ISSN: 2475-6296

Review Article

Journal of Clinical & Experimental Immunology

HDFx, a Natural Biologic is Associated with Elevated DNA Methylation, Reduced DNA Oxidation and Telomerases Down-regulation in Macrophages and Monocytes Derived from Surviving Animals Subjected to Experimental Shock and Burns: Males vs. Females and Relation to Resistance Against Bacterial & Viral Infections

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Submitted: 14 Aug 2020; **Accepted:** 19 Aug 2020; **Published:** 01 Sept 2020

Introduction

Circulatory shock and burns are significant and sustained states of hypoperfusion and lead to decreases in circulating blood volume combined with decreased tissue and organ oxygenation. This hypoperfusion state often causes sepsis resulting in a state of "multiple organ failure" [1-3]. Due to severe body burns, battle field casualties are most susceptible to the latter resulting in numerous loss of lives.

Septic shock is often treated with catecholamines, inotropic agents, vasopressin, and corticosteroids to maintain arterial blood pressure, venous return, cardiac output, and distribution of blood to key peripheral tissues (i.e., brain, heart, lungs, and kidneys). Despite the use of these drugs, this often results in decreased cardiac output, intensified peripheral ischemia, and multiple organ failure, particularly of the heart, kidneys, lungs, and liver, followed by death. With the increased number of hospital-borne infections caused by "superbugs" and coronaviruses, increased numbers of septic shock patients are becoming more and more prevalent.

Another major concern are the large numbers of subjects, who are infected with multiple, very contagious diseases crossing Western country borders, illegally, and not being subjected to proper medical evaluation [for recent reviews, see [4-6]. Many of these subjects have been found to harbor deadly communicable diseases that have, until recently, been eliminated in Western countries, such as drug-resistant tuberculosis, measles, bubonic plague, dengue fever, leprosy, cholera, and smallpox, among others [4-6]. Not only do such communicable diseases pose high risks for contracting corona viruses, but increase risk for cardiovascular diseases [7].

A major concern in the septic shock and coronaviral patients are the rapid pathological changes that take place in the postcapillary venules, tiny microscopic blood vessels usually only 20-40 um wide [8, 9]. Blood pools n these microscopic vessels, particularly in the lungs, due to loss of vasomotor tone, increased adherence of leukocytes, monocytes, and macrophages to the inner endothelial cells of the venules followed by release of numerous cytokines and chemokines, often leading to tears in the endothelial cell walls and elevated body temperature. These events give rise to what is termed a "cytokine storm", resulting in rapid morbidity and mortality. Unless these inflammatory reactions can be curtailed very rapidly, the patient will not survive. Knowing these events, first- hand, in animals and patients, we have been working for more than 50 years on potential new countermeasures [10-56]. Severe burns with major skin denudation poses extraordinary problems for both the patient and the ER physician [57, 58]. For many years, a search has gone-on for drugs/substances that could accelerate wound healing in burn victims.

Roles of Estrogenic Hormones in Resistance of Women vs. Men in Resistance to Disease and Circulatory Control Mechanisms

A major problem in these studies, is that, it is well-known that female mammals, including women, are more resistant to loss of

blood volume, trauma, endotoxins, and diseases in general [59, 60]. Why this is so, is not known for sure, but is thought to be attributed to the presence of estrogenic hormones, as when menopause is reached, there appears to be little difference in resistance of men vs. women of similar ages . Approximately, 45 years ago, using male and female rats (young and old), we reported that resistance to circulatory stress reactions was associated with a heightened elevation of the phagocytic prowess of macrophages in the liver and spleen; young, but mature female animals showed much greater abilities to phagocytize foreign particulate matter than males of similar age [33-35]. Administration of estrogenic hormones to old female or male animals resulted in the stimulation of phagocytic indices in liver and splenic macrophages. The presence of estrogenic hormones in female mammals and women clearly control regulation of transcapillary blood flows, distribution and vasomotor tone [33, 35, 46, 51, 53, 61-65]. Recently, we have found that this estrogenic stimulation (endogenously or exogenously) appeared to be associated with the serum levels of ionized magnesium and a new stress protein, HDFx [unpublished findings [66, 67].

Discovery and Attributes of HDFx, an Endogenous Stress Protein

Approximately 140 years ago, Elie Metchnikoff, the father of immunology, using injury of starfish, hypothesized that the body under stressful and injurious circumstances would produce powerful immunological stimulants which could act on different parts of the immune system and serve to protect the host against major, dangerous insults , inflammatory conditions , wounding, and diverse diseases [68]. Metchnikoff's early studies pointed to the potential importance of macrophages and phagocytic leukocytes in natural innate) resistance against pathogenic microorganisms. For more than 65 years, studies initiated by Zweifach and co-workers, have shown , through a great deal of work, a strong support for the idea that there is a physiological relationship between the microcirculation, macrophages, phagocytic leukocytes, alveolar macrophages, splenic macrophages, natural killer (NK) cells, and "pit" cells in the liver to host defense [1, 2, 10, 48, 52-54, 69-71].

Using Metchnikoff's hypothesis, we posited all bodily insults, including endotoxins, gram-positive bacteria, funguses, parasites, hemorrhage, trauma, burns, etc. should produce protective factors (i.e., host defense molecules) in all surviving animals, including humans. Indeed, as predicted, we found one such powerful immune-stimulant we termed HDFx [72, 73]. This novel stress protein, HDFx, protects/ameliorates (to different degrees), so far, against experimental sub-lethal hemorrhage, trauma, diverse endotoxins, fungal micro-organisms (*Candida; Aspergillosis), combined* injuries (e.g., hemorrhage plus trauma; burns plus trauma), centripetal forces, experimental deep vein thromboses, endotoxin-induced fevers, NASH, and experimental pulmonary hypertension, among others [unpublished findings, 72-82].

