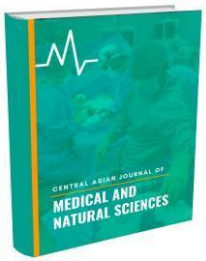

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Article

The Biochemical and Immunological Landscape of Chronic Inflammatory Diseases: Implications for Tissue Homeostasis

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Abstract: Chronic inflammatory diseases (CIDs) are a group of persistent conditions characterized by dysregulated immune responses and prolonged inflammation, contributing to tissue damage and systemic complications. These diseases, including rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease, disrupt tissue homeostasis through complex biochemical and immunological mechanisms. Key inflammatory mediators such as cytokines (IL-6, TNF-α, IL-1β) and chemokines play crucial roles in sustaining the inflammatory state, leading to immune cell infiltration, oxidative stress, and metabolic dysregulation. Additionally, chronic inflammation is closely linked to alterations in lipid metabolism, glucose homeostasis, and the gut microbiome, further exacerbating disease progression. Immunologically, a persistent imbalance between pro-inflammatory and anti-inflammatory responses leads to aberrant immune activation, autoimmunity, and fibrosis. Regulatory T cells (Tregs) and anti-inflammatory cytokines like IL-10 and TGF-β play a crucial role in modulating immune tolerance and preventing excessive tissue damage. However, their dysfunction in CIDs contributes to chronic inflammation and impaired tissue repair. Advances in molecular diagnostics and biomarker identification, including high-sensitivity C-reactive protein (hs-CRP) and specific autoantibodies, have enhanced early disease detection and prognosis. Understanding the biochemical and immunological landscape of CIDs provides valuable insights into therapeutic interventions aimed at restoring tissue homeostasis. Emerging treatments, such as biologics targeting inflammatory cytokines, immune checkpoint inhibitors, and personalized medicine approaches, offer promising strategies for managing CIDs. This review explores the intricate biochemical and immunological pathways underlying chronic inflammation and highlights potential therapeutic targets to restore balance and improve patient outcomes.

Keywords: Chronic Inflammatory Diseases, Cytokines, Tissue Homeostasis, Immune Regulation, Biomarkers, Targeted Therapy

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1. Introduction

Over This collective discourse endeavors to weave a cohesive tapestry of biochemical and immunological paradigms pertinent to chronic inflammatory maladies, thereby enhancing the comprehension of the interdisciplinary nexus inherent in the life sciences. Its aim is to elucidate the intricate biochemical and immunological terrain surrounding chronic inflammatory disorders, the significance of which has garnered considerable attention in recent discourse [1]. The essay meticulously delineates the biochemical and immunological dimensions of these conditions, subtly underscoring their potential ramifications on the corporeal realm, particularly concerning tissue homeostasis. A series

of overarching objectives are scrutinized: to bridge the vast expanse of existing literature by meticulously surveying prior works and interlinking those that may have been neglected or that reside at the confluence of these diverse fields; to craft a vivid portrayal of this landscape, thereby suggesting the organic form it may ultimately assume; to explore the immune responses and biochemical mechanisms that underpin chronic inflammatory states; all the while maintaining a thoughtful discourse on the relevance of therapeutic science, with a particular emphasis on the organic reality of tissue, which shall be positioned more prominently in the narrative, ideally casting an insightful gaze towards how future approaches may be rendered more meaningful, contemplative, and beneficial [2]. The newly interconnected or recently uncovered works serve as a welcoming gateway for readers and new encounters, with the essay constructed with these individuals in mind, fostering an open dialogue between these realms [3].

Literature Review

1. Overview of Chronic Inflammatory Diseases

Chronic inflammatory diseases are a diverse group of disorders characterized by persistent inflammatory responses in tissues [1]. A wide range of illnesses can be categorized under chronic inflammation, such as autoimmune conditions including rheumatoid arthritis, psoriasis, and systemic lupus erythematosus. Other disease classes include neuro-degenerative disorders, obesity-related diseases, inflammatory bowel disease, chronic pulmonary obstructive disease, allergies, and cardiovascular diseases. Chronic inflammation can become a cause of cancerogenesis [2]. A common nexus of pathophysiological mechanisms merges these conditions, which occur when the immune system runs out of control and attacks both foreign and host tissue antigens producing tissue damage and death (immunopathology). Traditionally, the immune response was conceived as a defensive mechanism driven by innate macrophages and neutrophils, along with adaptive lymphocytes and their B-cell antibody-producing derivatives. This protective function was supposed to end once the triggering pathogen was eliminated, which would provide tissues a homeostatic condition. Yet, pathologies exist where the immune response remains active and inflammatory. Such chronic forms evade common perception and understanding spawning multidisciplinary initiatives to apprehend the complete biochemical and immunological landscape of chronic inflammation, hoping to deliver integrated solutions for its resolution [3]. The clinical evidence becomes obvious only when disease progression is already set, thereof an early diagnosis is not possible for many diseases leading to high morbidity rates in patient populations. To the trained eye of the physician, symptoms that can be misleading in the generalist practice can reveal a larger picture involving active immune components and suggesting referral to a specialized clinic [4]. Thus, at the beginning of the 21st Century, the patient's journey in the medical care system begins calling for different health professionals to provide specialized pieces of information on the same health condition, which aggravates the state of vulnerability already inflicted by the ongoing disease pathology [5]. The multimorbid nature of chronic inflammatory diseases and the silo-based organization of modern healthcare render the journey through state-of-the-art medical care an intricate foray in a labyrinthic maze of tests, referrals, drugs, and multidisciplinary opinions and a source of significant distress, especially for chronic patients consumed by years of unfruitful struggle. Beyond, this journey is also a heavy burden on public and private healthcare systems, the annual direct costs of chronic inflammatory diseases now exceeding those associated with cancer [6].

