مركزية. التليف هو ناتج عن الالتهاب المزمن ويعد حالة تتميز بتراكم الأنسجة الليفية. يتم تحفيز هذه العملية بواسطة وسائط تحفز تكاثر الاورومات الليفية وتحولها إلى اورومات الليفات عضلية، التي تعد فعالة رئيسية في إنتاج مصفوفة الخلايا خارج الخلية. يؤثر الالتهاب المطول على التوازن بين تخليق المصفوفة الخلوية خارج الخلية وتفكيكها، مما يؤدي إلى مجموعة متنوعة من الأمراض الالتهابية المزمنة. ان فهم التطور النسجي والآليات المناعية يمكن أن يساعد في تحديد الأهداف العلاجية المحتملة.

الكلمات المفتاحية: الالتهاب المزمن، التليف الذي تتوسطه المناعة، إعادة تشكيل الأنسجة، مصفوفة خارج الخلية، الاورومة الليفية العضلية، الحركيات الخلوية المحفزة للتليف.

1. Introduction

Chronic inflammation is a common cause of various diseases and primary chronic disorders like atherosclerosis, lung diseases, type II diabetes, and organ fibrosis. The fibrosis-induced organ fibrosis is more difficult to treat than chronic inflammation reduction. [1]. Expansion of the extracellular matrix (ECM) leads to tissue and organ dysfunction, causing pathological events. Cell-based therapeutics are being developed to deplete excess ECM. Chronic inflammation contributes to excessive ECM collagen deposition, with tissue-infiltrated macrophages being major contributors. Chronic inflammation also results in tissue remodeling of the collagen skeleton [2]. The remodeling of the collagen skeleton involves both expansion and regression of the endothelial cell (ECM) during chronic inflammation. Evidence suggests macrophages may play a role in tissue collagen remodeling and repair, but their mediating mechanisms remain unclear. This research is in its early stages, recognizing macrophages' importance in various pathophysiological settings [3]. Macrophage biologists have developed various manipulation systems for macrophages, including specific ablation and cell line establishment. They highlight macrophage-remodelling mechanisms contributing to inflammation-induced tissue fibrosis and discuss future directions for understanding macrophage roles in fibrillogenic and anti-fibrillogenic activities [4].

2. Understanding Chronic Inflammation

Chronic inflammation is a disease characterized by the presence of mononuclear leukocytes in diseased tissue, which directly associates with tissue fibrosis through antigen-driven T helper activation and TNFα regulation. It can be classified into systemic diseases like autoimmune diseases and localized diseases like primary organ-focused diseases [5]. Chronic inflammation, involving autoantigen-driven loss of tolerance, activates B cells and autoantibody production. Localized chronic inflammation involves undefined injury in tissue macrophages, mast cells, and T cells, leading to extensive fibrosis. Evidence shows covert fibrotic repair is aberrantly induced but lasts beyond bounds, causing gradual tissue

loss [6].

Fibrosis is a pathological wound healing process that results in organ malfunction in chronic inflammatory diseases. It is triggered by prolonged immune, fibroblast, and myofibroblast activation, depleting the patient's functional tissue and leading to organ failure. Tissue macrophages, acting as strong antigen-presenting cells, stimulate naïve T helper cells to differentiate into Th1/Th2 and provide CD4 help [7]. Dermal granulation tissue, induced by skin inflammation from hapten contact sensitization, is a useful model for studying chronic fibrotic inflammation during wound healing (Figure 1) [8].

