Themed Section: Cellular Metabolism and Diseases

EDITORIAL

Cellular metabolism and diseases

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LINKED ARTICLES

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Abbreviations

CVD, cardiovascular diseases; GLP-2, glucagon-like peptide-2; NAFLD, non-alcoholic fatty liver disease; NAM, nicotinamide.

Many common diseases have been studied in the framework of inherited or somatic mutations, which affect gene expression, signal transduction and cellular differentiation among several other processes. In the last years, the biomedical research re-evaluated the essential role of the bio-energetic and metabolic features in the pathophysiology characterization of diseases. Metabolism influences and/or is influenced by any cellular processes. The dysfunctional metabolic states impact normal physiology and trigger molecular and cellular mechanisms implicated in several human diseases. The new frontiers in disease research are to understand these metabolic features and/or to modulate metabolism and metabolic processes for therapeutic utility.

This *British Journal of Pharmacology* themed issue assembles contributions from scientists that study metabolism over a broad range of topics. The aim is to provide an up-to-date overview of the current understanding of metabolism deregulation in human diseases, to summarise the current clinical picture regarding the use of metabolic regulating drugs, and to discuss the future directions towards more specific therapies.

The themed issue is started by Lorenzo Galluzzi and colleagues (Buque *et al.*, 2020). The authors provide an overview of the possible mechanisms of cancer prevention by nicotinamide (NAM). Preclinical and clinical evidence shows that NAM, a precursor of vitamin B3, is oncopreventive in a broad range of neoplastic diseases and this review discusses the molecular and cellular mechanisms underlying NAM anticancer activity. Cancer metabolism has long been associated with the so-called 'Warburg effect', which describes the glycolytic behaviour of cancer cells regardless of the oxygen availability. However, recently, cumulating evidence demonstrates a heterogeneous metabolism with some cancer cells harbouring an oxidative behaviour (Pavlova and Thompson, 2016). In both contexts, the cancer cells reprogram their metabolism to support proliferation with a consequent impact on the tumour environment, including the phenotype of infiltrated immune cells. This leads to an impaired cancer immunosurveillance and a negative effect on the efficacy of cancer immunotherapies (Leone and Powell, 2020).

Similarly, the complex interplay between immunity and metabolic reprogramming has been largely investigated in the last few years. Immunometabolism studies the intracellular metabolic pathways in immune cells, helping us to better understand the mechanisms and functions of the immune system in health and disease (O'Neill *et al.*, 2016). In this issue, Claudio Mauro and colleagues discuss how targeting metabolism may be a viable approach for the treatment of chronic inflammation (Certo *et al.*, 2020). During inflammatory diseases, both

endothelial and T cells need to generate sufficient energy to support their functions. Therefore, a rearrangement of their metabolism is necessary to meet these demands. This review specifically focuses on the crosstalk between endothelial and T cells, their metabolic reprogramming following activation, as well as how metabolism may become a therapeutic target for the treatment of chronic inflammatory disorders.

Cardiovascular and metabolic diseases are the number one cause of morbidity and mortality worldwide (Welsh *et al.*, 2017; Maffia and Guzik, 2019). Mitochondria are organelles that produce the largest amount of energy that cells need to survive and function. As central players in the regulation of cellular metabolism, it is not surprising that mitochondrial dysfunction has emerged as one of the main pathogenic mechanisms underlying cardiovascular diseases (CVD) and metabolic disorders (Tian et al., 2019). In the current issue, Sebastiano Sciarretta and colleagues discuss the role of mitochondrial dynamics in cardiovascular pathophysiology, including heart failure, genetic and metabolic cardiomyopathies, atherosclerosis and stroke, as well as discussing the potential of targeting mitochondrial dynamics as novel therapeutic targets in CVDs (Forte *et al.*, 2020). By the same token, Santo-Domingo and colleagues discuss mitochondrial ion channels in pancreatic β-cells as therapeutic targets for the treatment of Type 2 diabetes (De Marchi *et al.*, 2020). Pancreatic beta-cells regulate glucose homeostasis and mitochondria play a crucial role in the homeostasis of these cells. Mitochondria double-membrane contains numerous channels used for the transport of ions, able to regulate mitochondrial energy production and signalling. The article offers an overview of these ion channels, highlight evidence from basic and clinical studies.

In the final review article, D'Agostino and colleagues discuss the brain control of appetite during sickness (Aviello *et al.*, 2020). The brain is the main controller of appetite and energy homeostasis. The authors discuss our current understanding of appetite-controlling mechanisms and how inflammation influences their function. Importantly, they discuss the pathophysiological significance of anorexia and negative energy balance during immune responses. Along these lines, fasting, caloric restriction and its mimetic, which are responsible for negative energy balance, have demonstrated the capacity to stimulate cancer immunosurveillance upon treatment with improved efficacy in preclinical models (Di Biase *et al.*, 2016; Pietrocola *et al.*, 2016). In multiple organisms, caloric restriction has been associated with extended longevity by reducing the occurrence of age-related diseases (Colman *et al.*, 2009; Colman *et al.*, 2014; Pifferi *et al.*, 2018; Hwangbo *et al.*, 2020). Moreover, prolonged

caloric restriction has also demonstrated clinical potential by reducing the level of oxidative stress markers (Redman *et al.*, 2018).

The themed issue ends with three original research contributions. The work by Hua and colleagues shows that the neuroprotective agent P7C3-A20 can affect metabolic dysfunction, lipid oxidative stress, necroptosis/apoptosis and inflammation in high fat diet-induced non-alcoholic fatty liver disease (NAFLD) in mice, by regulating the gut microbiota (Hua *et al.*, 2020). Ejarque and collaborators demonstrate that the adipose tissue is a key organ for the beneficial effects of the gastrointestinal hormone glucagon-like peptide-2 (GLP-2) on glucose metabolism and obesity control (Ejarque *et al.*, 2020). Finally, oxidative stress and an insufficient autophagic process are associated with inflammatory processes and are common features of many CVD. Carnevale and colleagues demonstrate that a combination of natural activators of autophagy could inhibit platelet activity and oxidative stress and improve endothelial cell survival and function in a synergic manner (Carnevale *et al.*, 2020).

In summary, this themed issue of the *British Journal of Pharmacology* will provide readers with a review of metabolism regulation in human diseases, discussing key metabolic mechanisms in cancer, chronic inflammatory disorders and cardiometabolic diseases, in addition to discussing the targeting of metabolic pathways for disease prevention or cure.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Kelly *et al.*, 2019).

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Conflict of Interest

The authors wish to acknowledge that MCM has co-authored papers with Norma Bloy, Atziber Buque, Maurizio Forte, Giacomo Frati, Lorenzo Galluzzi, Guido Kroemer, Sebastiano Sciarretta and Francesco Versaci.

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