2. Basic Concepts in Biochemistry and Immunology

There are several basic concepts from biochemistry and immunology that are necessary to understand while thinking about the biochemical and immunological landscape of chronic inflammation diseases (CIDs). The molecular details of the fundamental aspects of these complex fields would give the basis to tackle more complex

interactions later. Biochemical and immunological processes are intimately related in the emergence of CIDs and if one wishes to understand the mechanisms behind a particular disease, it is important to take both fields into account [7]. Biochemical and immunological essence was developed throughout history and has become what is known today. Biochemistry is the study of life at the mechanical level. This field approaches necessary and sufficient conditions for life in terms of biochemical pathways that enable the buildup and sustain of living organisms by dealing with the bio-molecules that underpin their existence; biochemistry is the field that underpins molecular biology. Immunology is the study of host defense against pathogens. With a broader approach, this field is concerned with immune systems, the cells and molecules that compose and interact therein, and the signals that regulate the immune response [8]. Both fields are tightly linked in the sense that biochemical signals, from the easiest form such as proteins after they die to the most complex, make an immune response feasible. On a deeper level, functionality separation cannot be made; vital processes of one kind of cell produce biochemical signals understood in both realms. There are two basic concepts from immunology that should be spent time on to comprehend their downstream effect on biochemistry. The first of these is self-tolerance [9]. The second of these is the immune system's complexity coupled with the innate-adaptive organizational duality make immune response highly redundant and slow to emerge. Yet, despite this potential robustness, immune dysregulations are highly diverse on their nature. Moreover, the immune system protects the host against foreign attackers, but also should refrain from attacking innocent bystanders—i.e., needs to be self-tolerant. Mystic origins of the self-non-self postulate have been gradually replaced by a more precise understanding of immune tolerance strictly in molecular terms, given the awareness of its importance both in health and disease. Given the high-quality signals that new biochemical technologies provide, immune knowledge acquired recently is more robust and detailed. This is particularly relevant to the regulation of self-reactive lymphocytes and the recognition of those strategies employed by pathogens to disarm their host's defenses [10].

2.1. Inflammation and Immune Response

Inflammation is a dynamic process initiated by harmful stimuli, such as pathogens, damaged cells, and toxic compounds. It is crucial to the survival of higher organisms after injury and can be divided into the following phases: initiation, propagation, and resolution [11]. The immune system plays a crucial role during the different phases of inflammation. Of note, two types of immune responses have evolved to handle inflammatory conditions: (1) an immediate and non-specific response, called the innate immune system, capable of rapidly and effectively eliminating pre-invasive pathogens, and (2) an antigen-specific and adaptive immune system, which generates long-lasting immunological memory [12]. A wide range of mediators regulates the immune and inflammatory responses: upon injury, pro-inflammatory cytokines, chemokines, and other kind of signals help leukocytes to accumulate in the infected tissue; once the immune response is triggered, drastic alterations in the environment influence the activation state, the recruitment, and the phenotype of infiltrating and tissue-resident inflammatory cells. A balance between the pro-inflammatory and the anti-inflammatory mediators is required to revert the process, allowing the tissue to go back to its homeostatic state [13]. When established, this equilibrium terminates the pro-inflammatory status, fostering the anti-inflammatory and pro-resolution signals necessary for the return to homeostasis. Failure in the correct timing of the last events can be at the basis of the transition from acute to chronic inflammation, a situation leading to irreversible damages in the tissue [14]. Chronic conditions, such as asthma, fibrosis, atherosclerosis, or autoimmunity, are hallmarked by the dysregulation of the pro-resolution and reparative mechanisms, as well as by an abnormal activation of inflammatory molecular pathways. The loss of tissue homeostasis results in massive fibrosis with the accumulation of ECM proteins and tissue de-differentiation. Blood vessels dilation, leakage, and neo-angiogenesis can be observed too [15]. Untimely inflammatory

events exacerbate the damage, evolving to dysplasia. Functional aspects can also be severely impaired, affecting, for instance, gas transport in the lungs or ability to pump blood in the heart. Deregulated mast cell responses foster the release of ECM-degrading proteases, which can weaken tissue integrity. Moreover, fibrosis stiffen tissue, which, in turn, impairs physiological functions and can result in involuntary contraction [16].

