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Mini Review

HDFx: A Biologic Ameliorates Deep Vein Thrombosis in Two Rodent Animal Models: In-Vivo Microcirculatory Studies and Relation to Human DVT

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INTRODUCTION

Deep vein thrombosis (DVT) is a prevalent syndrome, particularly in the aged, which often leads to significant morbidity and mortality. It also leads to costly, extended hospitalization. Pharmacologic manipulation and anti-coagulant drugs are the standard approaches to treatment of DVT patients. There are more than one million cases of DVT each year in the USA. Despite many decades of research, the precise vascular mechanisms still remain to be revealed [1]. According to recent observations, by numerous investigators, DVT is a multifactorial syndrome, which has a variety of underlying causes: genetics, endothelial cell injury (due to injury, trauma, and /or surgery), hypercoagulability (due to cancer, pregnancy, protein mutations), and venous stasis [1]. Although most DVTs resolve by themselves, many do not, and leave fibrotic alterations. These fibrotic changes in venous vessels often result in post-thrombotic syndromes, leading to chronic pain, leg-cramping, limb edema, stasis, and venous ulcerations [2,3]. More than 150 years ago, the great pathologist, Rudolph Virchow, was the first to establish the principles of thrombogenesis in humans [4,5].

In-vivo animal models remain the best way to investigate new, beneficial therapies for DVT [1]. Recently, three of us discovered a novel biologic molecule which according to in-vivo TV -image quantitative microscopy performed on intestinal, cutaneous, skeletal muscle and cerebral circulations (at magnifications approaching 6,500x-normal), in our laboratories, appeared to exhibit the ability to maintain patent blood flows in arterioles, metarterioles and post-capillary venules under hemorrhagic shock, intestinal ischemic shock, diverse endotoxins, and sublethal trauma [6,7]. We termed this biologic molecule host defense factor -x or "HDFx" [6].

Discovery of HDFx and Its Protective, Anti-Inflammatory and Regenerative Properties

Working with mice, rats, guinea-pigs, and rabbits more than 50 years ago, one of us showed that treatment of these diverse animals with various colloids, lipids, and special peptides made these mammals tolerant to sublethal hemorrhage, sublethal bowel ischemic shock, sublethal body trauma, sublethal centripetal forces, and diverse endotoxins [8-32]. In addition, in-vivo examination of the microcirculatory beds of intestinal, cutaneous, skeletal muscle and cerebral cortex , in these injured animals, revealed that most of these protective treatments resulted in non-sticking of monocytes, platelets, phagocytic leukocytes, and macrophages to the inner endothelial walls of the post-capillary venules, thus producing smooth surfaces to result in near-normal transcapillary blood flows. Blood flows through precapillary sphincters (micro vessels only 4-6 um in lumen sizes) were often near-normal. Further extensive investigations

on thousands of animals revealed that the surviving animals showed a release of a 35-40 kD protein, HDFx, into the plasma, which appeared to come from macrophages and natural killer (NK) cells [6]; the greater the stressful incident, the greater the amounts of HDFx released by the macrophages and NK cells [6]. Surprisingly, CD4 and CD8 T-lymphocytes which released cytokines (e.g., TNF-alpha, interleukins, etc), during the injurious and sublethal stresses, were attenuated by HDFx [6,7].

In addition, HDFx accelerated wound healing in peripheral injured tissues of the stressed animals [33].

In view of these unique findings we decided to investigate whether HDFx would ameliorate or prevent DVT in two rodent models [34].

HDFx in Experimental Therapy of DVT in Rodent Models: Direct In-Vivo Observations on the Microcirculation

Using mice and rats, we employed mesenteric, femoral and inferior vena cava (IVC) blood vessels to induce thromboses [34]. We often preferred permanent occlusion of the IVC with the sacrifice of all side branches distal to the left renal vein [34]. This procedure has a profound effect on venous flow; verified by measuring venous pressure [34]. This model demonstrates a correlation between venous stasis, increased release of tissue factor, and augmented coagulation inside the vein. Since this model has a high survival rate [1], it lends itself to measurement of chronic thrombus formations and thrombus resolution. We utilized a second model of thrombus formation perfected by Vogel et al [35]. In the latter model, two ligatures are placed around the posterior IVC and all side branches closed off distal to the left renal vein and proximal to the bifurcation are ligated. Then various amounts of thrombin (100-2,000 ug/kg) are injected inside the right femoral vein to induce thrombus formation.

Employing both of the above rodent models we found that the systemic injections of purified extracts of HDFx (i.e., two doses/d for seven days) resulted in dramatic reductions in thrombus size formations (i.e., 60-75%) and dramatic improvement in stasis, improvement in microcirculatory blood flows, vast improvement in vascular tone and vascular reactivity, as measured quantitatively, in-vivo, with an image-splitting TV recording system at microscopic magnifications approaching 6,500x-normal [34]. This TV microscope recording system, partly pioneered by our group, allows one to quantitatively measure lumen sizes , micro vessel diameters and lumens, sizes of micro-vascular smooth muscle cells and sizes of endothelial cells on arterioles (18-35 um in size), metarterioles (14-18 um in size) , muscular venules (40-70um in size), and precapillary sphincters (3-6 um in size) [36-42].

Careful in-vivo microscopic examination of the post-capillary venules (16-35 um in size) revealed that sticking of white blood cells and platelets to the endothelial walls, seen after the thrombi formations (with the above rodent models), were dramatically-attenuated (65-75%) using treatment with HDFx [34]. In addition, using our high-powered in-vivo microscopic observations, we clearly noticed there was a reduction in release of circulating and released inflammatory cytokines usually found in thromboses such as TNF-alpha, IL-6, chemokines, and other inflammatory mediators [34], which we have found in animal models of sublethal hemorrhage, intestinal ischemia, body trauma, and bacterial infections [6].

CONCLUSIONS AND FUTURE THOUGHTS

DVT is a growing concern, particularly among the elderly. Many anti-thrombotic and anti-coagulant drugs are currently in use to treat and prevent DVT. However, most of these drugs often do not relieve patients of complications which arise from DVT such as swelling, erythema, renovascular complications, tissue necroses, limb loss, acute respiratory distress syndrome (ARDS), pulmonary hypertension, cardiovascular collapse, thromboembolism, and subsequent death. We have found a new biologic in every mammal so far investigated that possesses a variety of unique host defense properties, including the ability to accelerate wound healing. A preliminary in-vivo microcirculatory study with HDFx, so far, indicates that it has the ability to attenuate thrombotic formations using two different rodent animal models. We believe it would be propitious to examine the prophylactic usefulness of HDFx in DVT patients.

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