Human Cartilage Glycoprotein 39 (HC-gp39) sits on the Nucleus of the Human Life: Dislodging Sudden Cardiac Death. Dedicated to the Memory of Nwakaibie Gladstone N. OFODILE

Peer review status:
No

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Article ID: WMC004908
Article Type: My opinion
Submitted on: 05-Jun-2015, 01:15:41 PM GMT   Published on: 17-Jun-2015, 06:01:00 AM GMT
Article URL: http://www.webmedcentral.com/article_view/4908
Subject Categories: PATHOLOGY
Keywords: Innate Immunity; Inflammation; Cell Death; Heart; Hormesis

How to cite the article: Ofodile O. Human Cartilage Glycoprotein 39 (HC-gp39) sits on the Nucleus of the Human Life: Dislodging Sudden Cardiac Death. Dedicated to the Memory of Nwakaibie Gladstone N. OFODILE. WebmedCentral PATHOLOGY 2015;6(6):WMC004908

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Source(s) of Funding:
The work was partly supported by the Charite' Universitaetsmedizin Berlin: I could use tools and material in the Medical Library: Charite Virchow Campus, during the preparation of this manuscript.

Competing Interests:
There is none
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Abstract

There is now abundant evidence that atherosclerosis is a chronic inflammatory disease that develops as a consequence of entrapment of oxidized low-density lipoprotein (LDL) in the arterial intima and its interaction with components of both innate and adaptive immunity. Emerging body of evidence supports the notion that a plethora of inflammatory molecules interact with the complement, oxidized and enzymatic modified LDL, working in concert, with the Toll-like receptor proteins, drive the pathogenesis of atherosclerotic lesions. The entrapment of oxidized low density lipoprotein (LDL) in the arterial intima is intimately associated with the accumulation of oxidized and ubiquitinated proteins, and, involving concomitantly the inhibition ubiquitin proteosome pathway in the heart. Therefore, this calls inevitably for a process that can mediate the elimination of misfolded, polyubiquinated protein aggregate during ischemia. This, thus, suggests that regulated autophagy should be vital to Human Life. A large body of data has implicated HC-gp39 in the pathogenesis of cerebrovascular and cardiovascular diseases and related conditions. In this continuum, recently emerging data suggest that HC-gp39 might interact with both low density lipoprotein(LDL) and high density lipoprotein (HDL) and Lipoprotein (a), and in a complex chain of events profoundly impact both thromboembolic stroke and myocardial infarction. In this context, large quantities of HC-gp39 are found in human atherosclerotic plaques. As disclosed by a plethora of laboratories, HC-gp39 serum levels directly correlate with cardiovascular morbidity and mortality , and all-cause mortality, unstable angina, left ventricular dysfunction, propensity to diabetes and its complications, hypertension, obesity and several types of cancer. These make a case indicating that defining the mechanisms by which HC-gp39 exerts its biological effects will significantly help in the development of targeted approaches to counteract these diseases.