3. Cellular and Molecular Players in Chronic Inflammation

Chronic inflammatory diseases encompass a diverse group of conditions, such as arthritis, inflammatory bowel disease, and psoriasis, that share persistent tissue inflammation, pain, and loss of function over time. The individual etiologies of chronic inflammatory diseases are extremely varied, rendering them a major health issue worldwide. At the systemic level, immune cells are essential for health as they eliminate pathogenic agents and ensure regular tissue homeostasis by actively engaging in several type of intercellular supports. However, partly due to excessive or poorly controlled immune activity, these same cells also play a major role in fueling inflammatory processes in a number of pathological contexts and eventually perpetuating them [17]. Recent investigations have drastically expanded knowledge about the biochemical and immunological landscapes of chronic inflammatory diseases and uncovered various factors involved in their progression. The picture that now takes shape is very complex and nuanced. It spans, on the one hand, the detailed roles and the increasingly acknowledged plasticity of several immune cell types involved in supporting inflammation in inflamed tissues (T-cells, B-cells, neutrophils, macrophages, mast cells) and, on the other hand, the elaborate, multifaceted and hardly predictable interactions and cross-talks some of these immune cells entertain with other cellular partners residing in or colonizing fibrotic areas (endothelial cells, fibroblasts, neurons)[18]. Additionally, the paths of spreading of (partially redundant) bio-mediators fueling these interactions have been delineated in the form of soluble molecules (pro-inflammatory cytokines and chemokines), cellular network and ECM remodeling, exosomes and other vesicles. In view of such a complexity, many ideas and hypotheses have been put forward to restrict, regulate and eventually revert the ongoing pathological status [19].

3.1. Immune Cells in Chronic Inflammation

Immune cells are the drivers of inflammation, a beneficial process for fighting infections and promoting repair. However, in chronic inflammatory diseases, the immune response is overly activated and not properly resolved [20]. The authoritative text of immune cells, in particular their maturation, adaptation, and functional extremes during chronic inflammatory diseases is not discussed in detail yet. While adaptive immune cells are generally analyzed, the focus here is on the biochemical and immunological landscape of all sorts of immune cells during tissue responses. Innate immune cells, such as neutrophils, macrophages, and DCs are often the first responders to tissue injury and infections [21]. Resident immune cells immediately act at the site of injury or infection. They produce pro-inflammatory cytokines and chemokines to enable the initiation, engagement, and resolution of immune responses. In order to avoid tissue damage, phagocytes such as macrophages and neutrophils engulf dying cells, pathogens, or their byproducts. If resident phagocytes become overwhelmed, non-resident immune cells, mostly monocytes, are recruited from the circulation to take over these functions [22]. Conversely, recruited immune cells also contribute to the inflammatory environment by producing more cytokines and chemokines. In healthy conditions, homeostatic mechanisms ensure that the tissue responses are properly resolved and that the local neutrophils no longer fight and remove pathogens. In chronic inflammatory diseases, the functions of these immune cells are altered, resulting in tissue damage and the exacerbation of inflammation. For example, macrophages adopt an intermediate phenotype during chronic inflammation and become less efficient at clearing pathogens or dead cells. Similarly, immune cells producing low amount of pro-inflammatory cytokines

are recruited and this low-grade inflammation contributes to the progression of chronic inflammatory diseases[23], [24].

2. Materials and Methods

2.1 Biochemical Signaling Pathways in Chronic Inflammation

In multicellular eukaryotes, biochemical and immunological networks are involved in maintaining tissue homeostasis[25]. Theoretical and experimental work demonstrated that inflammation can be reversible and that progress on the increasing identification of switches was made. Additionally, the research highlighted how genetic variations in regulatory components of inflammatory processes, including immune cells involved, can still increase in quantitative understanding of the pathology of inflammatory diseases. Inflammation is a complex process in which cytostatic signals are turned into directed patterns of infiltration of e.g. macrophages and T cells[26]. These processes are intrinsically networked, and can therefore malfunction in many ways. Topological analysis of yeast signalling networks has uncovered architectural principles that make networks switch-like, i.e., behave like a trigger causing deterministic all-or-nothing change. Using an iterative approach genome-wide expression profiling was combined with DICE, an algorithm that determines which enzyme/s is best suited to mediate which transcriptional changes. This integrated approach allowed confirming some known biology but mostly yielded results on phenomena occurring downstream of gene transcription; this information could only previously be obtained by many small, patient studies. The results raise new biological insights, providing novel leads for subsequent research. Thus, this systems biology approach increases understanding of eukaryotic signal transduction regulation [27]. The immune system comprises biochemical and immunological networks for detecting and eliminating invading pathogens. A healthy immune system ensures prompt clearance of pathogens and timely resolution of inflammation[28]. However, under certain circumstances, the immune system fails to act precisely, leading to the development of chronic inflammation. Chronic inflammation has been linked with a wide range of chronic diseases, including inflammatory bowel disease (IBD), arthritis, asthma, atherosclerosis, and neurodegenerative diseases, among many others. A regulatory network model was developed, integrating both the intrinsic cellular control system and extracellular metabolism network. On the basis of this dynamic model, the crosstalk between the Wnt/β-catenin and Ras/ERK pathways was computationally and experimentally explored [29]. It is found that crosstalk on β-catenin can largely enhance the ultrasensitivity of ERK, which is a primary dynamic mechanism of crosstalk. Based on this observation, it is postulated that in some cases pathway crosstalk is originated from the nature of cellular network architecture rather than from conventional types of proteins or topologies. This work demonstrates that systems biology can provide insight into the dynamics of subcellular signaling of immune cells, and reveal a new way of understanding crosstalk [30].

