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Inflammasomes and autoimmunity

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Abstract

The NOD-like receptor (NLR) family members are cytosolic sensors of microbial components and danger signals. A subset of NLRs control inflammasome assembly that results in caspase-1 activation and, in turn, IL-1 β and IL-18 production. Excessive inflammasome activation can cause autoinflammatory disorders, including the hereditary periodic fevers. Autoinflammatory and autoimmune diseases form a disease spectrum of aberrant, immune-mediated inflammation against self, through innate and adaptive immunity. However, the role of inflammasomes in autoimmune disease is less clear than in autoinflammation, despite the numerous effects IL-1 β and IL-18 can have on shaping adaptive immunity. We summarize the role of inflammasomes in autoimmune disorders, highlight the need for a better understanding of inflammasomes in these conditions and offer suggestions for future research directions.

Keywords

NLR; Inflammasome; NLRP3; ASC; caspase-1; autoimmunity

NLR-induced assembly of the inflammasome

Multicellular organisms have developed an intricate network of innate and adaptive signals to mount effective responses to both endogenous and exogenous insults. The Nod-like receptor (NLR) family of proteins is a group of intracellular pattern recognition receptors (PRRs) of the innate immune system that play a vital role in the recognition of a wide spectrum of danger- and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively)¹. In humans, the NLR family is composed of 22 genes, whereas the mouse genome contains at least 34 NLR-encoding genes². Of the NLR proteins, NLRP3 (also known as NALP3 or cryopyrin), NLRP1, NLRC4 and absence in melanoma 2 (AIM2)

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activation results in the formation of large protein complexes termed inflammasomes. The mechanism of activation of NLRs is still a subject of active debate, but once activated NLRP3, NLRP1, NLRC4 and AIM2 undergo a conformational change allowing for interaction with an inflammasome-adaptor protein, ASC (PYCARD), which, in turn, interacts with caspase-1 (NLRP3 is shown in Figure 1 as an example). The resulting inflammasome serves as a molecular platform that mediates the autoactivation of caspase-1, which cleaves the pro-forms of IL-1 β and IL-18 to active forms. Inflammasome activation is critical for host defense to pathogens, but recent work has also found a role for the inflammasome in the pathogenesis of several diseases with an inflammatory component, such as type 2 diabetes (T2D), inflammatory bowel disease (IBD) and atherosclerosis³⁻⁶ (Table 1). However, this review will focus on the role of inflammasomes in diseases characterized by inflammation against self, highlighting autoimmune diseases in particular.

Inflammasome activation and the continuum of diseases caused by immune-mediated inflammation against self

Diseases classified by excessive or chronic activation of the immune system can be placed in a disease continuum, with autoinflammatory disorders on one end of the spectrum and autoimmune diseases at the other⁷. Autoinflammatory diseases are clinical disorders that present with recurrent inflammation and unexplained fevers as part of their phenotype, due to abnormally increased inflammation mediated by cells of the innate immune system⁸. In autoinflammatory disorders, tissue damage results from self-directed inflammation, due to activation of innate immune cells, including macrophages and neutrophils. For example, disturbed homeostasis of cytokine cascades in the periodic fevers, and aberrant bacterial sensing, as in Crohn's disease, predispose to site-specific inflammation that is largely independent of adaptive immune responses. By contrast, autoimmune diseases can be classified as inflammation against self mediated by the adaptive immune system, with development of immune reactivity towards native antigens. Hyper-reactivity of both T and B cells (as well as aberrant dendritic cells) is typically observed in conjunction with autoantibodies and antigen-specific T cells targeting self, resulting in tissue destruction. Autoimmune diseases can cause multiorgan involvement, but the primary end-organ target typically drives the clinical presentation and disease definition.

To date, several prototypical autoinflammatory disorders have been strongly linked with mutations in inflammasome-forming NLRs⁹. Overactivating mutations in the NLRP3 inflammasome increase the release of IL-1 β and cause cryopyrin-associated periodic syndromes (CAPS)¹⁰. Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and Neonatal Onset Multisystem Inflammatory Disease (NOMID) syndrome comprise the various CAPS caused by NLRP3 gene mutations, of which over 50 different mutations have been identified^{9, 10}. The three CAPS conditions have clinical similarities but are distinguished by their phenotypic severity. Signs and symptoms of these disorders include recurrent rash, fever/chills, joint pain, fatigue, deafness, systemic amyloidosis, CNS disabilities, vision loss and joint and bone deformation. Direct, continuous inhibition of IL-1 β by anakinra, riloncept or canakinumab ameliorates all clinical manifestations, except bony overgrowth in NOMID syndrome^{11, 12}.

