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Editorial

Why a Stress Protein, HDFx, May be Useful as an Ameliorative in the Treatment of "Cytokine Storms", Depression in Cardiac Hemodynamics and Coagulopathies in Coronavirus Diseases Such as COVID-19, SARS, and MERS

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Introduction

Recently, it has been found that diseases produced by coronaviruses (i.e. COVID-19, SARS, MERS, etc.) present with a growing array of symptoms, including high fevers, coagulopathies, depression in cardiac hemodynamics, and cytokine storms, among other characteristic signs [1-7]. If, however, these four pathophysiological signs could be attenuated, significantly, we believe the course of the coronaviral pathologies could be lessened, particularly in the lungs and probably result in far less deaths, less hospitalization, less hospital costs, and much faster recoveries.

Discovery of a stress protein, in our laboratories, termed "host defense factor x (or HDFx) and its use in a variety of lab animals has led us to find that HDFx can increase survival of rats, mice, rabbits, dogs, and guinea-pigs subjected to circulatory shock, hemorrhage, body trauma, endotoxins and septic shock [8-14]. Physiologically, HDFx is capable of attenuating high fevers, cytokine storms, deep vein thromboses, and cardiac depression induced by several endotoxins [8-15]. HDFx has also been found to lessen depressed cardiac output, increase coronary blood flows, increase transcapillary blood flows and tissue oxygenation induced by different endotoxins, trauma, and funguses (e.g. *Candida*; Aspergillosis) [8,9,11-14].

Discovery and unique physiological properties of HDFx

Our laboratories, for almost 55 years, have been working on novel approaches to develop host defense molecules which can stimulate the innate and adaptive immune systems [12-47]. In this period of time, to the present, we discovered HDFx. We found HDFx to exist not only in rodents, farm animals, and piglets, but in cats, dogs, monkeys and baboons as well [8-15].

About 135 years ago, the Nobelist and father of immunology, Elie Metchnikoff, hypothesized that the body under stressful circumstances would produce powerful immunological stimulants which could act on different arms of the immune system and serve to protect the host against major, dangerous injurious insults, inflammatory conditions, severe wounding, and various diseases [48]. Metchnikoff's early studies pointed to the importance of macrophages and phagocytic leukocytes in natural, innate resistance against pathological micro-organisms [48]. Over the past 65 years, considerable evidence has been brought forth to substantiate a strong relationship between

the functional (physiologic) state of the microcirculation, macrophages, phagocytic leukocytes, natural killer (NK) cells, the reticuloendothelial system (RES) and "pit cells" in the liver to host defense and resistance to hemorrhage, trauma, burns, circulatory shock, combined injuries and pathogenic micro-organisms (i.e. bacteria, funguses, viruses, and rickettsia) [8-15,49-54].

Using Metchnikoff's hypothesis, we posited all bodily insults, including endotoxins, should produce protective factors (i.e. host defense molecules) in all surviving animals, including humans. Indeed, as predicted, we found one such powerful immunostimulant we termed HDFx [8,9,11,12]. This novel stress protein, HDFx, protects/ameliorates (to different degrees), so far, against experimental sublethal hemorrhage, fungal micro-organisms (Candida; Aspergillosis), combined injuries (e.g. hemorrhage plus trauma), centripetal forces, sublethal body trauma, NASH, and bacterial endotoxins [8,9,11,12].

A unique attribute of HDFx is its ability to accelerate wound healing [10]. Most importantly, it has been shown to inhibit release of select cytokines and chemokines, including tumor necrosis factor-alpha (TNF-alpha), IL-beta, IL-8, IFN-gamma and numerous macrophage factors [8]. Clearly, HDFx has the ability to modulate/prevent cytokine storms, at least in experimental animals [8,13,14].