2.1.1 Role of Cytokines and Chemokines

The maintenance of tissue homeostasis is a vital facet of human physiology. Most tissues are composed of distinct cell populations that are regularly yet orderly renewed. This tissue turnover involves the permanent withdrawal of quiescent cells, the proliferation of progenitors, and the differentiation, maturation, and/or activation of newly formed cells [31]. This sequence of events is tightly controlled and orchestrated by a combination of signals that cells receive from neighboring or remote cells. These signals largely depend on cell-cell contacts but also on the release of biochemical cues, most commonly in the form of hormones, growth factors, cytokines, and chemokines. For instance, the negative feedback loop in chondrogenesis involves fibroblastic growth factors acting on mesenchymal cells, which results in the inactivation of the stem cell germ cell factor [32]. Chronic inflammatory diseases afflict hundreds of millions of persons

worldwide. Some 5-7% of the adult population actually suffer from autoimmune diseases such as rheumatoid arthritis, Graves' disease, and celiac disease, which are just but a subset of the approximately hundred known disorders under this category [33]. Several additional hundreds of millions are affected by other chronic inflammatory conditions including neurodegenerative diseases such as Alzheimer's and Parkinson's, atherosclerosis, asthma, or type 2 diabetes. Although chronic inflammatory diseases became the major cause of morbidity and mortality in the western world at the turn of the century, an enriched toolbox of diagnostic procedures and drugs has been developed over the past years that have had a positive impact in the clinical management of these patients. Promptness in the delivery of effective treatments is crucial for the mild outcome of chronic diseases, which are inherently incurable conditions that can hardly be diagnosed at early stages [34]. Beside socioeconomic factors, the pace of disease evolution is indeed strictly related to the timing of intervention. Unfortunately, most patients are being treated only after the onset of overt symptoms, by which time the irreversible tissue damage has already taken place. On the other hand, currently available therapeutic options allow only to either palliate symptoms or to slow down the progression of the disease. Thus, they rarely eliminate the cause and never promote the removal of the chronic disease [35]. Lastly, a notorious side effect of the chronic intake of anti-inflammatory drugs, particularly over corticosteroids, is the severe weakening of the immune response of patients under other subsequent infections are actually likely to become responsible for the patient's death, such that the over 16% of deaths in modern, wealthy societies are reported to be a consequence of autoimmune diseases around the world. On the other hand, given [36].

3. Results

3.1 Genetic and Environmental Factors Influencing Chronic Inflammatory Diseases

Chronic inflammatory diseases represent an increasing global burden. The pathogenesis of these conditions is multifactorial, encompassing a complex interplay of genetic susceptibility, immune and microbiome dysregulation, and environmental factors. This special issue underscores the biochemical and immunological landscape of chronic inflammatory diseases and uncovers its implications for tissue homeostasis. This collection provides insights into the biochemical and immunological mechanisms shaping chronic inflammation under pathophysiological conditions [37]. The underlying molecular mechanisms driving chronic inflammation are deeply examined to aid the implementation of personalized curative and preventive strategies. Chronic inflammatory diseases encompass a wide spectrum of conditions influencing multiple organs and systems [38]. The onset and progression of chronic inflammatory diseases are influenced by an intricate interplay of various genetic and environmental factors. The genetic basis of chronic inflammatory diseases is widely recognized. Inherited predisposition can determine an increased risk of developing distinct inflammatory conditions. A number of gene polymorphisms, most notably located in the HLA region, have been found to be associated with a wide spectrum of inflammatory conditions. The advent of genome-wide association study technology has led to the identification of a number of novel risk alleles for various inflammatory conditions. These risk alleles have highlighted specific pathways in the development of inflammation [39]. Besides, environmental triggers such as physical or chemical pollutants, diet, microbiome dysbiosis, and viral or microbial infections, can substantially shape the inflammatory response. Inflammatory predispositions in the context of genetic background were suggested to enhance sensitivity to specific environmental pollutants. The interaction of environmental triggers with genetic predispositions in driving inflammation has been broadly investigated and highlights the cumulative effect on disease risk [40]. On the nutrition side, a high intake of a certain type of diet, such as those rich in sugars fats, or salt, has been suggested to result in a proinflammatory condition. The implication of intestinal dysbiosis and microbial infections as initiators of chronic inflammation along the gut-intestinal axis is widely

recognized. Individuals carrying specific genetic mutations are more sensitive to the onset of autoimmune gut inflammation in the presence of specific dysbiosis and infections. Lifestyle modifications or pharmaceutical strategies may mitigate the impact of environmental risk factors [41], [42], [43].