The NLRP3 inflammasome has also been linked with polygenic inflammatory disorders, such as gout and pseudogout, which are dependent on the synergistic interaction between free fatty acids and monosodium urate crystals driving inflammation through the NLRP3 inflammasome¹³. The resulting inflammation leads to neutrophil and macrophage activation, especially in the joints¹⁴. Blockade of IL-1 β with anakinra has a dramatic effect, exemplifying the critical role of inflammasome activation in disease progression¹⁵.

The understanding of the role of inflammasomes in autoimmunity is less clear. The innate immune system influences the development of the autoimmune response¹⁶, and a T cell-independent phase has been postulated for the initiation of rheumatoid arthritis (RA), a systemic autoimmune disease¹⁷. Genetic links between the inflammasome-inducing NLRs and autoimmune diseases are limited, but this does not exclude a potential role for inflammasome activation in the progression of these diseases. A role for the inflammasome in some autoimmune diseases is likely, considering the wide spectrum of endogenous danger signals that activate NLRs¹⁸ and the role that inflammasome products, such as IL-1 β and IL-18, can play in shaping adaptive immunity (Figure 2)¹⁹. IL-1 β can act on lymphocytes in several ways including upregulating IL-2 receptor expression, prolonging survival of T cells, enhancing antibody production by B cells and increasing B cell proliferation^{20, 21}. IL-1 β and IL-18 also play a critical role in driving the differentiation and amplification of Th17 and Th1 cells, respectively^{22–24}. So, in general, IL-1 β and IL-18 amplify T and B cell responses and might serve as a crucial link translating NLR activation into adaptive immune responses. Here, we focus on the potential role of inflammasomes in autoimmune disorders and highlight the importance of future research in this field. An overview of current links between the inflammasome and autoimmunity will facilitate the investigation of its importance for clinical care, potentially identifying new therapeutic targets for several autoimmune disorders.

Rheumatoid arthritis

RA is a self-perpetuating autoimmune disease that can affect several tissues and organs but principally leads to chronic inflammation of the synovial membrane of joints causing pain and swelling and which may result in irreversible joint destruction. Although the precipitating causes of RA are unknown, autoimmunity plays a critical role in progression of the disease, as both T cells and autoantibodies are involved²⁵. Clinical trials exploring the possibility of treating RA by blocking IL-1 activity with anakinra found reduced joint swelling, pain and inflammatory blood markers strategy²⁶, but the use of anakinra is less favored because other anticytokine therapies are more effective²⁷. Nevertheless, IL-1 blockade was moderately effective, and inhibition of the inflammasome could prove to be a more effective therapeutic target than specific IL-1 blockade as inflammasome inhibition would block IL-1 and IL-18 activity, both of which play a role in disease progression^{27, 28}.

The evidence linking the inflammasome and RA pathogenesis is somewhat ambiguous; an epistatic relationship was reported whereby dual polymorphisms in the *NLRP3* and *CARD8* genes caused increased IL-1 β production and was associated with an increased susceptibility and severity of disease in RA patients²⁹, but a prospective study from the same research group did not find any association of the *NLRP3* single nucleotide polymorphisms (SNPs) alone with either susceptibility to RA or the incidence or severity of early RA³⁰. Furthermore, a difference in *NLRP3* expression is not responsible for differences in the nature and extent of synovial inflammation seen in RA and osteoarthritis patients³¹. Nevertheless, these studies do not rule out the possibility of the *NLRP3* inflammasome playing a functional role in RA, both in initiating and maintaining the inflammatory phases of the disorder. Patients with excessive *NLRP3* activation commonly develop joint pains and arthritis^{10, 32}, suggesting excessive inflammasome activation could be involved in RA pathogenesis. However, the role of the *NLRP3* inflammasome in the etiopathogenesis of RA requires further study.

