Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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issues in larger animals and humans. Optimization of the physiochemical properties of triazole 1.1 using molecular modeling to design a CNS-permeant derivative with retained GPCR selectivity may serve as a fruitful endeavor. There is a significant need for nonaddictive analgesics and derivatives of triazole 1.1 may be a prospective solution.

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Letter

COVID-19 and Metabolic Syndrome: NF-κB Activation. Crossroads

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December 2019 as the cause of severe pneumonia in a cluster of patients in Wuhan, China. Subsequently, this viral pathogen was described as a novel RNA betacoronavirus [1]. As with other members of its group, SARS-CoV-2 is able to cause a severe acute respiratory syndrome, in this case named coronavirus disease 2019 (COVID-19).

Since the first clinical reports, age and the presence of cardiovascular disease, diabetes mellitus, and chronic lung disease, among other comorbidities, were identified as major risk factors for death among patients with COVID-19 [2,3], including those with severe cases admitted to intensive care units [4].

It is also noteworthy that these comorbidities are constant in different countries. In fact, Garg *et al.* [5] recently reported that almost 90% of hospitalized cases in the USA had one or more of the following underlying conditions: hypertension, obesity, chronic lung disease, diabetes mellitus, and cardiovascular disease. Emerging data suggest that diabetes mellitus and obesity (body mass index, >30 kg/m^2) are common risk factors in patients with COVID-19, with high prevalence rates that reach nearly 21% [3] and 40% [6], respectively. However, the case mortality rate varies in relation to individual countries and the epidemic impact of obesity in regional areas.

Recent research underscores this concept, with reports that obesity and diabetes mellitus are special risk factors for the progression of severe COVID-19 inflammatory lung response [7]. However, most of the recently published studies do not report a high prevalence of severe COVID-19 in patients more vulnerable *a priori*, such as those with cancer, hematologic malignancies, solid organ transplants, or autoimmune disease; in fact, the prevalence of these patients in series was unexpectedly low (1–8%, depending on the inclusion criteria). Besides, these studies have some limitations related to the multivariate subanalysis of comorbidities in this patient group [2,4].

All these facts led us to an interesting question. Could there be a main and common inflammatory pathway in coronavirus infection in patients with chronic underlying diseases? We propose the hypothesis of nuclear factor binding near the κ-light chain gene B (NF-κB) pathway activation.

Activation of the transcription factor NF-κB is a pivotal mediator of proinflammatory gene induction and functions in both innate and adaptive immune cells. This factor is highly regulated and involves a large array of genes [8]. The immune effects include the promotion and development of macrophages, dendritic cells, and neutrophils and hence the production of proinflammatory cytokines such as IL-1, IL-6, IL-12, and tumor necrosis factor-α, among other chemokines. The activation of naïve T cells, and particularly CD4$^+$ T-helper cells, is a key component of the inflammatory process. The deregulation of NF-κB activation could cause the

aberrant T-cell activation, which is associated with the autoimmune and inflammatory response [8]. NF-κB is even involved in inflammasome regulation, including NLRP3.

Obesity and insulin resistance are characterized by the induction of a mild, chronic proinflammatory state [9]. The NF-κB pathway is involved in insulin resistance in peripheral tissues and in β-cell dysfunction [10]. Besides, free fatty acids can also promote inflammation and activate the NF-κB and JNK1 pathways [11]. What is more, the same NF-κB is described as a key factor in the low-inflammation state in atherosclerosis [12] and hypertension [13].

The crossroads for COVID-19 disease was reached with the laboratory experiments of Pfefferle *et al.* [14], who found that overexpression of Nsp1 during infection with SARS-CoV-2 strongly increases signaling through the nuclear factor of activated T cells (NFAT) pathway and enhances the induction of IL-2. It therefore triggers immune cell activation, cytokine deregulation, and immune-dependent pathogenesis. Infection by SARS-CoV-2 might even be able to strongly increase this deregulated immune system response, specifically using cyclophilin A for its replication [15]. In fact, both NF-κB and NFAT pathways share common regulation signals, such as Foxp3 and Foxd1, and a similar mechanism of activation against infection.

So, the NF-κB pathway might help to explain why COVID-19 is especially severe in individuals with obesity and other traditional cardiovascular risk factors because this population would have low-grade overactivated NF-κB/NFAT pathways, hence facilitating viral replication. Finally, the NF-κB pathway in patients with COVID-19 should be reevaluated to assess specific therapeutic targets to control the host inflammatory response (pulmonary phase), such as cyclosporine A or tacrolimus, in specific protocols/clinical trials or including alisporivir (an antiviral agent derived from cyclosporine A) in ongoing clinical trials as a specific antiviral therapy against SARS-CoV-2. Both strategies (separately or even in combination) might contribute to reducing the mortality of COVID-19.

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Authors' Contributions

P.G.-V. wrote the manuscript and designed the hypothesis. M.C.-M. wrote and edited the manuscript. D.C.-R., M.R.-L., and I.M.L.-B. contributed to the discussion and structure of the text. All authors read and approved the final version of the manuscript.

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Spotlight

Discrete Fiber Structures Dictate Human Gut Bacteria Outcomes

Bruce R. Hamaker [1,*] and Thaisa Moro Cantu-Jungles [1]

Supplementation with resistant starches of different structures led to divergent shifts in key bacterial taxa abundance and distinct butyrate or propionate outcomes. A recent randomized controlled trial (RCT) reported by Deehan *et al.* showed similar responses within treatment groups and dose-response plateauing at 35 g/d. These results support a proposed alignment of discrete dietary fiber (DF) structures with gut bacteria.

The recent article by Jen Walter's group in *Cell Host & Microbe* [1] describes an RCT showing a significant advance in our understanding of how DFs can be used to achieve a targeted positive effect in the gut. It is now established that DFs that are fermented by the gut microbiota lead to improvements in diet-induced metabolic diseases, through lowered gut and systemic inflammation and improved