A unique ability of HDFx is that it accelerates wound healing and inhibits/ameliorates the release of certain dangerous cytokines reducing the degrees of "cytokine storms" [83].

HDFx Ameliorates "Cytokine Storms", Depression in Cardiac Hemodynamics, and Coagulopathies: Sexual Differences

Recently, we have reported that HDFx can attenuate thrombus formations and "deep vein thromboses" in experimental animals, and reduce endotoxin-induced fevers, reduce diverse cytokine releases, as well as modulate depression in cardiac hemodynamics induced by diverse endotoxins [80, 81]. All of these beneficial results of HDFx suggested that there was a substantial influence/interaction with sex hormones, as the female animals demonstrated greater beneficial responses, with HDFx pretreatment, when compared to male animals of the same age [84].

Using LD_{50} and LD_{80} rodent models of trauma and scalding, and removing circulating and peritoneal macrophages and monocytes, with specific assays, we have found animals pretreated with HDFx exhibited less DNA oxidation, 6-8x increases in DNA methylation and post-translational histone alterations in the extirpated macrophages/monocytes taken from the survivors (e.g., 14-21 days with trauma survivors; 48-72 hr after burn survivors) [85, 86]. The significantly greater effects of HDFx were noted in the aged-matched female rodent animals (i.e., Chi-square analysis, $P<0.01$) [86].

Using these similar rodent models, with the diverse macrophages and monocytes, harvested from the HDFx-treated survivors, we found reduced DNA oxidation, and that telomerase activities were down-regulated from 15-25% in the surviving cells [86]. Female animals (age-matched) demonstrated greater beneficial responses [86]. We, thus, believe these preliminary studies, when combined with our recent publications, provide presumptive evidence that epigenesis can be modulated by HDFx.

HDFx: Macrophages, Monocytes, and Epigenesis

During the past decade, epigenesis has emerged in these cell types demonstrating DNA methylation, alterations in histones, posttranslational histone processing, and telomere alterations [for recent review see 87]. In view of our evolving research, the potential importance of HDFx has emerged in relation to host resistance. We, thus, hypothesized that these immune cell types should demonstrate upregulation of DNA methylation, histone alterations, less DNA oxidation, translational/phenotype changes in macrophages, monocytes and natural killer (NK) cells taken from animals which survive diverse forms of sepsis and circulatory shock which would be related to the amounts of HDFx generated by the circulatory stresses [85, 86]. Due to differences in susceptibilities of female vs. male mammals, and our previous studies, on the reticuloendothelial system and microcirculatory control mechanisms, we predicted that when subjected to sub-lethal stresses, the female animals, including women, would

produce higher contents of HDFx in macrophages/monocytes extracted from the survivors than the comparable cells from males/men. So far, our studies bear this idea out, at least in animals [see above references].

We believe that our experimental epigenetic studies, with HDFx, underlie some of the cogent reasons for why HDFx results in increased survival and increased resistance to sublethal stresses, including coronaviruses, some contagious diseases, and most-likely has played a major role as to why convalescent plasma, from survivors infected with COVID-19, given to victims with COVID-19 has induced survival, not only antibodies.

Conclusions and Future Thoughts

A very surprising number of hospitalized patients with non-infectious, and infections, induced by bacteria, viruses, and fungal micro-organisms, become infected with "superbugs" where no antibiotic/antibiotics can effectively improve hope for survival. Our group has discovered an endogenously- found host-defense factor, HDFx, in all mammals, so far investigated, including sub-human primates, which protects/ameliorates against sub-lethal hemorrhage, intestinal ischemic shock, traumatic injuries, endotoxins, several gram-negative bacteria and funguses, combined injuries, centripetal forces, and burns. We have identified the major sources of HDFx, namely macrophages and NK cells. HDFx seems to alter macrophage and monocyte phenotypes indicated by exhibition of DNA methylation, histone deacetylation, histone methylation, telomerase-downregulation, and significant increases in cell sizes [85]. Since young, mature female animals seem to possess larger quantities of HDFx in their macrophages and monocytes than male animals of similar ages, we believe this may help to explain why women up until menopause show greater resistance to atherogenesis and cardiovascular diseases than men of similar age, but demonstrate no significant difference after menopause. It is our belief that the epigenetic alterations produced by HDFx are major factors in normal body defense and natural resistance to deadly viral diseases such as influenza and coronaviruses like COVID-19, SARS, and MERS.

Acknowledgements

Over the years, our HDFx research has been supported, in part, by research grants from The National Heart, Lung and Blood Institute, The Institute on Drug Abuse, and unrestricted grants-in-aid from several pharmaceutical companies. Early-on, much of our initial studies were carried out at The New York University School of Medicine and The Albert Einstein College of Medicine where Dr. Altura was Assistant to Professor of Anesthesiology and Associate Director of Research. Dr. Altura also carried out some of the initial studies in laboratories in The New York City Medical Examiner's where he was also an Associate. Some of our research efforts have also been supported by a research grant from The Bio-Defense Laboratories at The U.S. Naval Hospital, Silver Springs, MD.

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