In mice, both antigen-induced arthritis (AIA) and collagen-induced arthritis (CIA) are used to explore disease mechanisms of RA, as these models share some clinical and pathological features with RA in humans. However, these animal models do differ from RA in several aspects, and therapies effective in these conditions might not be as useful in a clinical

setting. However, disease progression was reportedly independent of NLRP3 and caspase-1 in these mouse models of RA^{33, 34}, and surprisingly, both studies identified an inflammasome-independent role of ASC. The mechanisms reported by which ASC contributed to the development of arthritis were different in these two studies. ASC was required for cytokine production and T cell proliferation in one report³⁴, whereas a dendritic cell-intrinsic role for ASC in lymphocyte activation was reported in the other study³³. Therefore, in mouse models of arthritis, the NLRP3 inflammasome does not play a role in disease progression. However, these are imperfect models of RA disease mechanisms in humans, and further clinical research is required to fully understand the role of inflammasomes in RA.

Multiple sclerosis

The initiation and progression of multiple sclerosis (MS) is driven by autoreactive T cells targeting oligodendrocytes. MS is a heterogeneous condition both in clinical presentation and disease duration. Although both Th1 and Th17 cells drive the pathogenesis of MS³⁵, innate immune cells also play a significant role in disease progression³⁶. Cytokines activated by the inflammasome, IL-1 β and IL-18, play a major role in the differentiation and survival of Th17 and Th1 cells, respectively^{19, 22, 37–40}, suggesting a possible role for inflammasome activation in the progression of MS.

To date, there has not been an association between inflammasome-forming NLR mutations or polymorphisms and MS, but this does not rule out a possible role for the inflammasome(s) in MS progression. Additionally, a recent case report described lesions in the brain of a patient suffering from MWS that resembled those seen in MS patients⁴¹. Although, this is not a direct link with MS, it does suggest the overactivation of the NLRP3 inflammasome can cause CNS inflammation, which could be involved in MS progression.

In experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, caspase-1 activation was required for development of EAE through the production of inflammatory cytokines IL-1 β and IL-18⁴². However, the data on the role of the NLRP3 inflammasome in EAE progression are conflicting; one report found a role for the NLRP3 inflammasome in development of Th1 and Th17 cells and EAE progression⁴³, whereas another report did not find a role for the NLRP3 inflammasome in EAE progression, but did find an inflammasome-independent role for ASC⁴⁴. Lymphocyte survival was significantly impaired in the absence of ASC, and ASC-deficient mice were resistant to EAE. The model and methodology were the same for the two reports; however, the gut microbiota can greatly influence adaptive immunity, and especially Th17 responses, in mouse models of autoimmunity⁴⁵. Therefore, it is possible that there are differences in the mechanisms of disease pathogenesis in these two independent mouse colonies in different locations. Future studies in other laboratories examining EAE progression in homozygous knockout *NLRP3*^{-/-} mice could clarify this discrepancy. However, there is substantial evidence in animal models for inflammasome involvement, in that caspase-1 activation plays a critical role in EAE pathogenesis. Clinically, caspase-1 expression is elevated in MS plaques and in the peripheral blood mononuclear cells (PBMCs) of MS patients compared to healthy brain sections and PBMCs, respectively^{46, 47}. Future studies exploring the efficacy of a caspase-1 inhibitor in primate models of MS would be useful in elucidating a causal role for inflammasome activation in MS. Nevertheless, the role of inflammasome activation and any NLR involvement in MS progression remains in question.

Type 1 diabetes

The progressive destruction of insulin-secreting islet cells of the pancreas by autoreactive T cells and autoantibodies leads to type 1 diabetes (T1D)^{48, 49}. Insulin replacement therapy is

used to manage T1D, but the disease and related complications, including cardiovascular disease, diabetic retinopathy and diabetic neuropathy, remain a serious burden on human health⁵⁰⁻⁵¹. The mechanisms causing T1D and its complications are not fully understood. However, based on results showing that IL-1 β can cause pancreatic beta cell apoptosis⁵², a multicenter, randomized clinical trial was recently launched that will investigate the effect of IL-1 antagonism on beta cell function in recent onset T1D patients⁵³ (www.clinicaltrials.gov). Despite extensive work investigating the role of IL-1 in T1D, it remains unknown whether NLRP3 inflammasome activation contributes to pathogenesis.

