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HDFx: A Novel Immunomodulator and Potential Fighter against Cytokine Storms in Viral Flu Infections

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Approximately 85 years ago, the first flu vaccine was made by Jonas Salk and Thomas Francis after it was discovered that viruses (influenza virus types A, B, and C rarely) cause flu [see 1, for review]. It was first utilized to protect the U.S. military forces against the flu in World War II [1]. The most dangerous (virulent) influenza , the 1918 H1N1 Spanish flu, pandemic infected about 5% of the world's population and killed approximately 2% of the world's population. In an attempt to prevent a pandemic, and an increased risk of Guillain-Barre syndrome (i.e., approximately one to nine cases per million doses), 25% of the people, in 1979, in the U.S.A. were given the vaccine [2]. Since that time, influenza vaccines have been vastly improved in design. Highly pathogenic avian influenza viruses of the H5 subtype are a current, serious problem for poultry and human health. Despite the advent of drugs like oseltamivir, and other antiflu therapies, severe influenza still kills tens of thousands in the U.S. A. every year and millions worldwide.

A disturbing trend in antimicrobial-antiviral resistance is the advent of "superbugs" which often complicates the treatment of flu-immunocompromised patients. To this must be added the numerous hospitalizations and increased morbidity from contaminated meats, vegetables, seafoods, and dairy products. Many of the emerging types of avian flus [e.g. H1N1, H2N2, H3N2, A(H10N8)] have a very serious hemorrhagic component to them which complicates effective treatment. Any new, effective treatment against severe flu infections should be able to prevent these types of hemorrhages, particularly in the lungs. Government resources are being overstretched and often remain powerless to combat flu plaque-like assaults.

Numerous pathophysiological responses, in the body, take place after infection by flu viruses [3]. The classical clinical signs are high fevers, coughs, headaches, muscle and joint pain, and severe fatigue. However, when the lungs become severely inflamed, by an overproduction of a host of mediators (primarily by respiratory epithelial cells and alveolar macrophages), i.e., cytokines or chemokines (e.g., interferons, tumor necrosis factor, interleukins, macrophage factors, etc), this gives rise to what is termed a "cytokine storm" [4]. These "cytokine storms" often proceed, unabated, to cause severe tissue damage and hemorrhages, followed by death which is preceded by multiple organ failure, triggered by a spillover of the cytokines and chemokines into the general circulation, particularly in the lungs, kidneys, and cardiovascular system [4-6]. These inflammatory responses are triggered as the infected cells die via apoptosis and necrosis. It must be noted, here, that surgically-operated hospitalized patients are often at great risk for developing influenza infections which result in severe "cytokine storms", particularly among the elderly population. These deadly scenarios have intensified immunological research into devising new therapies that could be utilized to either prevent or stem the course of events leading to massive release of diverse cytokines [7-9]. Our laboratories, for more than 30 years, have been working on a new approach

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to develop host-defense factors that stimulate various arms of the innate and adaptive immune systems. To this end, we have discovered a new host-defense factor we have termed "HDFx", that is a conserved protein found , so far, in rats, mice, guinea-pigs, rabbits, dogs, and subhuman primates [10-14].

Discovery and Unique Characteristics of HDFx

About 135 years ago, Elie Metchnikoff, the father of immunology, hypothesized that the body, under stressful conditions, would manufacture/release molecules that could stimulate various arms of the immune system and serve to protect the host against major injuries, insults and diseases [15]. Metchnikoff's early studies pointed to the importance of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. During these past 30-40 years, a vast body of information and studies , derived from animals and people, have demonstrated a strong relationship between the functional (physiological) state of the microcirculation, macrophages, leukocytes, natural killer (NK) cells,and "pit cells" in the liver to host-defense and resistance to pathogens, trauma, circulatory shock, hemorrhages, infections of diverse types, and sepsis [16-23].

A great many experiments, carried out on thousands of animals, in our laboratories have clearly shown that "HDFx" is protective (to varying degrees) against a variety of systemic bodily insults, ranging from hemorrhage, trauma, combined injuries, endotoxins, a variety of lethal bacteria (e.g., *E.coli, S. enteriditis C.welchii,* among others), fungi (e.g., A. fumagatus, C. albicans), and centripetal forces to septic shock [10-14, 24-28]. A unique attribute of "HDFx" is its ability to protect against "cytokine storms" in animals that are septic or administered several different endotoxins [10, 13, 14, 23, 25, 28, unpublished findings]. "Cytokine storms" are clearly known to be a major cause of lethality in hospitalized patients infected with numerous types of bacteria, viruses, or fungi who become resistant to antibiotic treatment [3, 4, 6]. To our knowledge, no other host-defense factor, except for "HDFx" , can stem the dissemination in the body of cytokines and chemokines in sepsis, at least in experimental animals. Septic shock, as occurs in severe flu infections, accounts for about 10% of all human deaths in the U.S.A. each year, and is a major cause of battlefield deaths and farm animal deaths each year.

"HDFx" has the unique ability to induce a "supercharged effect" in macrophages, NK cells, lymphocytes, Kupffer cells, as well as "pit cells" in the liver, at least in all animals we have investigated to date [10, 13, 14, 23, 25, 28, unpublished data]. But, for this kind of effect to take place, in an expeditious fashion, we believe the microcirculation, in the various critical circulatory regions in the body (i.e., lungs, liver, spleen, heart) must perforce produce optimal blood flows and stem the bleeding that occurs in severe flu infections. Fortunately, we have identified "HDFx" as being a protein molecule that possesses such vasoactive properties that manipulates the microcirculation and curtails bleeding, even in the lungs (e.g., after endotoxin administrations) [10-14, unpublished findings].

Conclusions

The discovery of a new, biologic host-defense protein, "HDFx", may provide a unique way to ameliorate and prevent the "cytokine storms" and hemorrhages seen in severe influenza infections noted in the civilian population, hospitalized patients, as well as in military personnel.

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