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Review Article

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HDFx and Methylated DNA; With Histones Upregulated in Macrophages/ Monocytes Derived From Animal Survivors Subjected to Traumatic, Endotoxin, and Hemorrhagic Shock: Importance of Epigenesis and Potential Reasons for Resistance to Bacterial, Fungal and Viral Infections

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Introduction

Each year approximately 60,000 people die from hemorrhagic shock in the U.S.A. with about two million deaths worldwide [1]. Deaths from traumatic shock, worldwide, has been difficult to estimate, due to battles/wars in many countries, but is thought to be more than two million victims/year [1]. Many reasons for these large numbers of deaths are known [for review, see1], for example, inadequate therapeutic measures, unavailability of adequate blood/ plasma/fluid replacement, seeing the patient too late, and unavailability of trained ER personnel, among the major reasons [for recent review, see1]. Another predominant reason for large numbers of hemorrhagic and traumatic shock deaths is the risk of sepsis in many of these victims, resulting in septic shock having mortalities in excess of 40- 75%, depending upon locality, with the lower numbers in the U.S.A. Lastly, and most important is "natural resistance of the body to infectious microorganisms" (i.e, bacteria, funguses, viruses, parasitic organisms, etc.). What is responsible for "natural resistance" has been studied for more than 150 years. We know that the "innate" and "adaptive" immune systems are key elements in defense against infectious microorganisms [2, 3]. But, which elements of these systems make-up major aspects of "resistance" and "host defense" still remains to be worked out. Using starfish, more than 140 years ago, the pioneer/father of immunology, and Nobel Laureate, Elie Metchnikoff, believed that white blood cells and macrophages were key to host-defense [4]. He also believed the body develops molecules/substances, which are key to resistance to infectious microorganisms [4].

Discovery of HDFx

A focus of our research for more than 50 years has been to derive unique countermeasures for the treatment of hemorrhagic, traumatic and septic shock [5-14]. Several years ago, we discovered a unique host –defense protein, in the blood of animals subjected to sublethal stresses such as hemorrhage, trauma, sepsis, centripetal forces, and combined injuries, among other stresses [15, 16]. This unique protein we named host defense factor-x (i.e., HDFx) [15]. We found this unique molecule also to possess the ability to accelerate wound healing [17]. Most of HDFx is derived from macrophages and natural killer cells (NK cells) [15].

HDFx, Macrophages, Monocytes, NK Cells, and Epigenesis

Macrophages, monocytes, and NK cells are major players in inflammatory diseases, atherosclerosis, shock and sepsis [1, 2]. Over the past 10 years, epigenesis has emerged in these cell types demonstrating DNA methylation, alterations in histones and posttranslational histone processing [for recent review, see 18]. In view of the potential importance of synthesis and release of HDFx, to "resistance" we hypothesized that these immune cell types should demonstrate upregulation of DNA methylation, histone alterations and translational/phenotypic changes in macrophages, monocytes and NK cells taken from animals, which survive diverse forms of lethal hemorrhage, trauma, and septic shock.

Harvesting of HDFx, Macrophages & Monocytes from Animals, which Survive Sublethal, Traumatic, Hemorrhagic and Endotoxin Shock: DNA Methylation, Upregulation of Histone Alterations, Phenotypic Alterations and Relationship to Epigenetics

Using LD_{50} and LD_{85} rodent models of hemorrhagic, traumatic and endotoxin shock (i.e., *E. coli; S. enteritidis* gram-negative endotoxins), and removing circulating and peritoneal macrophages and monocytes, and specific assays, we have found a 6-8x increase

in DNA methylation and posttranslational histone modifications in survivors , at 14-21 days post- shock, clear signs of epigenetic modifications [15-19].

Examination of these cells, under the microscope, demonstrated increased cell sizes; 10-12 % in the macrophages and 6-9% in the monocytes [19]. There was a indirect relationship between the amount of HDFx in the cells to the increases in methylated DNA, posttranslational histone modifications, and cell sizes [19]. In addition, we found a direct relationship to the plasma concentrations of tumor necrosis factor-alpha (TNF-alpha), IFN-gamma, IL-1beta, and IL-6, cytokines associated with immune cell epigenesis [for review, see 18]. Histone modifying enzymes can alter macrophage phenotypes [18]. For example, key in these transformations are histone acetyltransferases and histone deacetylases (HDACs). Histone acetylation is linked to transcriptional activity [for recent review, see 18] while histone deacetylation is linked to transcriptional repression [18]. We have found HDFx upregulation, in rat macrophages, to be associated with both enzymes [19]. Histone methylation has been linked to both transcriptional activation and repression [18]. Our preliminary studies have shown upregulation of histone methylation in macrophages obtained from animals, which survive hemorrhagic, endotoxin and traumatic shock at 14-21 days after injury [19].

We believe that these epigenetic preliminary results, from our laboratories, underlie reasons for why HDFx treatment and prophylactic administration of HDFx results in increased survival and resistance to sublethal stresses after induction of diverse forms of circulatory shock, trauma, heart disease, sudden-death ischemic heart disease, pulmonary hypertension, and stroke, among other lethal cardiovascular stresses in diverse experimental mammalian species.

Conclusions and Future Thoughts

Most of hospital- induced infections in humans are caused by gram-negative bacteria while many, in our environments, are caused by viruses, including those by coronaviruses. These “superbug”-induced infections, as well those caused by many funguses, have no vaccines available and little in the way of reliable countermeasures. We have discovered an endogenous host-defense protein (i.e., HDFx) in all mammals, so far investigated, including subhuman primates, which protects/ameliorates against sub lethal hemorrhage, traumatic injuries, endotoxins, gram-negative bacteria, combined injuries, and centripetal forces. We have found the major cellular sources of HDFx, namely, macrophages, NK cells and monocytes. HDFx appears to be able to alter phenotypes in these innate cell types after exposure to these various sublethal stresses via epigenetic changes, most likely via DNA methylation, histone deacetylation and histone methylation. We believe these epigenetic alterations induced by HDFx may be major factors in normal bodily- host defense and natural resistance to deadly viruses such as influenzas and coronaviruses like COVID-19, SARS and MERS. It is our hope that when the complete molecular structure of HDFx is identified and tested it will be able to prevent infections from deadly diseases and will act as a secure ameliorative treatment for infections caused by deadly viruses such as those produced by influenzas and coronaviruses.

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