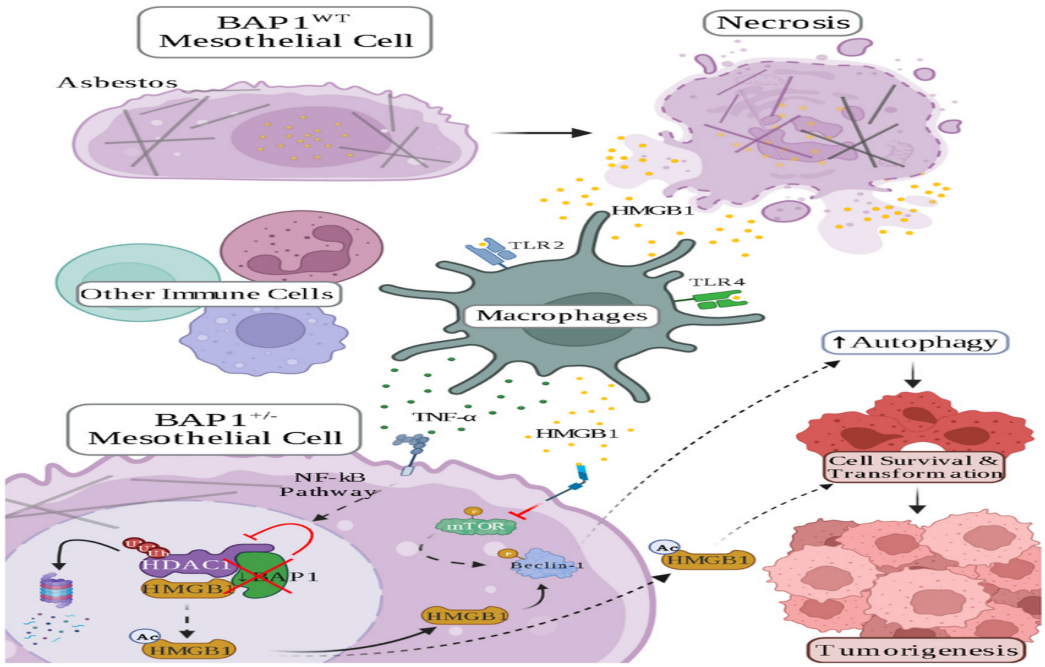

Figure 1. The regulation of chronic inflammation and cell transformation [9].

2.1. Definition and Mechanisms

Fibrosis is an irreversible process where normal tissue architecture is replaced by excess connective tissue, often resulting from diseases like chronic lung disease, liver cirrhosis, pancreatitis, chronic kidney disease, and scleroderma, caused by extensive tissue damage from viral infection, chemicals, and injury [10].

Chronic inflammation, a persistent condition beyond the acute phase, is a significant cause of fibrosis. It is primarily mediated by macrophage infiltration

and activation in tissues, as demonstrated by experimental observations and genetic manipulations. Inflamed tissues contain various macrophage populations, derived from circulating monocytes recruited to inflamed sites under inflammatory chemokines [11]. Inflammation-associated macrophages are derived from CCR2+ inflammatory monocytes or CX3CR1hi resident monocytes. CCL2, upregulated by inflammatory factors, recruits inflammatory monocytes. Macrophages in inflamed tissues express tissue factors, causing T cell polarization. M2 macrophages in tissues have been implicated in chronic inflammation-associated fibrotic disease processes, transitioning from inflammation to fibrosis [12].

2.2. Etiology and Risk Factors

Cardiac fibrosis can result from various conditions, such as myocardial stress, cardiac valve disturbances, or toxins, leading to chronic inflammation and fibrosis. Transgenic mice with a constitutively active TGF-β receptor can cause a rapid fibrotic response. Injuries or cellular loss trigger mechanisms to restore tissue, such as the epithelial-mesenchymal transition (EMT). The fibrotic process involves various cells, often influenced by pro-fibrotic factors. The timing of these processes is crucial, with chronic TGF-β administration causing fibrosis through both EndMT and EpicMT, while acute administration stimulates myofibroblast proliferation. The timing of inflammation and its differential effector mechanisms is important in both fibrotic and non-fibrotic outcomes [13].

Chronic granulomatous inflammation, characterized by abundant pro-inflammatory and pro-fibrotic mediators and cells, can lead to fibrosis, while conditions of limited inflammation may result in healthy tissue fibrosis. Classifying fibrotic diseases based on organ involvement is challenging, but a unifying view focusing on “fibrosis” remains unclear. It’s possible to consider an inflammatory and fibrotic syndrome, with duration determining disease progression and outcomes [14].

3. Histological Changes in Inflammation

Chronic inflammation is a long-lasting immune response that can persist for months, years, or even indefinitely. It is characterized by the presence of mononuclear cells, fibroblast recruit-

ment, neovascularization, and extracellular matrix remodeling. It can be caused by pathogenic infections, toxic exposure, autoimmunity, or ischemic necrosis. Chronic inflammation is more sophisticated and expensive due to its complex interplay of pro-inflammatory and anti-inflammatory cytokine networks, requiring more resilience from host tissues [15, 16].

Chronic inflammation is characterized by the accumulation of vascularized granulation tissue and chronic inflammatory cell infiltrates. It takes time for inflammation to become chronic enough for diagnosis. Chronic inflammation is implicated in chronic inflammatory diseases like tuberculosis, hepatitis, silicosis, and chronic obstructive pulmonary disease. Understanding and characterizing the biochemical and functional mechanisms of inflammation is crucial for its evolution from acute to chronic [17].

3.1. Cellular Components

Fibrosis is a pathological process resulting from acute tissue injury, which is further perpetuated by disorganized tissue repair, forming hyperplastic scars. This leads to loss of tissue architecture and organ function. Fibrosis can occur in any tissue type and is characterized by excess extracellular matrix deposition by activated fibroblasts or myofibroblasts. However, the cellular and molecular mechanisms behind this process are underexplored. Understanding the tissue remodeling during chronic inflammation and its aberrant carryover to fibrosis can help develop new therapeutics to manage protective immunity and limit chronic inflammatory diseases [18, 19].