3.1.1 Genetic Susceptibility

Chronic inflammatory diseases are characterized by perturbation to the tissue homeostasis involving dysfunction of the mechanisms that control immune response and tissue injury [44]. The biochemical and immunological understanding of human chronic inflammatory diseases is critical to developing therapeutic strategies to prevent tissue damage and provide a more efficient repair. Chronic inflammatory diseases, namely asthma, psoriasis, and rheumatoid arthritis (RA), have a multifaceted etiology considered as a set of environmental, genetic, and immunological factors. In this respect, the genetic predisposition has a critical role in the pathogenesis of chronic diseases and different aspects are addressed. Population-based studies identified a set of genetic susceptibility carried in polymorphisms of human leukocyte antigens [45]. In sporadic cases a combination of human leukocyte antigens alleles and cytokines gene polymorphisms were associated to the disease, confirming the role of adaptive and innate immune system in psoriatic immunopathogenesis. Twin studies defined a genetic concordance in monozygotic twins of 71%, 16% of dizygotic twins and revealed an early age of disease development. RA is an autoimmune disease affecting approximately 1-3% of individuals worldwide [46]. The results show that the ethnic background of the Brazilian population can influence the genetic susceptibility to RA. Brazil is a multiracial country and it's conceivable that the RA susceptibility is influenced by the nonCaucasian ethic contribution. Meta-analyses of candidate gene studies in asthma showed strikingly positive results, highlighting the principle of genetic polymorphisms influencing disease predisposition and phenotype. Asthma is the most common chronic disease affecting over 300 million people worldwide. Genome-wide association studies (GWAS) were successful in identifying genetic markers associated to an increasing number of common, complex diseases. The genetic component of asthma is essentially polygenic [47]. Moreover, different from autoimmune diseases, there is strong evidence that genetic variability contributes to the large range of associated phenotypes. These genetic components affect individuals through different pathways. For example, single nucleotide polymorphisms have been reported within genes that modulate inflammatory response and the physicochemical barrier function of respiratory mucosa. Other gene polymorphisms have been described within enzymes modulating the protective response towards oxidative stress and, as consequence, all these conditions contribute to different disease-associated traits [48]. The Brachyury gene is a transcription factor highly evolutionarily conserved in terms of gene structure, expression, and product. Positional candidature, subsequent analysis of allelic variation in the candidate genes. Meta-analyses is applied to all population-based case-control studies worldwide. PTPN22 gene, an essential negative regulator of T cell receptor signaling, was identified-independently in different studies-as RA risk gene [49], [50], [51]. Five relevant large polymorphisms in the PTPN22 gene influence RA susceptibility, and that one of them does so indirectly by the factor pathogen, which increased a focus on the gene-environment interaction underlying autoimmune diseases. These results clarify-partly controversial-previous findings, released much discussion, and ultimately provided information that can be used in future study designs and modeling of such interactions. Sequencing and high-throughput genotyping technologies provide a crucial tool on the careful selection of candidate genes also in non model species allowing the rapid accumulation of extensive information on candidate genes also in non-model species. So far, this information is predominantly compiled and distributed in manual format, which is generally hard to query, manipulate, and system-model-based [52], [53], [54].

