Challenges and Insights amidst the Covid-19 pandemic: Nutrition, the immune system and disease risk

Anastasia Z. Kalea[a] *and Dorothy Klimis-Zacas*[b]

For this issue of Genes and Cell Metabolism, we invited distinguished authors to contribute their reviews months before the COVID-19 pandemic, which has led to a rapid expansion of scientific knowledge in this specific area, bringing colossal challenges to our healthcare systems, social life and economic structures.

Preliminary data from the COVID-19 pandemic suggest that cardiovascular disease, hypertension, obesity and other comorbidities, and old age are associated with poor outcomes of COVID-19 infection [1]. In immunocompromised individuals, such as patients with lupus, who are considered more vulnerable to viral infections [2], suggested that the risk and severity of SARS-CoV-2 may be linked to an inherent epigenetic dysregulation. ACE2 hypomethylation and overexpression in peripheral blood mononuclear cells in these patients might facilitate viral entry, viremia, lead to an excessive immune response to SARS-CoV-2, and increase the likelihood of cytokine storm.

The authors provide up-to-date commentaries on topics relevant to the above key themes, such as the impact of genetic and epigenetic dysregulation, and how these affect the immune system, cardiovascular function, cancer and diseases of aging. They discuss the knowledge gaps as far as the molecular basis of these effects is concerned, but also reflect on the significant methodological challenges in overcoming these. Current knowledge on how nutrition status or nutritional interventions – in a few cases – may rescue disrupted pathways is also critically addressed. B-complex vitamins such as folate and cobalamin become the usual 'suspects by association'. Indeed, the central point is *S*-adenosylmethionine (SAM), the methyl group donor for both histone methyltransferases and DNA methyltransferases.

Indeed, only two decades after the term 'epigenetic' epidemiology was mentioned in the literature, we have a much better understanding on common epigenetic variations and how they may explain the missing heritability of disease. We are convinced that most of the interindividual variation in DNA methylation levels may be attributed to environmental factors such as diet. In the effort to identify robust disease biomarkers using a single blood sample, appropriate epigenetic traits to focus on need to be variable in the population but stable over time. Interestingly, a growing body of evidence suggests that viruses, even RNA viruses that replicate in the cytoplasm, interfere with the host's epigenome [3].

As we all currently become familiar with predictive modelling approaches to explore aspects of the pandemic, Ordovas and Westerman (pp. 000–000) explore how sophisticated 'multivariate predictive modelling' has progressed in realizing the potential for DNA methylation as a predictive biomarker of CVD risk. They discuss how a methylation-based risk score may be used to enable the discovery of high-risk individuals that would be missed by alternative risk metrics. The authors present the recent efforts by large-scale consortium-based epigenome-wide association studies (EWAS) to look at 'epigenetic fingerprints' of disease and emphasized the need to use 'incident' data to identify markers for disease prediction. Although the recent 450k array is advanced in comparison to the 27k version, it is clear that its clinical value at this point in time is very limited, as it targets only 2% of the CpG sites and it also misses intragenic CpG sites. While we explore new bioinformatic approaches, study designs and statistical methods to address this, the authors explain how these common EWAS approaches on 'incident' instead of 'prevalent'

[a]Division of Medicine & Institute of Cardiovascular Science, University College London, London, UK and [b]School of Food and Agriculture & Graduate School of Biomedical Science and Engineering, University of Maine Orono, ME, USA

Correspondence to Dr Anastasia Z. Kalea, PhD, RD, Rayne Building G04, 5 University St, University College London, London WC1E 6JF, UK. E-mail: a.kalea@ucl.ac.uk

Curr Opin Clin Nutr Metab Care 2020, 23:000–000

DOI:10.1097/MCO.0000000000000667

CVD are complemented by present analysis strategies. They discuss the value of a 'Mendelian Randomization' approach and they critically discuss how this methodology could help avoid some of the typical problems of cross-sectional approaches, without being free from its own set of biases [4]. As it often happens in scientific research, triangulation may be necessary to validate data through cross-verification from more than two sources, and achieve a more comprehensive understanding of phenomena, by using different tools and having consistent findings.