Septal damage caused by delayed Type I hypersensitivity triggers a protective immune response that is amplified over time. The initial damage releases cytokines, activating innate lymphoid cells and Th2 cells. Th2 cells migrate and activate in draining lymph nodes, releasing downstream cytokines, promoting the activation of resident macrophages to a profibrotic phenotype. Resident macrophages also increase IL-10 secretion, limiting inflammation. After airway mucosal barrier damage, tissue-resident macrophages become activated, leading to chronic inflammation and fibrosis. Fibronectin-specific macrophages play a specific role in chronic fibrotic disease, producing IL-10 to reduce inflamma-

tion and profibrotic mediators (Figure 2). Persistent tissue damage triggers multiple immune mechanisms, exacerbated pathogenic immune response sequences [20].

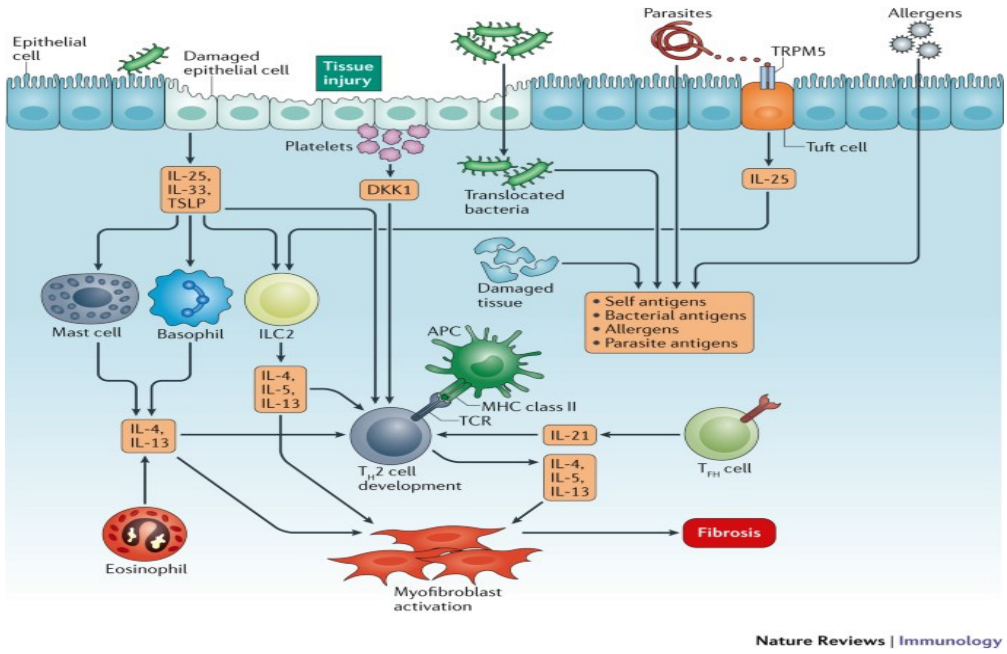

Figure 2. Initiation of type 2 immune responses [21].

3.2. Tissue Architecture

Chronic inflammation significantly impacts organ architecture and function, leading to massive alterations in organ structure. Inflammatory cytokines from immune cells stimulate the transdifferentiation of fibroblasts to myofibroblasts, forming dense fibrotic tissues in inflamed organs. This fibrosis often results in organ dysfunction, leading to organ failure. The severity of inflammation-induced fibrotic tissue formation determines the chronicity and adverse outcomes of chronic inflammation-related diseases. For example, chronic gastritis causes tissue stiffness leading to precancerous lesions, while chronic pneumonia causes pulmonary fibrosis, leading to respiratory failure and lung cancer [22]. Chronic kidney disease caused by organ fibrosis affects 10% of the global population. No treatment exists to completely reverse organ fibrosis, so alternative therapies are needed. Inflammatory cell-dependent mechanisms of chronic inflammation-induced organ fibrosis are crucial for developing such therapies. Chronic

inflammation-associated organ fibrosis, also known as "tissue scarring," results in the loss of normal tissue architecture and may lead to chronic scarring syndrome (CSS). This process, which includes tissue architecture remodeling, is gradual and complex, making it better to investigate subtasks separately [23, 24].

3.3. Extracellular Matrix Alterations

The extracellular matrix (ECM) is a crucial component of tissues, secreted by fibroblasts and containing fluid-phase proteins like collagens, glycoproteins, and proteoglycans. These components play a unique role in tissue assembly, virulence, and maintenance. Chronic inflammation can alter ECM components, leading to abnormal remodeling and physiological abnormalities like tissue stiffening and organ failure. Although the link between ECM abnormalities and inflammation is a critical checkpoint in disease progression, it is unclear how the ECM actively participates in the inflammatory process [25].

The extracellular matrix (ECM) is a crucial structure for protein and cell organization within the tissue microenvironment. It is subjected to various physiological and pathological stimuli, such as stretching and high-pressure chemical environments, which induce biochemical modifications in macromolecules, resulting in changes in physicochemical properties. These changes affect the expression profile and activity of tissue-resident cells, particularly fibroblasts and macrophages. Chronic inflammation triggers pro-inflammatory and pro-fibrotic stimuli, coordinating responses for inflammation and fibrosis progression [26].

