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Mise au point

GDF15 : A modulator of immunity and a predictive biomarker of cardiovascular events: A strategy in COVID-19

GDF15 : un modulateur de l’immunité et biomarqueur prédictif des atteintes cardiovasculaires: une stratégie dans le COVID-19

Luc Rochette\textsuperscript{a,}\textsuperscript{*}, Geoffrey Dogon\textsuperscript{a}, Eve Rigal\textsuperscript{a}, Marianne Zeller\textsuperscript{a}, Catherine Vergely\textsuperscript{a}, Yves Cottin\textsuperscript{b}

\textsuperscript{a} Pathophysiology and Epidemiology of Cerebro-Cardiovascular Diseases Research Unit (PEC2, EA 7460), University of Burgundy and Franche-Comté, UFR des Sciences de Santé, 21079 Dijon, France\textsuperscript{b} CHU Cardiology Unit, Dijon, France

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ABSTRACT

In the recently published manuscript entitled “GDF15 a rising modulator of immunity and a strategy in Coronavirus disease 2019 (COVID-19) in relationship with iron metabolism” and we examined the potential properties of Growth and differentiation factor 15 (GDF15) as an emerging modulator of immunity in COVID-19. We commented new aspects of the biology of GDF15 and investigated the potential value of GDF15 as a biomarker. Is GDF15 a biomarker of the inflammatory process and oxidative stress state? Recently, it was reported that 1500 clinical trials related to COVID-19 have been registered, but none have yet found an optimal strategy. In these conditions, more clinical studies are needed before any of these agents can be considered antiviral agents.

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RÉSUMÉ

Nous avons récemment publié une revue intitulée : « GDF15 a rising modulator of immunity and a strategy in Coronavirus disease 2019 (COVID-19) in relationship with iron metabolism » et nous avons examiné les propriétés potentielles du facteur Growth and differentiation factor 15 (GDF15) comme modulateur émergent de l’immunité dans le COVID-19. Nous nous sommes intéressés aux aspects biologiques du GDF15 comme biomarqueur. Est-ce que le GDF15 est un biomarqueur du processus inflammatoire et de l’état du stress oxydatif ? Récemment, il a été rapporté plus de 1500 projets d’études cliniques ciblés sur le COVID-19 ; mais aucune des stratégies ne semble optimale. Dans ces conditions, des études cliniques complémentaires sont nécessaires afin que les composés testés soient définis comme des agents antiviraux.

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1. Introduction

In the recently published manuscript entitled “GDF15 a rising modulator of immunity and a strategy in Coronavirus disease 2019 (COVID-19) in relationship with iron metabolism” [1] we examined the potential properties of Growth and differentiation factor 15 (GDF15) as an emerging modulator of immunity in COVID-19. Innovative and specific biomarkers can serve as new diagnostic markers for the detection of disorders to guide the prognostics and emerging therapeutics. A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. Inflammation-related markers are prominent among the most validated biomarkers that are currently in use. New biomarkers have emerged as relevant contributors in the energy homeostasis field and have appeared as valid biomarkers of various...
diseases. We commented new aspects of the biology of GDF15 and investigated the potential value of GDF15 as a biomarker in the general population and predictive biomarker of adverse events.

2. GDF15: A protein of the transforming growth factor-β (TGF-β) superfamily

GDF15 belongs to the transforming growth factor-β (TGF-β) superfamily of proteins. TGF-β family proteins bind to distinct type I and type II serine/threonine kinase receptors. Signaling induced by the TGF family ligands is necessary for multiple processes during development, tissue homeostasis, and organ functioning. GDF15 is synthesized as a precursor protein: proGDF15. Glial-derived neurotrophic factor (GDNF)-family receptor α-like (GFRAL) is an endogenous receptor for GDF15 detected selectively in the brain. GDF15 is not normally expressed in the tissue but it is prominently induced by “injury” [2]. Serum levels of GDF15 are also increased by aging and in response to cellular stress and mitochondrial dysfunction. GDF15 acts as an inflammatory marker and plays a role in the pathogenesis of inflammatory and metabolic diseases.

3. COVID-19 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)

COVID-19 was first reported in Wuhan, China, in late December 2019. The sudden on-set and worldwide dissemination of infections by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has led to a pandemic challenge of global health. The latter are RNA viruses which can infect humans as well as animals. COVID-19 was declared a global pandemic on 20 March 2020. SARS-CoV-2 has caused a pandemic of respiratory, cardiovascular and metabolic diseases [3]. Several studies have found that inflammatory markers are elevated in older patients and are associated with senescence or cancer [4]. Mortality in COVID-19 patients has been linked to the presence of the so-called “cytokine storm” induced by the virus. The cytokine storm is characterized by significant proinflammatory cytokine release leading to a dysregulated and hyperactive immune response. In COVID-19, the cytokine profile is characterized by increased IL-2, IL-6, IL-7, interferon-γ (INF-γ), monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor-α (TNF-α) pathway [5]. The cytokine storm observed in patients with COVID-19 contributes to the endothelial vascular dysfunction, which can lead to acute respiratory distress syndrome, multiorgan failure, and neurodegenerative processes. Multiple sclerosis is a common chronic immune mediated demyelinating disease of the central nervous system [6]. Sclerosis immunopathogenesis involves brain inflammation, and blood-brain-barrier disruption. GDF15 is a strong predictor of bad issues in patients critically ill with COVID-19 (Fig. 1). People with diabetes and related comorbidities are at increased risk of its complications and of COVID-19-related death. Older age, multi-morbidity, hyperglycaemia, cardiac injury and severe inflammatory response are predictors of poor outcome.