A recent study analyzing 1,084 patients with T1D and 3,273 healthy patients found a strong correlation with a SNP in *NLRP1*, rs12150220, and T1D⁵⁴. However, the association did not reach genome-wide significance. This SNP is located in the NACHT region of NLRP1, but the effect of this SNP on NLRP1 inflammasome function is unknown. A more recent study did not find any association between this *NLRP1* SNP and T1D in a pediatric population in Brazil, but this study was only comprised of 196 patients with T1D and 192 healthy individuals⁵⁵. However, a SNP in *NLRP3*, rs10754558, was associated specifically with T1D susceptibility in this pediatric population in Brazil⁵⁵. This particular *NLRP3* SNP was recently associated with mRNA stability⁵⁶ and, therefore, it is possible that stable expression of NLRP3 could be protective against T1D. However, the effect of this SNP on inflammasome activation or the consequent secretion of IL-1 β and IL-18 are, as yet, unknown, and the reason that the *NLRP3* rs10754558 G allele was less frequent in patients with T1D is also unknown.

The role of the NLRP1 or NLRP3 inflammasomes in nonobese diabetic (NOD) mice, a strain that develops T1D spontaneously, has not been studied. Future studies exploring the effect of *NLRP1* and *NLRP3* gene deletion or mutations in NOD mice could be valuable. However, caspase-1 is not required for development of T1D in the NOD mouse⁵⁷, suggesting that deficiency of either NLRP1 or NLRP3 would not alter the development of T1D in NOD mice, and moreover, disease mechanisms in the NOD model do not always correlate with T1D pathogenesis. Future studies inserting the rs12150220 *NLRP1* or rs10754558 *NLRP3* SNP in NOD transgenic mice might provide a mechanistic explanation for its association with T1D. Furthermore, although caspase-1 is not involved in the development of T1D in NOD mice, it is involved in the degeneration of retinal capillaries in diabetes⁵⁸. Whether this is through the NLRP1 or NLRP3 inflammasome is unknown, but if either inflammasome is involved, then specific NLRP1 or NLRP3 inhibitors might provide a valuable therapeutic approach to prevention of diabetic retinopathy in T1D patients. A significant amount of research remains to be done in this field, but initial evidence suggests that the NLRP1 or NLRP3 inflammasome could play a role in the predisposition to development of T1D or progression of diabetic retinopathy. Therefore, future work may provide novel therapeutic strategies for T1D or its complications.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease driven by an immune response against ubiquitous self-antigens. Autoantibodies against nuclear antigens, especially double-stranded DNA are commonly detected. To date, there has not been any association with inflammasome-forming NLR mutations or polymorphisms and lupus. However, leukocytes from SLE patients have increased AIM2 expression, but this study did not find a correlation between AIM2 expression and SLE Disease Activity 2000 scores⁵⁹. A preliminary study showed that IL-1 blockade with anakinra provided therapeutic benefit for patients with SLE⁶⁰. Additionally, both IL-1 β and IL-18 are involved in disease progression in the mouse model of lupus, suggesting the involvement of at least one inflammasome⁶¹⁻⁶². Chloroquine, used widely for SLE, decreases aberrant NLRP3 expression during disease

progression, a mechanism possibly related to its therapeutic effect⁶³. If inflammasome activation plays a role in lupus progression, then AIM2 is a good candidate to be the main NLR involved, based on its ability to recognize cytoplasmic DNA⁶⁴. However, the involvement of AIM2 or any other inflammasome-forming NLRs has not been studied at this point and it is possible for multiple inflammasomes to be involved in the activation of IL-1 β and IL-18. Future studies deleting the *NLRP3*, *NLRP1* or *AIM2* genes in transgenic lupus-prone mice and examining disease progression will help elucidate the role of the inflammasome in lupus, and could provide initial evidence for a new therapeutic strategy for its management