4. Fibrosis in Chronic Inflammation

Fibrosis is a condition that can occur in any tissue type and is influenced by cellular and molecular mechanisms. Trauma or injury, often involving an exogenous stimulus, activates innate immune cells, with macrophages playing a central role in initiating the inflammatory response. Chronic inflammatory lesions have similar histological features, consisting of T-lymphocyte and macrophage-rich inflammatory cells and areas of myofibroblastic tissue deposition [27]. The pathological events leading from normal tissue ho-

meostasis to the formation of a fibrotic scar have several hallmarks, such as lesion development in atherogenesis, liver disease, or rheumatoid arthritis. Post-injury, early inflammatory responses are apparent, followed by prolonged inflammation, recruitment of adaptive lymphocytes, macrophage infiltration, lymphatic proliferation, extracellular matrix production, and myofibroblast/fibroblast formation (Figure 2) [28].

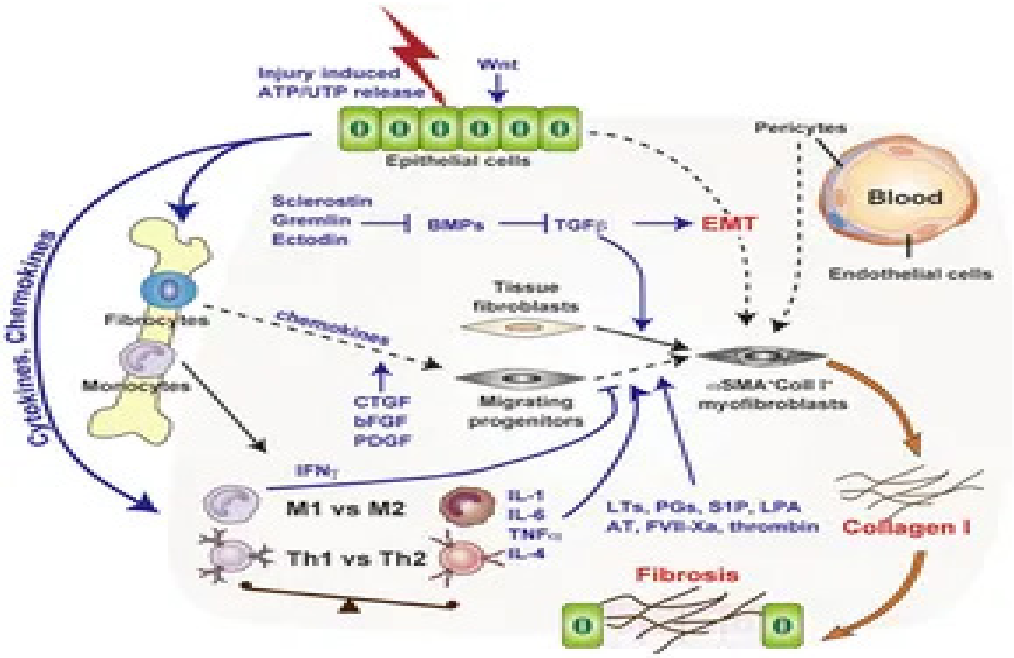

Figure 3. Molecular and cellular mechanisms of chronic inflammation-associated organ fibrosis [1].

4.1. Pathophysiology of Fibrosis

Fibrosis is a condition that can occur in any tissue type and is triggered by tissue trauma or injury. It is characterized by the activation of the innate immune system, which recruits inflammatory cells and repair cells to facilitate tissue and functional repair [29]. This process is triggered by chronic inflammation, which can be caused by microbes, chemicals, or physical injuries. The characteristic tissue remodeling associated with these diseases is a combination of aberrant wound healing and is irretractable. A series of intricate host responses is initiated to repair tissue damage through inflammation resolution and to try to eliminate infection. The cellular and molecular mechanisms involved in fibrotic

responses are similar across different tissue types [30]. The recruitment of 'counter-regulatory' leukocytes, such as eosinophils, monocytes, and macrophages, is crucial for tissue remodeling and repair. These phagocytes transform IL-4/TGF-β activated cells into contractile myofibroblasts through PDGF and MMP-3, and release IL-1β due to intramicroglial polarisation. Regenerative responses include proliferation, migration, and transformation of fibroblasts to activated myofibroblasts. Understanding these fibrotic processes has led to the development of immunotherapeutic targets and novel therapeutics [31].

4.2. Role of Fibroblasts

Chronic inflammatory diseases often cause organ remodeling due to the abnormal activation of resident fibroblasts, mesenchymal cells that produce the extracellular matrix. These cells have diverse roles in physiological and pathological processes and can be classified into three groups: unstable, quiescent, and deep. During health, fibroblasts play a crucial role in tissue growth, organ functions, and tissue repair. Chronic inflammation is marked by fibrosis, or scarring, which results from abnormal repair in response to chronic injury. Understanding these fibroblasts is essential for understanding and treating chronic inflammation [32]. Fibroblasts play a crucial role in the process of endothelial cell (ECM) remodeling, providing most ECM components and becoming myofibroblasts that generate contractile forces. They can produce various ECM components and remodeling enzymes, and can modulate the inflammatory environment through cytokines and soluble factors. Fibroblasts undergo activation in response to tissue damage, loss of homeostasis, or chronic infection, enhancing T cell immune responses and supporting B cell survival. However, they can also be reprogrammed in chronic inflammatory situations, leading to functional decline and adverse immune outcomes [33].

