

# Why a Recently -Discovered Host-Defense Factor, HDFx, May Ameliorate and Prevent Inflammatory Lesions Induced by Sarcoidosis

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## Article Info

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Sarcoidosis is a very rare disease of the immune system whereby numerous inflammatory cells, known as granulomas, attack many body organs, particularly the lungs and lymph nodes [1-3]. It seems to have a predilection to attack people between the ages of 20 and 40, and often recedes without any treatment. But, in severe cases, sarcoidosis becomes chronic and will cause permanent cellular damage to numerous organs within the body and, often, death when the inflamed nodules interfere with cardiac function [1]. Unfortunately, the cause(s) of the disease process is not known, nor is there any known cure [1-3]. Sometimes, if caught early enough, administration of corticosteroids will relieve many of the symptoms [1,2,4]. Most often, the disease process proceeds without the patient knowing it. The ensuing chronic inflammations lead to permanent thickening or scarring of multiple organ-tissues [1-3]. In the USA, alone, about 200,000 people currently have the active disease [1]. The sarcoidosis mortality rate is approximately 5% [1,5].

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Interestingly, the granulomas, found in the lungs in sarcoidosis, are composed of macrophages, epithelioid cells, and multinucleated giant cells surrounded by T-lymphocytes, monocytes, mast cells, and fibroblasts [for review, see 1]. These granulomas are thought to arise from an exaggerated cell-mediated immune response to one or more unidentified antigen (s) [1]. Despite some of the best scientists, working to identify the antigen (s), this has remained elusive [1,6,7]. There is, however, considerable agreement that alterations/activation in the pathophysiology of alveolar macrophages and T-lymphocytes, leading to alveolitis, are critical in the progression of the disease [1-3], [6,7].

In view of the obvious roles of macrophages in production of sarcoidosis -induced alveolitis, we believe that a reasonable therapeutic avenue would be to prevent/ameliorate activation of the alveolar macrophages.

Another major problem in preventing lung damage in sarcoidosis is the massive release of cytokines, often leading to undetected "cytokine storms" [for review, see 1]. In this phase of the disease, multiple cytokines are released from lymphocytes, macrophages, and monocytes which perforce act to release other dangerous molecules such as IL-2, TNF-alpha, GM-CSF, MCP-1, interferon-gamma, and a variety

of chemoattractants, chemokines and growth factors [1,6]. Collectively, these substances, in conjunction with the continual release of multiple cytokines, can result in further clumping of cells in the lung capillaries and blockage of pulmonary blood flows and ischemia of the lung parenchyma causing irreversible death of multiple lung tissue segments [1,6,7]. So, any "true" therapeutic treatment, in our opinion, should be able to not only prevent/block release of the dangerous cytokines and chemokines, but should be able to open-up blocked capillaries leading to tissue perfusion. In addition, an important aspect of any therapeutic modality should, hopefully, lead to tissue repair and regeneration. Can any known therapeutic molecule (s), potentially, prevent/ameliorate the granulomas and alveolitis, the release of cytokines and chemokines, increase tissue perfusion, and help with lung tissue regeneration? Since sarcoidosis is an inflammatory disease and is seen worldwide, it may have more than one etiology. As has been suggested more than 30 years ago, its manifestations may have an underlying, infectious bacterial component(s) [for recent review, see 8]. The presence of cytokines such as IL-2, IL-4, IL-6, IL-10, TNF-alpha, IL-12, IL-15, and IL-18 as well as chemokines in sarcoidosis may, indeed, be suggestive of the presence of infectious bacterial microorganisms. So, it is logical to us to conclude that agents which could prevent the activation of macrophages, monocytes, and T-lymphocytes which produce, and release, these cytokines and chemokines, in patients with sarcoidosis, should be helpful as prophylactic and therapeutic agents.

#### Discovery of HDFx and The Rationale for Its Use in Sarcoidosis

For more than five decades, our laboratories have been working on a new approach to develop host-defense factors that stimulate/and inhibit various arms of the innate and adaptive immune systems [9-25]. To this end, we have discovered a new host-defense factor, termed "HDFx", that is a conserved protein found in mice, rats, guinea-pigs, rabbits, dogs, pigs, and sub-human primates [26-32], unpublished findings]. More than 135 years ago, Elie Metchnikoff, the great father of immunology, hypothesized that the body, under stressful conditions, might produce powerful immune-stimulants which perforce would act on different arms of the innate immune system and serve to protect the host against insults and diseases [33]. Metchnikoff's early studies pointed to the important contributions of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic microorganisms. Over the past 40 years, considerable evidence has accumulated to support a strong relationship between the functional (physiological) state of the microcirculation, macrophages-phagocytes, natural killer cells, and the reticuloendothelial system (RES) to host defense and resistance to all types of pathogenic microorganisms, trauma, circulatory shock, diverse infections, and combined injuries which affect multiple organ systems [1-3,6,7].

A large body of experimental studies, from our laboratories, has shown that HDFx is protective (to different degrees) against a wide variety of systemic bodily insults ranging from

hemorrhage, trauma (to different organs), endotoxins, a variety of gram-negative and to gram-positive lethal bacteria and fungi (e.g., E.coli, S. enteritidis, C. welchii, mycobacteria, S. aureus, and aspergillous, among others) [26-32], unpublished findings]. Other unique attributes of HDFx are that it can accelerate wound healing, promote tissue regeneration, restore normal microvascular and endothelial cell tone as well as prevent chemoattraction of macrophages, leukocytes, and platelets to the postcapillary venular walls in all tissues, so far investigated (i.e., lung, kidney, heart, intestine, and skeletal muscle) [9,12-14,23-32,34-36] unpublished findings]. In view of these uncanny attributes, we believe that HDFx could be useful in the prevention and treatment of sarcoidosis.

A major thrust for our group is to secure adequate funding to elucidate the complete, complex molecular structure of HDFx and then via genetic engineering to produce large quantities of HDFx for further testing in human subjects and animals to confirm our hypothesis.

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