Celiac disease

Celiac disease (CD) is an inherited disease characterized by destruction of the lining of the small intestine that is triggered by eating gluten, gliadin and other proteins found in wheat, barley and rye⁶⁵. Several characteristics are shared between CD and inflammatory bowel disease (IBD), but CD is diagnosed by a defined dietary trigger, the presence of HLA-DQ2 or HLA-DQ8 genotype and the presence of autoantibodies to tissue transglutaminase. Several disorders might be associated with CD susceptibility, including several different autoimmune diseases, such as RA and SLE. Indeed, a case report describes a child who was diagnosed with both a cryopyrinopathy and CD⁶⁶. Although this occurrence could be coincidental, it is also possible that excessive IL-1 β and IL-18 production due to a mutation in *NLRP3* could have contributed to the generation of gliadin-reactive T cells. Furthermore, in a pediatric population of CD patients, the *NLRP3* SNP (rs10754558 G allele) was less frequently observed in CD patients compared to healthy patients⁵⁵; interestingly, this same result was also observed in patients with T1D⁵⁵. As the functional consequences of this SNP are unknown, it is as yet too early to know if *NLRP3* is involved in predisposition to or progression of CD. Nevertheless, downstream products of *NLRP3* inflammasome activation, such as IL-1 β , control the IL-23 response to gliadin, and therefore affect Th17 cell differentiation and survival⁶⁷. Additionally, the receptor for the IL-18 protein (IL18RAP and IL18R1) is a susceptibility locus for CD, and IL-18 is believed to play a role in the pathogenesis of disease by inducing Th1 responses^{68, 69}. Therefore, it seems possible that the *NLRP3* inflammasome could be involved in CD pathogenesis; studies of *NLRP3* knockouts or insertion of the *NLRP3* rs10754558 G allele SNP onto HLA-DQ8 transgenic mice, a mouse model of CD, would help clarify the role of the *NLRP3* inflammasome in its pathogenesis.

Vitiligo and vitiligo-associated multiple autoimmune disease

Vitiligo is an autoimmune disease caused by the T cell-mediated destruction of melanocytes, presenting as white patches on the skin due to a loss of pigment. The mechanisms underlying disease progression are unclear, but a wide array of stress factors can provoke an autoimmune response to melanocytes. However, only 0.5–1% of individuals will develop progressive depigmentation in response to stress factors, implicating a hereditary predisposition in a subset of the population⁷⁰. Additionally, as with several other autoimmune disorders, patients with vitiligo often are afflicted with concurrent autoimmune disorders. A recent association study found a strong association of *NLRP1* variants with vitiligo alone and vitiligo-associated multiple autoimmune diseases⁷¹. The functional effects of the *NLRP1* SNP variants are unknown, and therefore the mechanism(s) linking *NLRP1* variations and vitiligo remain(s) unknown. However, *NLRP1* is highly expressed in both T cells and Langerhans' cells, a distribution pattern that suggests a potential role for *NLRP1* in skin autoimmunity⁷². Studies examining the effects of *NLRP1*, *NLRP3* or *caspase-1* gene deletion in a recently described mouse model of autoimmune vitiligo⁷³, would help determine the potential role of the inflammasomes in vitiligo.

Autoimmune Addison's disease

Addison's disease (AAD) is an autoimmune condition associated with immune destruction of the adrenal cortex resulting in a deficiency of mineralocorticoid, glucocorticoid and adrenal androgen production. The pathogenesis of autoimmune AAD, which is the most common disease of the adrenal cortex, is a complex process, influenced by both genetic and environmental factors. Based on the association of *NLRP1* SNPs with other autoimmune disorders, a study examined the correlation of six *NLRP1* SNPs with AAD (101 AAD and 254 healthy individuals), and the frequency of the rs12150220 SNP in *NLRP1* was significantly increased among AAD patients⁷⁴. However, based on the low prevalence of AAD, the study was unable to examine a sufficiently large cohort of patients to reach genome-wide significance. This study demonstrates an association of the *NLRP1* SNPs and genetic susceptibility to AAD, but the exact role of the NLRP1 inflammasome in AAD progression remains unclear.