4.3. Mediators of Fibrosis

Fibrotic scar tissue forms after tissue injury, but prolonged inflammation can lead to fibrosis, a chronic condition characterized by excessive extracellular matrix deposition. Organ fibrosis, like liver cirrhosis, severe pulmonary fibrosis, cardiac fibrosis, and renal fibrosis, can be fatal due to irreversible

damage. Chronic inflammatory diseases like systemic sclerosis, rheumatoid arthritis, and Crohn's disease also have excessive fibrosis in affected organs. Immune cells can induce ECM remodeling and/or aberrant fibrosis through various factors and cell surface molecules [34].

Profibrotic immune cells, which drive the differentiation and proliferation of activated fibroblasts, can be classified into two types: antigen-nonspecific innate immune cells and antigen-specific adaptive immune cells. These cells, such as macrophages, mast cells, basophils, eosinophils, and innate lymphoid cells, are typically resident in tissues and recruit to inflammation sites. They produce multiple profibrotic immune mediators, including type-2 cytokines, tumor necrosis factor (TNF)-α, IL-1, IL-6, and IL-12. Senescent fibroblasts, triggered by stress signals, have been recognized as a source of profibrotic mediators in various contexts of fibrosis [35].

5. Immune System's Role in Fibrosis

Fibrosis is the abnormal formation of excess fibrous connective tissue during chronic inflammation and tissue repair. It is a common pathway to organ injury and failure in diseases like systemic sclerosis and idiopathic pulmonary fibrosis. Fibrogenesis involves various cell subsets, with myofibroblast activation being the key fibrogenic event. Both innate and adaptive immune cell populations are involved in regulating myofibroblast activation and fibrogenic responses. During inflammatory responses, activated immune cells orchestrate fibrosis processes in response to external stimuli and microenvironmental factors [36].

Fibrosis is a condition characterized by the activation of innate immune cells, leading to a chronic inflammatory response. TGF-β plays a crucial role in fibrotic development by influencing MMP/TIMP expression, T cell function, and ECM production. Chronic inflammation, caused by microbes, chemicals, or physical trauma, favors fibrotic progression. Host responses attempt to repair tissue damage and eliminate infection. Th2-type cytokine response, TLR signaling, and genetic polymorphisms play a crucial role in fibrosis. Understanding the interplay between trauma stimuli and tissue re-

pair is crucial for addressing the causes of chronic inflammation and the host's genetic disposition to fibrotic progression [37].

5.1. Immune Cell Infiltration

Chronic inflammation is linked to the infiltration of immune cells, which promotes histopathological remodeling. Fibroblasts deposit a collagen matrix, which is processed by matrix metalloproteinases to create a permanent fibrosis matrix. The process begins with tissue injury over 48 hours, leading to a "danger signal" response where innate immune cells are recruited [38]. Macrophages infiltrate the tissue and proliferate to remove dying cells and debris, or stimulate transmigration of myofibroblast populations. Failure to clear the tissue results in fibrosis. Antigen-presenting macrophages enhance T-cell polarization, lymphocyte infiltration, proliferation, and further macrophage recruitment. Infiltrating cells stimulate tissue-resident cell transformation using local soluble factors. In chronic stages, abundant collagen-rich scarring is deposited, and macrophage recruitment, proliferation, and inflammation may persist for weeks or months [39].

5.2. Cytokines and Growth Factors

Growth factors, particularly TGF-β isoforms, play a crucial role in wound healing. They promote cell proliferation, migration, and matrix component synthesis by inflammatory cells, mainly fibroblasts and macrophages. These processes are essential for successful wound healing. However, inflammation can persist if the acute phase is not downregulated or if additional growth factors or stimuli are encountered, leading to a chronic inflammatory state. Cytokines released associated with autoimmune and fibrotic disease can control autoimmunity and revert fibrotic status. Constitutive activation of TGF-β receptors can predispose to chronic renal injury, often exacerbated by loss of Grail function [40]

Exposure to environmental toxins in skin cancer can trigger a cascade of events leading to autoimmunity and fibrotic progression. This suggests that molecular switches control fibrous tissue persistence. If these switches are turned off, inflammation-favored growth factors can downregulate inflammation and fibrosis. Conversely, if growth factors turn on additional

receptors or intracellular signaling, tissue persistence and progressive fibrotic disease follow. Multiple tissues can have independent fibrotic responses, and cellular and molecular mechanisms show similarities [41].