HDFx attenuates thrombus formations and cytokines and dramatically improves microcirculatory-capillary blood flows and tissue oxygenation in two models of deep vein thromboses

Recently, using two different models of deep vein thromboses in rats and *in-vivo* microcirculatory studies, we found that systemic injections of HDFx can ameliorate chronic thrombus formations and thrombus resolutions, and make dramatic improvements in microcirculatory blood flows concomitant with vast improvement in vascular tone [15]. Careful *in-vivo* microscopic examination (up to 6,500x) of the post-capillary venules (16-35 um), of intestinal and skeletal microvasculatures, revealed that sticking of white blood cells and platelets to the endothelial walls, seen after the thrombus formations were dramatically-attenuated after several injections of HDFx [15]. Measurement of release of several inflammatory cytokines (e.g. TNF-alpha; IL-6) from CD4 and CD8 T-lymphocytes, showed markedly attenuated levels after HDFx injections concomitant with decreased endothelial injury [15]. Overall, these findings, most likely are very important in recent histopathologic studies, in seven COVID-19 patients, who demonstrated widespread alveolar capillary thromboses and microangiopathy in their lungs on autopsy [55].

HDFx inhibits endotoxin-induced fevers and cytokine-release and cardiac depression: Relation to sepsis after coronaviruses

Considerable evidence has accumulated since the discovery of SARs, MERS and COVID-19 coronaviruses, that morbidity/mortality from these viruses is a result of several lung pathologies, high fevers and falls in arterial blood pressure with concomitant depression in cardiac hemodynamics; a result of multiple organ failure, most likely caused by sepsis as a result of systemic invasion of the body by numerous bacteria [1-7]. Interestingly, we have found that HDFx can ameliorate/counteract sepsis, and high fevers, induced by numerous endotoxins and bacteria (i.e. many gram-negative and gram-positive), in experimental animals, most likely via its beneficial actions on multiple arms of the immune system, and on the prevention of release of cytokine-induction of high fever via actions on the hypothalamus [14]. HDFx's benefits on the innate immune system (i.e. macrophages; NK cells, liver pit cells, complements, among other cell types) [8-11,13,14] most likely plays a critical role. Although we have not, as yet tested HDFx against coronavirus-infected experimental animals, the actions of HDFx in experimental endotoxin- and bacterial-induced multiple organ failures would suggest HDFx might, indeed, ameliorate/prevent many of the pathological actions of COVID-19, SARS and MERS.

Recently, it has been suggested, on the basis of an analysis of 5 severely ill patients in Shenzen Hospital, China, who had COVID-19 disease, that treatment with convalescent plasma from COVID-19 survivors may have enhanced their ability to survive when combined with other therapeutic measures [56]. In this study, Shen., *et al*. speculate that a passive antibody therapy is the most likely source of the

protection provided by the convalescent plasma therapy. However, since all experimental sublethal stresses we have utilized in experimental animals results in a stimulation/release of HDFx into the plasma, we believe the convalescent plasma obtained from the COVID-19 survivors, via its containment of HDFx, may have played a leading role in the sequelae of events from preventing death.

Conclusions and Future Thoughts

The discovery of a new biologic, HDFx, by our research group, and its unique physiological actions against gram-negative bacteria, gram-positive bacteria, and fungal micro-organisms, as well as against experimental deep vein thromboses, appears to possess several qualities that could prove useful in amelioration/prevention of sepsis and multiple organ failure induced by coronaviruses. HDFx can ameliorate/prevent high fevers induced by endotoxins and gram-negative bacteria and several funguses, when injected into rodents. HDFx can ameliorate cardiac depression induced by the endotoxins, gram-negative bacteria and some funguses in experimental animals. It also can prevent/ameliorate the release of certain cytokines from T-lymphocytes and accelerate wound healing. In view of this combination of beneficial, physiological attributes, we believe HDFx should be very helpful in the prevention/treatment of multiple organ failure and sepsis induced by coronaviruses like COVID-19. If we are correct, then use of synthetic HDFx at the start of the Wuhan, China viral spread might have saved tens of thousands of lives, prevented drastic shutdowns of businesses, prevented shutdowns of houses of worship, and saved tens of thousands of jobs and livelihoods worldwide.

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