In their review, Chakraborty and Stover (pp. 000–000) provide a concise overview on how uracil misincorporation in DNA and its repair may be linked to genomic instability and DNA mutations, two causal factors of cancer and aging diseases. Uracils play a central role as a barrier against infectious agents, being protagonists in antibody diversification in adaptative immunity, but also acting as potent antivirals [5]. The authors explain how in immune cells, uracil in DNA drives beneficial genomic diversity for antigen-driven immunity.

They refer to studies that explored the causal role of B-complex vitamin deficiencies on uracil misincorporation and highlight the role of deoxyuracil in DNA, as linked to pathologies such as 'megaloblastic anemia', where folate and cobalamin deficiencies impair erythroblast hematopoiesis. The disruption of the folate-mediated one carbon metabolic reactions affecting DNA methylation, and the pyrimidine biosynthetic pathways contribute to high rates of genomic uracil misincorporation, DNA damage and cell death. The authors remind us that elevated uracil in nuclear DNA is the single biomarker that correlates with incidence of 'neural tube defects'. Supplementation with folate then, a well known preventive intervention, provides more substrate to synthesize dTMP, the precursor to pyrimidines synthesis, as the key intermediate 5,10-methylenetetrahydrofolate is available. Finally, the authors discuss uracil accumulation and 'retroviral immunity', and explain how retroviruses such as HIV during replication, may attack and integrate into themselves via the suicidal autointegration pathway, which is inhibited by the uracil-rich immune cells (macrophage and T cells). Folate deficiency has been associated with faster disease progression after infection of T lymphocytes by HIV type 1 (HIV-1) [6] and others reported how nutritional deficiencies in HIV disease affect symptoms and disease manifestation [7]. Indeed, it would be interesting in the future to obtain data from randomized control trials in order to fully appreciate the role of uracil accumulation in the DNA and the mechanism by which it affects disease pathogenetic processes. One of the main limitations to allow for comparisons is to solve methodological challenges such as the lack of uniform and standardized analytical methods to measure uracil in the DNA [Róna *et al.* 2016] [8].

Extending from this theme, Watkins and Rosenblatt (pp. 000–000) reviewed studies of clinical findings in patients with a number of inborn errors of cobalamin or folate metabolism, as related to immune dysfunction. Folate and B12 work together for the *SAMe* purpose. The authors take a closer look at the inborn errors of metabolism for both vitamins, as these relate to immune function, because deficiencies would particularly affect rapidly proliferating tissues, namely bone marrow hemopoietic precursors. Interestingly, the limited number of studies has shown that these inborn errors do not seem to affect the immune function.

There are exceptions noted in reports of some patients with defects in intestinal cobalamin absorption (i.e. intrinsic factor deficiency, Imerslund–Gräsbeck syndrome) neutrophil function is impaired leading to immune dysfunction. Small but significant studies also noted that genetic variants in the transcobalamin gene, a cobalamin transport protein associated with folate malabsorption, interestingly led to development of clear symptoms of a combined immune deficiency described by very low IgG levels, recurrent infections, and low T and B lymphocyte counts. Severe combined immunodeficiency is also linked to MTHFD1 deficiency, as the defect affects a multifunctional folate metabolic enzyme in the cytoplasm.

With the above in mind, it is crucial to understand, appreciate and determine the role of dietary patterns as a whole, and their individual components (nutrients and bioactive compounds) on the genome, epigenome, transcriptome and metabolome, in order to identify personalised strategies to potentiate the immune system, impact clinical outcomes and response to infectious diseases, and inflammatory response and resolution. The reviews in this issue provide food for thought, as they explore the new scientific evidence and hope for reliable nonpharmacological and pharmacological solutions to target the new virus and reduce its complications.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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