5.3. Adaptive vs. Innate Immunity

Chronic inflammation is caused by complex interactions between immune cells and non-immune cells, causing tissue remodeling. Prolonged inflammation can switch the balance of the immune response, leading to tissue damage and fibrotic repair. The mystery of immune-mediated chronic inflammatory diseases lies in an aberrant "acquired" immune response against harmless stimuli, including autoantigens. Recent findings suggest that these adaptive immune responses operate through peri-cellular reprogramming of healthy cells, modifying their responses to redundant signals that regulate tissue repair and remodeling [42, 43].

The parenchyma, the ideal organ functional unit, is composed of adapted cells producing a tissue-specific extracellular matrix. Chronic inflammation is represented by abundant macrophages, mast cells, and collagen 1, while covered tissues undergo remodeling into "convalescent" stages with fewer immune cells and myofibroblasts. Peripheral follicular dendritic cells are crucial for adaptive immunity in lymph nodes. Immune-tissue cell interactions offer qualitative information on persistent chronic diseases [44].

6. Models of Chronic Inflammation and Fibrosis

Animal models are crucial for studying the immunological and physiological changes in chronic inflammation. Due to the variability of fibrotic diseases and tissue reactions to injury, several experimental models mimic human chronic fibrotic disease. Careful consideration is essential when choosing models for mechanistic and therapeutic studies, as no single organ-based model system is representative of all vascular remodeling and fibrosis. Most fibrotic human diseases are modeled in rodents, but some have been developed in guinea pigs, dogs, and humans. Chemical irritants, like Croton oil, are used in these models, which induce erythema and cell infiltration [45]. Thermal burns are invasive methods studied, but they are aggressive and should

be reserved for experts. No chemical or physical models induce skin fibrosis other than scarring after inflammation. The mechanism of scarring is limited, involving inflammation or excessive collagen production by various cell types [46].

6.1. Animal Models

Fibrosis is a chronic condition characterized by the accumulation of excess collagen in tissue due to inflammatory reactions. This can cause issues like cutaneous ramifications, burn scars, surgical scars, Crohn's disease, pulmonary fibrosis, and pericardial and peritoneal patches. A new animal model has been developed to study pathological subcutaneous fibrosis. In vitro, calcium carbonate and Carrageenan compounds were injected to create retrievable connective tissue, which was well tolerated and associated with multiple angiogenesis processes. This innovative animal model fills a gap in current models and fills a gap in understanding fibrotic conditions [47]. The study found that multiple injections of calcium carbonate compound in rabbits caused chronic inflammation, foreign body-induced granuloma, and connective tissue formation. The biomaterial was found to be ineffective in absorbing, and the inflammatory condition was well tolerated. Histological analysis showed efficient CAP band formation, granulation tissue, dense connective tissue, and interstitial edema. The study suggests that normal immigrant workers may not seek medical attention due to different work standards and traditions [38].

6.2. *In Vitro* Studies

Studies using tissue explants or primary cells are emerging approaches to study fibrosis mechanisms. In vitro culture of murine or human cells is desirable due to its simplicity and ease of interpretation. The simplest approach is to co-culture fibrogenic cells with macrophages, which can be quantified using a colorimetric assay. Primary human fibroblasts are obtained from thorascopic biopsies in surgery for a surgical lung biopsy. Fibroblast activation can be stimulated with a combination of TGFβ and IL-4. The power of an in vitro system to identify fibrogenic antibodies, small molecules, inhibitors, or RNAi leads to the development of preclinical animal studies in transgenic or knockouts of the druggable target molecule [49, 50].

7. Clinical Implications of Fibrosis

Fibrosis is a chronic disease characterized by excessive accumulation and improper deposition of collagen-rich extracellular matrix proteins by myofibroblasts. This leads to denser, stiffer, and less compliant tissues, resulting in impaired organ function and eventual organ failure. Fibrosing diseases can be classified into two major scenarios: recurrent/chronic disruption of tissue homeostasis due to metaplasia or direct injury, and environmental health exposure causing tissue deposition of inorganic particles. Symptoms resemble those of excessive ECM deposition and desmoplasia in solid tumors [51].

Fibrosis is a key pathogenic mechanism in various diseases affecting different organs and a long-term irreversible sequel to kidney, lung, heart, and liver diseases. It remains under-investigated and has unmet medical needs due to a lack of efficient drugs. Myofibroblasts, diverse and lineage-heterogeneous cells, are the main cause of fibrosis. Causative triggers include novel genetic models induced by mutations and knockouts, demonstrating that both epithelial and endothelial injury can induce myofibroblasts and initiate cancer lesions [52].

7.1. Diagnosis and Biomarkers

Chronic inflammation caused by autoimmune diseases, infections, or injuries can result in organ-threatening scar tissue, affecting many organs and causing serious morbidity. These conditions include asthma, systemic sclerosis, liver cirrhosis, chronic hepatitis B virus infection, and chronic kidney disease. Understanding the biology of chronic inflammation can help identify actionable targets for therapeutic intervention, leading to better treatment and overall health [53].

