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Bioterrorism Agent and New Tool for Monogenic Auto Inflammatory Disorders

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Abstract

The discovery that several of these conditions are caused by mutations in proteins involved in the mechanisms of innate immune response, including components of the inflammasome, cytokine receptors, and receptor antagonisin, has revolutionised the treatment of monogenic auto inflammatory disorders, an expanding group of hereditary diseases characterised by apparently unprovoked recurrent episodes of inflammation, without high-titre autoantibodies or antigen-specific T cells. The purpose of this review is to summarise recent research and experience regarding the therapeutic use of biologic medications in paediatric and adult patients with monogenic auto inflammatory diseases.

The stages of frozen shoulder, which depict the progression of processes from capsular inflammation and fibrosis to spontaneous resolution of this fibrosis, are largely understood. The underlying pathophysiologic mechanism, however, is still poorly understood. The treatment of frozen shoulder is still debatable due to this. A crucial step in the creation of a novel treatment for people with frozen shoulder is figuring out the pathophysiological causes of the condition. The basic pathophysiology of frozen shoulder is reviewed in this article along with what is currently known about it. Despite conflicting and ambiguous findings, papers on the pathophysiology of frozen shoulder have shown that cytokines, growth factors, matrix metalloproteinase, and immune cells are involved in both inflammation and fibrosis. Fibroblast activity is governed by proinflammatory cytokines and growth factors generated by immune cells, while matrix remodelling is controlled by matrix metalloproteinase and their inhibitors. The biology of these processes at specific stages needs to be better characterised in order to increase our understanding of the disease continuum. To more precisely define the function of cytokines, growth factors, matrix metalloproteinase, and immune cells, additional fundamental investigations utilising standardised protocols are necessary. The findings of these investigations will shed much-needed light on the pathogenesis of frozen shoulder and aid in the discovery of novel therapeutic targets.

Keywords: Cytokines; Pathogenesis; Auto inflammatory; Metalloproteinase

Introduction

Recently discovered hereditary diseases known as monogenic auto inflammatory disorders (AIDs) are characterised by recurrent febrile episodes that appear to be unprovoked and are accompanied by inflammatory symptoms that can affect a variety of organs and systems, most frequently the skin, serous membranes, musculoskeletal system, gastrointestinal tube, eyes, and/or nervous system. Instead of autoantibodies or antigen-specific and auto reactive T cells, as in the chapter of autoimmune illnesses, recurring febrile and inflammatory episodes occur in monogenic AIDs. Their pathophysiology is mostly caused by mutations in genes encoding proteins involved in the control of the innate immune system or in the modulation of the inflammatory response, which leads to a massive production of proinflammatory cytokines, especially interleukin. Clinically, monogenic AIDS is distinguished by significant variation in terms of age of onset, frequency and severity of episodes, clinical symptoms, or responsiveness to treatment [1]. This is likely because of the vast variety of mutations that can occur in various genes. Monogenic AIDs-related mutations may have a high penetrance, which frequently results in a more aggressive phenotype, or a low penetrance, which frequently results in a less severe clinical picture with a later onset, fewer episodes per year, and atypical or paucisymptomatic phenotypes. As a result, identifying patients with low-penetrance mutations may be challenging, and in these situations, it is crucial to establish the proper differential diagnosis. Recent advances in treatment have been made possible by our growing understanding of the molecular mechanisms behind monogenic AIDSs [2].

A frequent shoulder condition known as frozen shoulder (FS) affects 2 to 5 percent of the general population and causes a progressive loss of shoulder motion. FS progresses through a number of stages that represent the progression of fibrosis from spontaneous resolution to capsular inflammation and fibrosis. The origin, pathophysiology, natural course, and best course of treatment for FS, however, are still up for debate. According to arthroscopic and imaging studies, the glen humeral joint's capsular tissue, which includes the rotator interval, is a key pathogenic location. It defined FS as the result of fibrosis and inflammation [3]. Early on, a synovial hyperplasia with enhanced vascularity manifests, and the subsynovium and synovium of capsular tissue gradually fibrose. Inflammatory synovitis and capsular fibrosis follow the immunological reaction that causes this illness to start. Although the macroscopic and histological characteristics of capsular contracture are well established, the underlying pathophysiological process is still not fully understood. Recently, a lot of work has gone towards developing an immunological response for FS, including inflammatory mediators. Recent years have seen a growth in the field's understanding of the pathophysiologic mechanisms underlying FS [4]. The pathophysiologic processes that underlie FS include capsular fibrosis and inflammation that are mediated by inflammatory cytokines, growth factors, enzymes, and matrix metalloproteinases (MMPs). A matrix of type I and type III collagen containing fibroblasts

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and myofibroblasts and regulated by aberrant cytokine production is the histologic hallmark of FS. In order to create a unique treatment for FS patients, it is crucial to understand the biological pathophysiology of FS. This article provides a biological review of the pathophysiology of FS.

Monogenic auto inflammatory disorders are categorised

Systemic hereditary monogenic AIDs include familial Mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), the family of cryopyrin-associated periodic syndromes (CAPS), which in turn include familial cold urticaria syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID, also known as "chronic infantile neurological cutaneous and articular syndrome" or CINCA syndrome) (DIRA).