3.2 Diagnostic Tools and Biomarkers in Chronic Inflammatory Diseases

Biomarkers, Image-Based and Other Methods of Non-Visual Analysis: A Modern Perspective on Chronic Inflammatory Diseases. Physical examinations and laboratory tests remain important, yet almost triassic, tools of diagnostic procedure. Any of their results like raised body temperature, leukocytes in blood, CRP in blood, ESR, increased level of liver enzymes, so on may suggest inflammatory process in a patient's organism [55], [56], [57]. These tests are like "telling the forest from the trees," i.e., defining common states. Nevertheless, special patterns of involved vessels or other lesions can't be always visible, but with still high probability present themselves by non-visible way, e.g., as changed eyes conditions from the ophthalmoscope examination. Reliable diagnostics and proper treatment of inflammation of inner organs often require imaging methods, and medicine has rapidly developed in this direction [58], [59], [60]. Biomarkers are of great application and are more sensitive to the treatment effects and earlier abnormalities. Biomarkers of inflammation and immune activation reflect global processes anywhere in the body and can, in combination with pathological findings, help to reveal involved processes mechanistically [61]. Serum or tissue proteins can be detected by ELISA and may be known to be associated with different processes of inflammation. Namely, one factor can be connected with several diseases of completely different nature but leading to non-specific inflammatory changes. Some morphological methods have more than directly visual applications. So, for instance, mass-spectroscopy of blood or biopsy material is a very informative method for diagnosis of many diseases and determination of the specific antibiotic for oncological cases; reaction of RAMAN effect can preliminarily distinguish malignancy of the tumour [62]. Recalling the "retrospective" statement that chronic inflammation significantly differs its landscape from the acute one, traditional biomarkers can't monitor all aspect of such quite enigmatic group of diseases. Thus now a serious attention is concentrated on looking for new, non-traditional biomarkers of a more discreet character [63]. This effort is combined with attempts to find the markers, pointed to some general features of disturbance in a tissue and/or its repair like apoptotic markers or some other ones and assessment of the state of the extracellular matrix. A specifically high interest can potentially show to the markers of cell damage/activation, which associate with the most affected cells and expression the most essential and profound events in a pathological progress [64]. Inflammation itself, both chronic and acute, forms the top frequent group of diseases, and the most often laboratory mistakes occur in diagnosis of urinary system inflammatory changes; however, overall negative predictive value of CRP was not so essential. Appeared to the gold standard, diagnosis seemed not to be such trivial as it used to be assumed [65]. All factors considered, it is clear that even having the most accurate knowledge over biomarkers, they can give not more than the probability of an incertitude calculation; a single biomarker usually can't give a reliable diagnostic or monitoring results. Further some other elements of pathologic progression, possibly even more involved, may be missed; since crucial treatment choice often depends on the results of diagnostics, it highlights the importance and complexity of the problem of biomarkers choice and interpretation [66], [67], [68], [69].

3.2.1 Serum Biomarkers

Serum biomarkers are instrumental not only for the initial diagnosis of chronic inflammatory diseases but also for monitoring disease activity, with the goal of maintaining a state of clinical remission and preventing long-term structural and/or functional damage. To this end, different serum biomarkers have shown promise, including acute-phase proteins, cytokines and chemokines, cell surface antigens, and signalling proteins[70], [71], [72]. Acute-phase reactants, produced by the liver during acute inflammation, have become the most widely used. A central role in serum inflammation biomarkers has been devoted to proteins of the acute-phase response (APR), mainly C-reactive protein (CRP) because they are readily measured by low-cost methods. The availability of immunoenzymatic assays has broadened the range and the number of

analytes, including cytokines and chemokines. Even though many reports suggest a direct association of serum inflammatory markers with severity of intestinal inflammation, the relationship between levels of biomarkers in the serum and colonic tissue remains difficult to interpret [73]. On one hand, the close structure-function relationship of the intestinal mucosa limits leakage of large plasma proteins (CRP = 118 kDa). On the other hand, the colon is the most external layer and the furthest from the liver, where the acute-phase reactants are synthesized. As a consequence, CRP levels in the serum of patients with pancolitis can increase only when the inflammatory process involves an extension great enough to spark a systemic reaction. Serum biomarkers that reflect disease activity might facilitate a personalized treatment approach for individual chronic inflammatory disease patients, whose disease course may follow different trajectories [59]. The consideration that elevated serum inflammatory marker levels are likely to correlate with, or be predictive of, a more severe inflammation suggests that aggressive disease management would benefit from a strict assessment of the initial serum status. However, higher biomarker levels may not always equate with a more critical disease stage and there are examples of patients fulfilling the current inclusion criteria and yet displaying CRP levels < 5 mg/L [74]. Furthermore, it is believed that the current status of inflammatory blood markers is not sufficient in itself to drive treatment decisions, except in patients in PC. The great body of literature on therapy outcomes may therefore call for a reconsideration of stool and endoscopic criteria. Nonetheless, the ubiquitous availability of automated instruments for CRP quantitation that ensures reliable and rapid results is an undisputable benefit in the current scenario [75]. However, many physio-pathological aspects of disease bio-markers are not taken into account. Lastly, a failure to integrate serum inflammatory markers in a standardized and population-based context with endoscopic and probably also imaging techniques often results in a significant disconnection between advancement of knowledge and medical practice. Integration of sophisticated equipment into the routine diagnostic alphabets in the clinical setting, including all disease stages and manifestations, and treatment will greatly help in the assessment of individual patients and thus may represent an area of further translational research [76]. Standardization and validation of new techniques in measuring serum biomarkers may transform current snapshot measurements in the context of the clinical trial to more informative and tailored diagnostic protocols. At the same time, it is confirmed the ongoing research into novel serum biomarkers, whose so far promising perspectives still demand validation on a large panel of patients of a heterogeneous population[77], [78].