The immune-mediated fibrosis process involves chronic inflammation leading to tissue remodeling and scarring in various organs. It involves specific immunological mechanisms and molecular mediators. Cell types play a crucial role in this process, including connexins, which form gap junctions and other assemblies. Connexins coordinate environmental cues, genetic material, and secondary metabolites between cells, affecting organ morphogenesis, repair, immune response, and fibrotic response. Fibroblasts, activat-

ed by mechanical inputs, inflammatory mediators, or fibrogenic growth factors, coordinate tissue remodeling, favoring the deposition of endothelial growth factor components and creating a tissue-specific microenvironment [54].

7.2. Therapeutic Strategies

The challenge of addressing aberrant immune processes leading to tissue fibrotic repair is complex, with inadequate uncoupling of immune responses contributing to treatment failure in clinical trials. A comprehensive understanding of pathogenic immune processes is needed to develop effective therapeutic interventions. Current clinical concerns include preventing cardiac fibrosis, tissue injury, and pro-fibrotic and tissue scarring. Monoclonal antibodies targeting 1-integrin and TGF-β have shown efficacy in animal models, but translation to clinical studies is often unsuccessful. Recent therapies target aberrantly activated fibroblasts and myofibroblasts, with gene therapy and a mouse model showing success in modulating myocardial fibrosis [55].

Advances in single-cell technologies reveal distinct immune cells and cytokine receptors across tissues, with key interactions between innate and adaptive immune cells determining the pro-fibrotic immune responses' impact on fibrotic remodeling, enhancing our understanding of druggable targets and tissue resilience [56].

8. Case Studies

Research shows that TE can support vascularization after 24 hours, while no cellular infiltration was observed in a longer culture period (7 days). After functional TE development, angiogenesis and inflammation are evaluated through histological analysis. Reconstructed TE should be considered at least 1 month after surgical implantation. In normal skin, the dermis undergoes active remodeling with collagen type 3 replacement and reduced myofibroblasts and vascular structures. However, no studies focus on the fibrotic evolution of pathological cases [57].

The study investigates the early phase of dermal vascularization and inflammation using markers like MMPs, TIMPs, inflammatory and pro-fibrotic cytokines, growth factors, and collagens. Results show that TE is char-

acterized by a "reactive" phase after grafting, facilitating angiogenesis and inflammatory cell recruitment. After a week, TE remains in an "acute-inflammation-like" phase, leading to chronic pathological situations. Severe macrophage infiltration and higher levels of type 5 collagen are noted in fibrotic cases. The behavior of TE helps define pathological conditions caused by fibrotic over-recruitment of macrophages [58].

8.1. Lung Fibrosis

Chronic fibrotic lung diseases, including idiopathic pulmonary fibrosis (IPF), have become a major research focus due to their long clinical course, high healthcare costs, unmet medical needs, and inability to translate therapeutic targets into effective treatments. Comprehensive human demographic, clinical, immunologic, and genetic studies, as well as vascular and cellular biology studies, are advancing knowledge about factors contributing to wound repair responses. Clinical trials have evaluated therapies that interrupt mediator cascades, but mixed results have been reported. As understanding the complex pathogenesis of fibrotic lung diseases increases, clinical approaches targeting different pathways are being explored [39, 60]. This review discusses the role of cellular populations, including inflammatory mononuclear cells and fibroblasts, in ECM deposition, remodeling, and degradation during chronic wound healing. It highlights the distinct component of chronic fibrotic lung diseases and their mediators. Chronic inflammation is often overlooked as a cause of fibrosis, but studies show that the disease caused by macrophages, T lymphocytes, and NK cells is fundamentally tied to fibrosis. Activated eosinophils and collagen fiber deposition are also found in myxoid degeneration in severe asthma [61].

8.2. Liver Fibrosis

Hepatic stellate cells (HSCs) are the primary cause of liver fibrosis. When activated, these quiescent cells undergo functional and phenotypic changes due to injuries like toxins, hepatitis, autoimmune disorders, and steatohepatitis. These changes lead to the transdifferentiation of HSCs into myofibroblasts, resulting in ECM accumulation. Bone marrow-originating fibrocytes or precursors have also been identified as new contributors to liver fibrosis. Cir-

culating fibrocytes, identified as CD45 + collagen type I + cells, contribute to fibrotic areas after liver damage. This suggests that antifibrotic strategies may be targeted by these cells [62].

Autophagy plays a complex and bidirectional role in liver fibrosis, with cells like HSCs, hepatocytes, KCs, and macrophages contributing or attenuating HSC activation. Upstream signals can lead to differential distribution or recruitment of ATG proteins for autophagosome formation, while ubiquitin ligases can target autophagy machinery, leading to defective autophagy and organelle accumulation [63].

8.3. Cardiac Fibrosis

Danger signals activate cardiac fibroblasts (CFs) during remodeling after injury, with cardiac infiltrated immune cells modulating ECM deposition and pro-inflammatory cytokine secretion. Excessive ECM protein accumulation leads to tissue stiffening and impaired organ function. Cardiac fibrosis is a common pathological feature of heart failure, and the heart's protective immune system can be aggravated by inappropriate activation of macrophages and cardiac-infiltrated immune cells in chronic diseases [64].