While some of them—including FMF, MKD, MS, and DIRA—are inherited autosomally recessively, others—TRAPS, FCAS, MWS, NOMID, NLRP12AD, BS, and PAPAs—are inherited autosomally dominantly. The genes encoding for the proteins involved in the activity of the inflammasome, a multiprotein complex that activates the processing and secretion of IL-1 and various other cytokines with proinflammatory effects, have been linked to monogenic AIDs in recent years, with the exception of MKD, which is brought on by a deficiency of mevalonate kinase, the second enzyme of the mevalonate/isoprenoid pathway [5]. A further characteristic of MKD is a 1–8% residual enzymatic activity, whereas the complete absence of this enzyme results in a unique metabolic condition known as mevalonic aciduria (MA).

Elements of Monogenic Auto inflammatory Disorders Treatment

Controlling symptoms, enhancing quality of life, and avoiding long-term consequences are the major three goals of therapy for people with monogenic AIDs. No steroidal anti-inflammatory medications (NSAIDs), high-dose corticosteroids, colchicine, or immunomodulatory have been the sole stay of symptomatic treatment for years. These treatments, with the exception of colchicine in FMF, frequently fall short of providing adequate control of symptoms and inflammation indexes, especially serum amyloid-A (SAA), which must be kept within a normal range because the result of its cleavage accumulates gradually in various tissues and results in systemic amyloidosis. Generally speaking, any treatment should be modified to keep the concentration of SAA within the reference range [6].

Growth factors and cytokines

Numerous investigations have shown that the pathophysiology of FS depends on the increased expression of inflammatory mediators in the synovial tissue of the joint capsule.

Unnatural tissue healing and fibrosis in FS are caused by an inflammatory cascade that is triggered by abnormal inflammatory cytokine production. The function of fibroblasts is regulated by cytokines and growth factors, and matrix remodelling is regulated by MMPs and their inhibitors. They are crucial for the transcription of MMPs, which regulate connective tissue turnover.

Immune Factors

Additionally, an immunological element involving B-lymphocytes, mast cells, and macrophages has been proposed for FS. According to several studies, FS starts as an immunological reaction that aggravates inflammatory synovitis and eventually results in capsular fibrosis. Tay found that the capsular tissue was devoid of leukocytes and macrophages and came to the conclusion that active fibroblastic proliferation is very similar to that seen in Dupuytren's contracture, but without inflamation and synovial involvement. Meanwhile, Hand found immune cells in the synovium and capsule of the rotator interval, including B-lymphocytes, T-lymphocytes, macrophages, and mast cells, suggesting an immunological response in FS [7].

To more clearly assess these cellular interactions, more thorough research is needed. From immune cells like macrophages, proinflammatory cytokines like IL-1, IL-6, IL-8, and TNF were produced. This suggests that the joint contains a significant number of these cells. According to Kane, a significant CD68 staining was a marker of an inflammatory cell.

Tumor Necrosis Factor-Associated Periodic Syndrome (TRAPS)

Because of the significant genetic variation and the diverse clinical spectrum of the disease, treating TRAPS seems to be more difficult than treating other monogenic AIDs.

High-dose NSAIDs only help a small number of individuals with their symptoms, whereas colchicine or immunomodulatory such methotrexate, cyclosporine, and thalidomide have very little effect. Corticosteroids are frequently effective at treating inflammatory episodes, and patients may require higher dosages if they experience recurrent relapses or even long-term use to prevent flare-ups. These individuals might develop metasteroidal comorbidities [8].

Additionally, corticosteroids do not appear to completely protect against the risk of developing reactive amyloidosis in most patients since they do not restore SAA levels.

Discussion

In FS histologic and imaging studies, increased vascularity was frequently found. Neovascularization has been highlighted as a critical stage in the etiology of the disease, with positive immunostaining of VEGF and CD34. Numerous investigations found that an FS group had higher levels of CD34 expression in their joint capsules than a control group. The findings of earlier research suggest that neoinnervation and neoangiogenesis in the glen humeral joint capsule are significant events in the pathophysiology of FS and provide evidence to explain the extreme pain felt by FS patients.

Conclusion

Due to their hereditary nature, monogenic AIDs typically manifest in infancy, beginning within the first hours to the first decades of life. However, some patients present with disease onset in adulthood or remain undiagnosed for extended periods of time, with recurrent inflammatory symptoms of variable severity that are frequently misdiagnosed and carry a high risk of long-term complications. Despite the fact that these conditions are now much better understood, most monogenic AIDSs have a delayed diagnosis due to their great rarity and relatively recent detection. The biologic treatments for the various AIDs caused by monogenic microbes that are covered in this article. In order to alleviate or suppress several complex clinical phenotypes and prevent the development of secondary amyloidosis, the use of biologics demands and dictates that diagnostic period must be anticipated in these conditions. To determine the most personalised treatment approach for various monogenic AIDs, extensive comparison studies are required. However, it is likely that it will also be necessary to translate all new insights into the immunopathology of these diseases

into more potent treatments. Additionally, a number of nonhereditary multifactorial inflammatory disorders that have clinical features with monogenic AIDS and may have an auto inflammatory origin may also be treated with a biologic treatment strategy, opening up new possibilities on the medical front lines.

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Conflict of Interest

The author has no known conflicts of interested associated with this paper.

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