Introduction

Human Cartilage Glycoprotein 39 (HC-gp39) (also named chitinase-3-like-1(CHI3L1) and YKL-40 is a potent inflammation and differentiation marker, and a regulator of adaptive and innate immunity. It is a C-Lectin that binds heparin-and collagen and chitin. It is phylogenetically highly conserved glycoprotein and a member of mammalian chitinase -like proteins, but has no enzymatic activity (1). HC-gp39 activity has been reported to be involved in a range of cardiovascular and cerebrovascular events (2-6). In this continuum, converging evidence derived from different laboratories implicates HC-gp39 in the pathogenesis of a battery of human disorders characterized by inflammation, oxidant tissue damage, and fibrosis, and further, revealed that high levels of HC-gp39 strongly correlates with exacerbation and the severity of disease processes. This indicates that HC-gp39 is present in the concerned tissues and organs and, participates critically in the disease pathogenesis. In this context, a large body of data has come to indicate that an adverse relationship links high serum levels of HC-gp 39, obesity, metabolic and physiologic response of different structure of the heart and blood vessels. This points to a special connection and/or interaction between HC-gp39 and the Heart. In spite of the repeated association of the activity of HC-gp39 with a range of human disorders, the nature of the cellular receptors critically underlying the biological effects of HC-gp39 is almost totally unknown, and , more enigmatic, the mechanism(s) by which HC-gp39 exerts its biological effects poorly defined.: However, based on presently available data, we are tempted to suggest that HC-gp39, like mast cells and dendritic cells might be equipped with intracellular pattern recognition receptors such as Toll-like receptor and/or Nod1 that on activation by exogenous danger signals like M-TriDAP( a degradation product of bacterial peptidoglycan ) induces a release of
proinflammatory mediators, in the process of exerting host immune defense against microbes , Enoksson M. et al., 2011 (7). Second: Human Cartilage Glycoprotein 39(HC-gp39) might equally be working in concert with multiple receptors and/or receptors with multiple or broad ligand-binding specificity, consistent with earlier notion of Janeway CA (8) with regard to macrophage-like cells (6 ). Now after scrutiny of the seminal work of Annaliese Recklies et al.(2002, 2004), providing evidence for the major intracellular pathway(s) implicated in HC-gp39 action, and, reading penvously, the exceptionally, eloquent studies of Mizoguchi A/ Mizoguchi E on the role of HC-gp39 in the pathogenesis of inflammatory bowel disease (2006-2008), and merging the information into a working body, with particular attention to the havoc intimately associated with high serum levels of HC-gp39, a Hypothesis was formulated, in October 2010 (Okom Ofodile 2010 AJPP Abstract): suggesting six mechanisms by which HC-gp39 mediates its biological effects, whereby the ability of HC-gp39 to impact on molecular and biochemical cascades designed to regulate and/or modulate Cell Death Pathway ( Apoptosis and Autophagy) and induce the activation, upregulation and sustaining of the process of Angiogenesis might represent the central component of these mechanisms (Okom Ofodile). In this context, HC-gp39 stimulates migration, and adhesion of endothelial cells and vascular smooth muscle cells, thereby pointing without question to important role for a mammalian chitinase-like protein, which they used to call Human Cartilage Glycoprotein 39 in angiogenesis (9). The mechanisms by which HC-gp39 exerts its biological effects may include: Modulation of autophagy program; Direct and/or indirect activation of the complement; Triggering ROS generation (this may result in development of oxidative stress : a status that could eventually lead to vicious circle of tissue damage as it impinges upon mitochondrial dysfunction, excitotoxicity, lipid oxidation and inflammation); ; Perturbation of TRIF regulatory function ( TRIF is an adapter protein that transduces signal from Toll-like receptors 4(TLR4) and TLR3, permits the induction of many cytokines including TypeI interferon receptor): leading to significant amplification of the inflammatory environment; Triggering a chain of events that will culminate in what they used to describe as accelerated hyperimmunity of autoimmunity as evidenced in the case of Rheumatoid Arthritis, and Triggering the induction of “ Autotoxicity”- a phenomenological process( leading to self-sustained vicious circle of tissue damage) first described by McGeer PL/ McGeer EG. A process driven almost solely by the major components of the innate arm of the immune system, Toll-like receptors and complement system. Autophagy ( a Greek word meaning to eat oneself), is an adaptive and essential process required for cellular homeostasis, which involves a lysosomal degradation pathway for cellular constituents and organelles. Defective autophagy correlates with diseases such as neurodegenerative disorders, cancer, metabolic and cardiovascular disorders, and inflammatory bowel disease (10-15). High plasma levels of HC-gp39 may contribute in significant ways to modulation, and concomitantly, perturbation of autophagy process. In this context, and because of the special nature of the heart, defective autophagy may be profoundly detrimental: defective autophagy will lead to perturbation of mitochondrial physiology-involving the disruption of Calcium homeostasis and then resulting in exaggerated production of ROS (reactive oxygen species). This may impact markedly on Gap junction (GP) stability leading possibly to Gap junctional uncoupling and eventually to sudden cardiac death. Further, HC-gp39 is an established antiapoptotic protein, and, if this same glycoprotein is also endowed with the ability to impact on autophagy execution machinery, there is and should be ample possibility that high plasma levels of HC-gp39 may profoundly disrupt the process of Efferocytosis. Defective efferocytosis may markedly exacerbate advanced atherosclerotic pathology, and, if not contained, may eventually lead to the death of the myocardium:-sudden cardiac death. Furthermore, exaggerated quantities of HC-gp39may interact, and, interact inappropriately with Fibroblast Growth Factor 23, and, thus, in turn, impact on the activity of Klotho protein resulting in modulation of a plethora of events involved in in the complex process of ageing, particularly via aberrant tissue remodeling. This event may bear enormous relevance to cardiovascular health and ischemic cerebrovascular events, as well. Collectively, these considerations suggest that HC-gp39 is critical for evaluating the strategies for the development of antiinflammatory, antioxidant and immunosuppressive agents for the treatment of cardiovascular and closely related diseases. Additionally, these pieces of notions provide provisional evidence that the innate immune system is activated in human heart failure, thus, raising the interesting possibility that this pathway may represent a target for the development of novel heart failure therapeutics. This opinion article strongly suggests that HC-gp39 may interact with lipids and lipoproteins, and in this context, impact profoundly upon both ischemic cerebrovascular disease and myocardial infarction. In this continuum, emerging discoveries led us to suggest that autophagy, human cartilage
glycoprotein 39, a macrophage-derived protein, and lipid metabolism may have co-evolved to share common regulatory elements, and whereby autophagy has emerged as an important mechanism intimately involved in the regulation of both the activation of HC-gp39 and that of the lipid metabolism. This notion, in turn, led us to propound that exaggerated quantities of HC-gp39 may, very possibly, link metabolic syndrome condition to ischemic stroke and myocardial infarction. Hence increased studies and fuller understanding of the nature of the signaling networks underpinning the crosstalk between HC-gp39, inflammatory cascades and autophagic program, on one side, and fuller understanding of the regulatory network governing HC-gp39 expression -and the core of its hormetic biphasic dose response relationship, on the one side, may carry significant relevance to both the pathobiology of cardiovascular disease, related cases, and development of drugs not presently available for the management of the disorders. In combination, given the parallel mechanisms found in cardiac and metabolic diseases and the overwhelming evidence that chaperones and autophagy enhancer are cardioprotective against most common heart disease, there is possibility that appropriate translation of the knowledge gained from the above considerations may enhance both short- and long-term health of the heart.

Acknowledgements

I thank immensely Mr. Burghard Grossmann (System Administrator, Medical Library, Charite Virchow Campus, Berlin, Germany) for his good technical assistance during the preparation of this manuscript. Dr Franz Theuring is gratefully acknowledged for help with the location. Okom Ofodile remains forever grateful to his Queens for their immense understanding, love and support.

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