4. Endothelial cell a direct target of SARS-CoV-2 infection: Endothelitis

SARS-CoV-2 encodes the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). The receptor binding domain on the surface subunit S1 is responsible for attachment of the virus to angiotensin (Ang)-converting enzyme 2 (ACE2), which is highly expressed in host cells. Endothelial cells are a direct target of SARS-CoV-2 infection, contributing to endothelial dysfunction with pronounced endothelitis and the recruitment of inflammatory cells [7]. The endothelium contributes to COVID-19-associated vascular inflammation, particularly endothelitis in several organs such as the lung, heart, and kidney. The inflammatory cascade in endothelial cells stimulates leukocyte recruitment and oxidative stress (OS) [8]. It is well documented that OS plays an important role in biology and induces vascular-related gene expression, promoting local inflammatory response and organ dysregulation. When OS occurs, vascular walls produce excessive reactive oxygen species (ROS), which cause damage to the structure and function of endothelial cells. Increased OS is a major pathogenetic mechanism of endothelial dysfunction by decreasing nitric oxide (NO) bioavailability, promoting inflammation and participating in activation of intracellular signals cascade, so influencing ion channels activation, signal transduction pathways, and ultimately gene expression. The mechanisms involved in this viral and inflammatory endothelialitis remain incompletely elucidated and direct infection of the endothelium by SARS-CoV-2 is open to question [9]. Growing evidence demonstrates a direct association between endothelitis and severe COVID-19, the role of endothelial damage biomarkers has been scarcely studied. Immune system and renin-angiotensin system dysregulation with associated cytokine release syndrome may be a key feature of early stage of SARS-CoV-2 organotropism and infection.

5. Is GDF15 a biomarker of the inflammatory process and oxidative state?

Biomarkers of the inflammatory process represented by various cytokines and D-dimers may be also used to forecast the outcome of SARS-CoV-2 infection [10]. Understanding the profile of specific biomarkers and their variations as a function of different COVID-19 outcomes has been the aim of many studies. The inflammatory process and complex interactions were observed between GDF15 and enzymatic activities, erythropoiesis, iron metabolism, and hepcidin [11, 12]. Hepcidin, which regulates iron homeostasis, is stimulated by...
iron and inflammation but is suppressed by hypoxia and erythropoiesis. Recent reports suggest that GDF15 has a critical role in regulating ferroptosis and iron metabolism. Ferroptosis is an iron dependent form of regulated cell death associated with accumulation of lipid-based ROS when glutathione (GSH)-dependent lipid peroxide repair systems are compromised [13]. In this field, several studies have assessed the potential antiviral effect of iron-chelating therapy, and some trials have attempted to evaluate the efficacy and safety of deferoxamine, a common iron chelator, in patients with COVID-19 [14].

Moreover, it is important also to discuss novel studies unraveling how deregulated lysosomal iron-handling functions contribute to viral infection, and can be harnessed for therapeutic interventions. It has been demonstrated the major role of lysosomes in the metabolic network governing the trafficking and intracellular distribution of iron [15]. Endolysosomal function can be considered a target in COVID-19. As supported by recent clinical data, patients who have already taken lysosomotropic drugs for pre-existing conditions likely benefit from this treatment, which prevents SARS-CoV-2 infection and transition to COVID-19 [16]. In this context, mesenchymal stromal/stem cells (MSCs), adipocyte mesenchymal stem cells (Ad-MSCs) and adipose-derived stem cells (ADSC) possessing potent immunomodulatory activities are proposed as a therapeutic option for the treatment of COVID-19. Experimental and clinical studies are exploring the therapeutic potential of both MSCs and derived-exosomes in moderating the morbidity and mortality of COVID-19 [17,18].

Due the role played by OS in the evolution of viral infection and in the development of COVID-19 complications, the use of antioxidants, as we reported; an adjuvant therapy seems appropriate. Thus, Alpha-lipoic acid (ALA) improves endothelial function by restoring the endothelial nitric oxide synthase activity and presents an anti-inflammatory effect dependent or independent of its antioxidant properties [19]. Antioxidants act as a cooperative network, employing a series of redox reactions. Experiments on overexpression of the antioxidative protection, and hence increased antioxidative capacity does not always result in the enhancement of the antioxidative protection, and hence increased antioxidative capacity does not always correlate positively with the degree of defense. In these conditions, more clinical studies are needed before any of these agents can be considered antiviral agents [20].

6. Conclusions

Finally, the virus life cycle in host cell provides potential targets for drug therapy. Recently, it was reported that 1500 clinical trials related to COVID-19 have been registered, but none have yet found an optimal strategy. The concept of COVID-19 as an endothelial disease provides a combining pathophysiological illustration of this “storming” infection, and also provides a background for a rational treatment approach [21–23].

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Competing interests

The authors declare no competing interest

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