

HDFx and Transferal of Plasma from Animals that Survive Lethal Hemorrhage, Bowel Ischemic Shock, Endotoxins, Centripetal Forces or Body Trauma to Naïve Animals Induces Cross-Resistance to these Various Experimental Forms of Injury and Trauma: Importance of Macrophages, NK Cells and Relevance to Design of Molecules to Treat/Ameliorate Effects of Corona Viral Diseases

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Introduction

Various, new viral diseases have been emerging on our planet for more than 100 years. Three of these, termed coronal viral diseases started to emerge in 2003 with SARS, followed a few years later by MERS and most recently by COVID-19 from Wuhan, China. Although the former two are known to have emerged in bats, the host for COVID-19 has yet to be identified, although it is thought also to have arisen from bats. This will be very difficult to track-down as there are more than 1,400 species of bats.

Discovery of HDFx and its protective properties including regenerative attributes

In 1957, Zweifach and Thomas reported that rats adapted to endotoxin shock became cross-tolerant to hemorrhagic and traumatic shock [1].

Working with anesthetized mice, rats and guinea-pigs more than 50 years ago, our laboratories showed that treatment of these diverse rodents with various colloids, lipids and peptides made these animals tolerant to sublethal hemorrhage, sublethal bowel ischemic shock, sublethal whole body trauma, sublethal centripetal forces, and endotoxins [2-24]. In many cases, using these diverse reticuloendothelial cell (REC) stimulants, we found that the plasma taken from the surviving animals often made naïve rodent animals cross-tolerant to these sublethal forms of systemic stresses [4,12,16-18,23,24]. Further, extensive investigations, on thousands of animals, revealed that macrophages and natural killer cells (NK cells) of the innate immune system, harvested from the survivors, produced quantities of a 35-40 KD protein [25] we termed "host defense factor x (i.e. HDFx) [22-25]"; the greater the initial degree of stress, the greater the harvested amount of HDFx in the surviving animals. Surprisingly, CD4 and CD8 T-lymphocytes which were found to release massive amounts of cytokines, in the naïve -traumatized and shocked animals, showed markedly reduced -released amounts of the cytokines (i.e., reduced levels of TNF-alpha, interleukins) [24-27].

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In view of these early findings, we decided to investigate whether crude extracts of HDFx would protect rodents against lung inflammations and pulmonary damage induced by two different fungi (i.e. aspergillosis, *Candida*) [24,25,27]. Not surprisingly, the answer was that HDFx was, indeed, ameliorative against the fungal lung-induced infections [24-27]. Pretreatment of the animals with HDFx was found to protect against the clots, endothelial wall sticking of leukocytes and monocytes, and reductions of pulmonary capillary blood flows seen with injection of the fungal toxins [24-27]. Most importantly, HDFx can prevent/ameliorate “cytokine storms”, at least in experimental animals, induced by fungal toxins and endotoxins [24,27-29].

In addition, we noted that HDFx seemed to possess healing/regenerative tissue properties [30]. Further studies by our group found that at least two forms of experimental hepatic cancers were ameliorated with treatment of the animals with HDFx [25]. Moreover, HDFx appears to reduce the symptoms of nonalcoholic fatty liver disease (NASH), at least in experimental animals [31].

HDFx possesses anti-inflammatory properties

As indicated above, we found that HDFx can prevent intravascular clots, endothelial cell wall sticking of leukocytes, monocytes and platelets induced by administration of endotoxins (i.e. *E. coli*, *S. enteritidis*) and fungal toxins (i.e. aspergillosis, *Candida*) in pulmonary, intestinal, and cerebral postcapillary venules, as observed by direct *in-vivo* TV microscopic observations (at magnifications up to 6,500x) [25,27]. In addition, when these microscopic blood vessels were challenged with bradykinin or histamine (agents that increase capillary permeability), prior injections of HDFx prevented or ameliorated these injurious local inflammatory responses [27].

Cellular origin of HDFx: Macrophages and NK cells

Through numerous experiments on rodents, rabbits, dogs and sub-human primates, we have identified the major sources of HDFx: the macrophages and NK cells. Neither monocytes, leukocytes, platelets, Kupffer cells nor “pit cells” appear to possess the biochemical machinery to generate HDFx [25]. Although we have not as yet identified the precise molecular signal (s) that set the production/release of HDFx into motion, in the presence of bacterial, fungal or viral agencies, we have found out that activation of several PKC isozymes, mitogen-activated protein kinases, proto-oncogenes, and nuclear factor-kB are required [32].

Do injections of plasma from COVID-19 survivors into human subjects induce resistance to the coronavirus in part due to the production of HDFx?

A few recent studies performed in Wuhan, China, have suggested that antibodies from plasma, produced in survivors of infection with COVID-19, when given to human volunteers, seem to enhance resistance to the morbidity and mortality effects of the coronavirus [33]. In view of our findings on diverse mammals, we believe one must posit the likelihood that the plasma obtained from the COVID-19 survivors, either contained elevated levels of HDFx or induced HDFx in the human survivors. Experiments on these people, that survive infection with COVID-19 should, therefore, be initiated.

Conclusion and Future Thoughts

Through numerous studies on mice, rats, guinea-pigs, rabbits, dogs, pigs, and sub-human primates, which were initiated more than 25 years ago, our laboratories have reported that survivors of these animals, when subjected to diverse forms of sub-lethal trauma, bacterial microorganisms, fungal microorganisms, circulatory shock or centripetal forces yield a 35 - 40 kD protein that can induce protection (in naïve animals) against these diverse forms of lethal injury. Extracts of HDFx can accelerate wound healing, possess anti-inflammatory properties, and increase transcapillary blood flows and, thus, prevent transudation of blood -formed elements into parenchymal tissues (e.g. lungs). Use of HDFx in high-risk patients could eventuate in markedly reduced hospitalizations, reduced hospital costs and reduction in coronal viral-induced infections and deaths worldwide. With adequate funding, we hope to elucidate the complete chemical structure of HDFx, a possibility long-overdue.

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