Concluding Remarks

Our understanding of NLRs and their role in human diseases has expanded exponentially in recent years. NLRP3 inflammasome activation is critically involved in autoinflammatory disorders, and a role for this particular inflammasome has been shown in animal models of several other diseases with an inflammatory component (Table 1). However, despite the potential of the NLRP3 inflammasome to affect adaptive immune responses via IL-1 β and IL-18 production, its role in autoimmune disorders has not been studied extensively. Several reports have linked various polymorphisms in different components of inflammasome-forming NLRs, including NLRP3 and NLRP1, to autoimmunity. Future work elucidating the effects of these identified SNPs on gene transcription, mRNA stability or protein function will provide substantial progress in determining the role of the inflammasomes in disease progression. Additionally, activators of NLRs continue to be determined, and the discovery of the range of molecules capable of activating the inflammasomes could provide breakthroughs in our understanding of specific disease progression. For example, the finding that gout-associated urate crystals are involved in activating the NLRP3 inflammasome was a significant advance in understanding the pathogenesis of gout and its treatment⁷⁵. Our understanding of NLRs and the inflammasomes in autoimmunity is still rather elementary, but preliminary studies suggest a potential role of inflammasome activation in at least some autoimmune disorders. Further progress in this research field could open up new strategies in treating autoimmune diseases and their complications.

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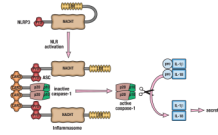


Figure 1. Activation of the inflammasome

The various inflammasomes are activated by a wide spectrum of DAMPs and PAMPs. NLRP3 activation and inflammasome formation is depicted as an example. Once activated, the inflammasome-forming NLR undergoes a conformational change, allowing for NLR binding to ASC via the pyrin domains (PYD). ASC acts an adaptor protein, and binds to pro-caspase-1 through caspase recruitment domains (CARD). This large complex is termed the inflammasome and provides the platform for the autoactivation of caspase-1 by proteolytic cleavage. Active caspase-1 (p20/p10) then cleaves pro-forms of IL-1 β and IL-18, allowing for their secretion and biological activity.

Table 1

The role of the inflammasomes in human disease

| Human disease | Cause of disease | Link to genetic mutations | Response to IL-1 blockade? | Inflammasome involved in animal model? |
|--|---|---------------------------|----------------------------|--|
| <i>Diseases with an inflammatory component</i> | | | | |
| Inflammatory Bowel Disease | Polygenic inflammation of GI tract | Yes ⁷⁶ | No | Yes ^{3, 5} |
| Type 2 diabetes | Polygenic/metabolic stress and inflammation | No | Yes ⁷⁷ | Yes ⁶ |
| Essential hypertension | High blood pressure without an identifiable cause | Yes ⁷⁸ | Not tested | Not tested |
| Alzheimer's disease | Degenerative brain disorder | No | Not tested | Yes ⁷⁹ |
| Atherosclerosis | Artery wall thickening as a result of build-up of fatty materials | No | Not tested | Yes ⁴ |
| Contact allergic dermatitis | Sensitizing allergens | Yes ¹⁰ | Not tested | Yes ⁸⁰ |
| <i>Autoinflammatory diseases</i> | | | | |
| MWS | NLRP3 mutation | Yes ¹⁰ | Yes ¹² | Yes ⁸¹ |
| FCAS | NLRP3 mutation | Yes ¹⁰ | Yes ¹² | Yes ⁸² |
| CINCA | NLRP3 mutation | Yes ¹⁰ | Yes ¹² | Not tested |
| <i>Autoimmune Diseases</i> | | | | |
| Type 1 diabetes | Self destruction of pancreatic β cells | Yes ⁵⁵ | Not tested | Not tested |
| Multiple sclerosis | Self destruction of oligodendrocytes | No | In progress | Yes ⁴³ /No ⁴⁴ |
| Systemic lupus erythematosus | Targeting of ubiquitous, mostly intra-nuclear self-antigens | No | Yes ⁶⁰ | Not tested |
| Vitiligo | Self destruction of melanocytes | Yes ⁷¹ | Not tested | Not tested |
| Addison's disease | Destruction of the adrenal cortex resulting in impaired cortisol production | Yes ⁵⁴ | Not tested | Not tested |
| Celiac disease | Destruction of the small intestine lining triggered by eating gluten | Yes ⁵⁵ | Not tested | Not tested |
| Rheumatoid arthritis | Self destruction of the synovial joints | Yes ²⁹ | Yes ²⁷ | No ³³ |