3.3 Therapeutic Approaches in Chronic Inflammatory Diseases

Numerous therapeutic approaches are available for the management of chronic inflammatory diseases and usually more than one therapy must be addressed or combined, due to the complexity of the enrichment and heterogeneity of these diseases. These therapies, including biological agents, small molecules or gene therapy can target the cascades of the mucosal immune response and induce and maintain clinical remission, but they must be better understood to avoid side effects. In this sense, the continuing research on biotechnological and personalized medical and the knowledge of damage tissue homeostasis is crucial for the treatment of some conditions [79]. Crohn's disease and ulcerative colitis are intestinal disorders that comprise the inflammatory bowel diseases that involves the intestinal mucosal immune system and is a chronic inflammatory have a relapsing and remitting condition. Together, IBD significantly affect the quality of life of affected patients possibly leading to disability [80]. The classical therapeutic strategies aim to control the exacerbated host immune response with the use of aminosalicylates, antibiotics and immunosuppressive agents such as corticosteroids, thiopurines, methotrexate and anti-tumor necrosis factor biological agents. Although successful in treatment, these drugs have limited effectiveness and variable response among the patients. Thus, there is a clear need for more specific and efficient novel therapeutic approaches, and also in the understanding of the natural disease and genetically

predisposed individuals [81]. Because many IBD patients do not respond to standard anti-inflammatory and immune modulator medications, bioengineered antibodies that target specific molecules or proteins that cause inflammation or are involved in the inflammatory process are known as biologic therapies. Bioengineered antibodies have provided optimistic data for the treatment of several inflammatory autoimmune or autoinflammatory diseases [82], [83]. Such advances in understanding the molecular mechanisms of the inflammatory response have fueled the development of highly selective biological agents, and biologic therapies have been used successfully to block single signal transduction pathways. Recent progress has highlighted the selective blockade of cell-surface receptors or ligands using bioengineered antibodies for a number of immunological receptors and proinflammatory cytokines[84], [85].

3.3.1 Pharmacological Interventions

Chronic inflammatory diseases (CID) are widespread disorders that affect up to 1.5 billion people worldwide and are the underlying pathology of many mortal diseases. Pathological inflammatory state inhibits the homeostasis recovery of the inflammatory tissues, leading to the formation of diseased tissues or organs. Additionally, chronic inflammatory response can trigger autoimmune disorder if the pathological environment lacks regulation in time [86], [87]. As a result, patients will suffer life-long misery from multiple symptoms, such as degeneration of tissues and organs, dysfunction of metabolism and immunity. Although drugs, surgery, and diet control are currently treating CID, the efficacy is still limited due to the pathological complexity and the differential severity among patients. Dietary control has been widely utilized as a preliminary therapy for inflammatory patients and it possesses good advantages for the prevention and treatment of inflammation, but it does not perform equal efficacy for all inflammatory patients[88], [89]. Surgery is an effective way to remove the pathogenic inflamed tissues, but it does not perform good benefit for metastatic or dormant sensitization tissues. Among all the therapeutic strategies, pharmacological interventions are the most frequently employed ways for the treatment of chronic inflammatory diseases in clinic. A large number of medications are classified under the scale of pharmacological intervention, including non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, and disease-modifying antirheumatic drugs (DMARD)[90], [91]. NSAID attack the inflammatory cells by scavenging the mature cytokines or ROS precursor. Besides, the chronic inflammatory state is always companied by hypo-oxygen in the tissues, so constant oxygen is supplied in the inflammatory tissues to attack the inflammation. However, drug resistance and lack of drug selectivity are some serious problems in pharmacological treatment. In-depth recognition of the biochemical and immunological landscapes of chronic inflammatory diseases can offer new insights for the development of therapeutic schedule[92], [93]. Furthermore, a bioresponsive MPhs/DS+FAs@DOX delivery system for inflammatory treatment after acute or chronic inflammation was designed and fully characterized, which can be adapted to homeostatic regulation of both types of inflammatory states. And it was demonstrated the efficacy and safety of the bioresponsive multi-composition drug delivery system using inflammatory tissue models with chronic or acute inflammation. This type of bioresponsive delivery system may present much potential in clinical treatment of inflammatory diseases[94], [95], [96].

3.4 Impact of Chronic Inflammation on Tissue Homeostasis

Previous results show the significant impact of chronic inflammation on tissue homeostasis. Prolonged and sustained implementation of inflammatory responses can disrupt normal physiological functions of the host [95], [96]. Various kinds of injury to the tissue can initiate an acute inflammatory response, which activates immune and non-immune cells for eliminating pathogen and damage. This process is subsequently followed by tissue repair and remodeling, but has to be strictly regulated [97], [98]. Chronic inflammation that is out of control can foster an infiltration and accumulation of extremely

diverse cells, followed by fibrosis and loss of function. After considerable time, chronic inflammation can achieve systemic metabolic changes and progress in the broad spectra of disease. However, in many cases of chronic inflammation, it is frequently coupled with the necessity of remodeling of affected tissues[99], [100]. For instance, the interplay between aging and inflammation regarding the alteration of stem/progenitor cell dynamics and the tissue regenerative process is well-documented. Restoration of tissue homeostasis is conceptually reasonable as a therapeutic goal, yet both theoretic proposals and practical methods face substantial challenges. In general, the biologically active life span of a host organism is filled with numerous types of chronic inflammatory incidents, which epitomizes an intricate relationship between chronic inflammatory state and the health of tissues, or the health of the whole organism in the end[101], [102], [103].