CD68 expression in the heart is influenced by macrophage location and pathology. Tissue-resident Epic-Mφs of embryonic origin adapt to endocardium-derived CMs as myocardial progenitors. These mature macrophages grow proliferatively and migrate deeper into the stroma or pericardium, enabling macrophage-centered modulation of cardiac structures. Aberrantly activated macrophages usually augment ECM protein accumulation, but their numbers in heart diseases are downregulated. Fabp4+ CMs, Fib+ CFs, and IgG+ CD68-int Mφs cluster in Creosote-treated S100A8/iPFKCD-KO hearts. Co-infection-induced vehicle-treated hearts show a rebound surge in cardiac macrophage number and occupancy, but no changes in gene expression [65, 66]

9. Future Directions in Research

Fibrosis is the excessive deposition of extracellular matrix, typically collagen, in tissues and organs, leading to organ dysfunction. It is a result of immune-mediated tissue remodeling in chronic inflammatory diseases. Macrophages, which account for 90%

of the cellular inflammatory infiltrate in fibrotic tissues, produce profibrotic factors like cytokines, chemokines, connective tissue growth factor, and matrix metalloproteinases. However, the contribution of different subsets of macrophages to fibrosis development remains unclear [67].

Macrophages produce profibrotic factors that induce fibroblasts to transdifferentiate into myofibroblasts. However, these mediators are not enough to induce fibrosis in healthy tissues. In chronically injured tissues, activated Th2 cytokine-producing macrophages may promote fibrosis. Ablation of these macrophages can ameliorate fibrosis and restore lung function. Some macrophages are antifibrotic and immune regulatory, secreting low levels of inflammatory cytokines and IL-10 [68].

9.1. Emerging Therapies

Chronic rhinosinusitis (CRS) is currently managed with symptom-relieving therapies like steroids and antibiotics. However, understanding the complex cellular and molecular mechanisms of chronic inflammation suggests that more effective treatments could target underlying causes, presenting opportunities for new immune-based therapies. A multi-faceted approach is expected to be more effective than single-target/class drugs. Emerging therapies aim to re-establish balance in diseased tissues, targeting inflammatory macrophages. Therapeutic agents targeting these macrophages are under development, with promising pre-clinical and clinical results. For example, inhibiting specific HIV entry coreceptors CCR5 or chemokine receptors using known pharmaceutical agents resulted in a significant decrease in macrophage infiltration in patients with eosinophilic CRS [69]. A new anti-macrophage mRNA vaccine targeting hCas9-ccl2 has shown significant improvement in allergic rhinitis animal models. Human trials are planned for this vaccine. Biologics targeting IL-4 type 2 CRSwNP inflammation are also in development. Dupilumab, a monoclonal antibody blocking IL-4 receptor signaling, showed clinical efficacy in trials. Monoclonal antibodies targeting IL-4, IL-5, or IL-13 have shown promise in clinical trials [70].

9.2. Personalized Medicine Approaches

The use of rabMAbs in induced implants in mice with thioglycolate-in-

flamed mice results in chronic inflammatory lesions and immune-mediated fibrosis. To modify these lesions, injections of further rabMAbs can be provided, and efficacy can be assessed through morphology or histology. Antibodies with insufficient efficacy can be de-immunized to minimize immune rejection in cross-species studies. RabMAbs do not block the action of non-modified antibodies directed against the same targets. Immediate induction of alternative approaches is possible after cessation of monoclonal application. A robust platform has been developed for efficient screening of potential rabMAb/target combinations, enabling precise and speedy selection of further targets [71].

Humans and mice share common pathways for tissue homeostasis and fibrosis, making the development of highly biologically refined drugs using human derivatives possible. Strategies are being implemented to humanize rabMAbs against promising mouse targets, while cognate derivatives like scFvs or nanobodies are being engineered for larger antibodies. Conventional humanization approaches are being used, with pre-screened tools for streamlining and enhancing success rates. Human rabMAbs are likely to be potent inhibitors due to their efficacy in mice [72].

10. Conclusion

The histological remodeling of tissues in homeostasis follows a specific pattern, typically involving injury repair by innate immunity, resolution by adaptive immunity, and long-term maintenance by the acquired immune system. However, tissues subjected to chronic inflammation display sustained remodeling to tissue fibrosis and immune-mediated tissue atrophy. The mammalian body is composed of numerous microenvironments, including the central nervous system and meninges, each with distinct immune compartments, surveillance mechanisms, mediators, and effector responses. Micrometastatic seeding, undetected by the innate immune system, can lead to invasive and pathologic tissue fibrosis and inflammatory encephalomyelitis that does not remit with tumor excision. Chronic inflammation results in irreversible alteration of tissue architecture and functionality, making it debilitating or incompatible with life.

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