3.4.1 Tissue Regeneration and Repair

Two of the most important attributes of chronic inflammatory diseases are sustained inflammation and altered immunity. From a biochemical perspective, it is of interest how local biochemical landscape alterations drive and sustain deleterious inflammation, exacerbating the disease, in addition to the altered immune responses and long-term consequences that chronic inflammation poses. Moreover, from a tissue health standpoint, it is equally important to understand how a perpetuated proinflammatory environment affects normal tissue homeostasis under the context of new advances in regenerative therapies. Consequently, this review will theorize the complex interactions between biochemical landscape alterations and activated immune cells in inflamed tissues and their consequences for normal tissue homeostasis and regenerative therapy[104], [105]. In most tissues, wound healing is a well-organized and coordinated process that renders the tissue regain of its normal structure. Following tissue injury, homeostasis is immediately re-established, and a cascading sequence of events leads to consequent clotting and inflammation aimed at preventing further damage from pathogens and restoring the tissue's barrier function. Subsequently, regenerative processes including repair of the injured vasculature and tissue remodeling take place[106], [107]. Inflammation is the first step in the healing process and serves to orchestrate and amplify all subsequent phases of healing. Acute inflammation may be appreciated as a phase where several types of leukocytes are recruited to the injury site. These transient resident inflammatory cells orchestrate subsequent stages of the healing process, which in normal conditions would guarantee the tissues' complete structural and functional rebuilding. An important mechanism in the control of inflammation resolution and return to homeostasis is the spatial temporal profile and characteristics of pro-resolving lipid mediators[108], [109]. Disruption can meet mis-regulated homeostatic signals, defective tissue healing, and chronification of inflammation[110], [111]. This may in principle set the basis for persistent inflammation, hence the importance of a comprehensive set of signals. Various inflammatory cells are known to regulate the succeeding processes of clotting, infection control, angiogenesis, tissue regeneration, and repair. It is currently accepted that monocytes or macrophages, among others, can promote growth factor release, inflammatory phase resolution, and tissue resolution by either phagocytic activities or transformation into anti-inflammatory macrophages. Other studies have shown individual growth factors accelerate repair by promoting extracellular matrix deposition[112], [113].

4. Discussion

4.1 Future Directions and Research Challenges

In the following years, as the study of chronic inflammatory diseases continues to evolve, research will focus on the use of emerging technologies and new research methods to better understand persistent inflammation, fibrosis, and cancer. In light of the complexity of the immune responses arising in chronic inflammatory diseases, the use of advanced imaging technology, artificial intelligent image analysis, molecular imaging,

reporter assays, real-time single cell tracking, and optogenetic systems will be integral tools to monitor and control immune responses both in vitro and in vivo [114]. Research will also increase the use of multi-omics approaches to understand the interactions that occur among multiple diseases and to use systems biology to mathematically model the interdependent risk factors associated with chronic inflammation. In particular, the communication between the immune system and the microenvironment and the influence of senescence secretomes will be studied in the laboratory. However, there are still challenges and open issues that need to be addressed [115]. One is the difficulty of predicting individual therapy choices. There is considerable variability in how individuals may respond to chronic inflammation, with some being high responders to a drug while others are low or non-responders. There is a need to closely monitor the diversity of immune cell states that might determine differing responses to drug therapy. There is uncertainty about whether tissue homeostasis can be reversed following long-term chronic inflammation. Chronic inflammatory disease can destabilize tissue homeostasis throughout life and beget numerous measures that injure tissues[116]. It is currently unknown whether such damage is repairable and how it may predispose to chronic diseases later in life. Indeed, applying a predictive framework built around wound healing dynamics provides new perspectives on how the inflammation-induced elaboration of fibrotic scars leaves tissues vulnerable to subsequent insults [117][119]. A more substantial momentum is necessary to explore innovative strategies to avoid injuries that result in chronic inflammation and to target its root causes rather than merely prophylactically combating symptoms. Given the inescapable multitude of factors that balance tissue health, intra- and interdisciplinary integration are required to provide a more comprehensive theoretical approach aimed at avoiding the occurrence of chronic inflammation[118].

5. Conclusion

Chronic inflammatory diseases disrupt tissue homeostasis through persistent immune activation, oxidative stress, and metabolic dysregulation. The imbalance between pro-inflammatory and anti-inflammatory responses contributes to disease progression and complications. Advances in biomarker identification and targeted therapies, such as cytokine inhibitors and immune modulators, have improved disease management. However, a deeper understanding of the biochemical and immunological mechanisms is essential for developing more effective treatments. Future research should focus on personalized medicine approaches to restore immune balance and prevent long-term damage. Addressing these challenges will enhance patient outcomes and improve therapeutic strategies for chronic inflammatory conditions.

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