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# Editorial overview: Immunomodulation 2020 – nuclear receptors

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The innate immune response is a principal trait of all living organisms, and serves as a universal mechanism to protect cells from microbial pathogens, foreign and malfunctional cells — such as tumor cells — and also the hazardous contents of dying cells [1–3]. Proper immune functioning is crucial to sustain growth and metabolic homeostasis, and the innate immune system has a long evolutionary history that can be traced back to the dawn of life. Diseases can occur when the immune system is challenged by new antigens, or when the immune response is unbalanced or compromised. Protection against infectious diseases requires a rich understanding of how pathogens can evade the immune response and how they can be neutralized through strengthening specific immune responses. This editorial was written in the Spring of 2020, when the global efforts to contain the spread of the novel coronavirus SARS-CoV-2 and mitigate the mortality rate of the COVID-19 pandemic perfectly illustrate the importance of understanding disease immunity [4]. Beyond its involvement in host defense against infection, the innate immune system also participates in the normal physiological function of organs, by maintaining tissue integrity, tolerating self-antigens, clearing and safely disposing of unwanted cells, and shaping the metabolic performance of the body [5]. Dysfunction of these physiological immune mechanisms also causes diseases that, akin to COVID-19 and related coronaviral SARS-CoV and MERS-CoV outbreaks, has reached pandemic levels – for example, metabolic syndrome, insulin resistance, diabetes, osteoporosis, cardiovascular disease, self-immunity and cancer.

The modulation of immune mechanisms by pharmacological means has become an intensive area of research. Genes of the innate immune response are controlled by a complex network of transcription factors, including the nuclear receptor superfamily of ligand-dependent transcription factors. Nuclear receptors can be activated or inhibited by a plethora of endogenous or exogenous molecules, including lipid metabolites, nutritional lipids and vitamins, microbiome-derived metabolites, pathogen-derived products, various hormones, and xenobiotics [6]. All of these signals have their own specific effects on immunity, with both desirable (i.e. pathogen elimination) and unwanted (i.e. metabolic side effects) outcomes. This section of the 2020 *Current Opinion in Pharmacology* Immunomodulation special issue has, as its chief focus, the role of nuclear receptors in the modulation of immune mechanisms.

Macrophages represent the first line of defense against pathogens, and are conspicuous by their ubiquity in all tissues of the body, where they help to control organ development, metabolism, tissue turnover and healing [7]. The immune functions of macrophages are determined at the checkpoint of

gene transcription – for instance, whether macrophages adopt a pathogen-killing activity and induce inflammation or, conversely, curb inflammation, is mostly determined at the level of gene transcription. Accordingly, transcriptional regulators, including nuclear receptors, have key roles in the orchestration of innate immune responses. The review of Leussink *et al.* [8] from the laboratory of *Noelia Alonso-Gonzalez* in Münster, Germany describes how the immunomodulatory capacity of macrophages is dependent on the regulation of their transcriptional activity by liver X receptors (LXRs). LXRs control the genes that orient macrophages towards diverse immune scenarios, such as pathogen elimination or self-tolerance of dying cells within tissues. Leussink *et al.* also address the different mechanisms by which LXRs contribute to macrophage activation, control macrophage number in tissues, and link lipid metabolism and immunity. A second LXR-centered review is provided by Glaría *et al.* [9] from the laboratory of *Annabel Fernandez Valledor* in Barcelona, Spain, who describe how LXRs control host-cell pathogen interactions, and detail how LXR-mediated transcriptional responses modulate the metabolism of infected cells and limit the infectivity and growth of several pathogens. Both articles support the notion that LXRs have diverse immunomodulatory functions, and that pharmacological intervention of LXR signaling may be a double-edged sword because of the undesirable side effects of ubiquitous LXR activation. Hence, therapeutic strategies designed to target LXR activity with cell-specificity and organ-specificity are necessary.

Macrophages reside in specific tissue niches, where their number and immune functions are shaped by tissue-specific cues [7,10]. Tissue-resident macrophages can be replenished from bone marrow-derived monocytes, and many examples are known where local proliferation also ensures the renewal of the tissue macrophage pool [11,12]. Various signals, including endocrine mediators, are possible regulators of tissue-specific macrophage development and replenishment, although much remains to be discovered about the underlying mechanisms. In this regard, the review by Porcuna *et al.* [13] from the laboratory of *Mercedes Ricote* in Madrid, Spain introduces the concept that nuclear receptor signaling participates in the control of tissue macrophage niche development, and the authors give examples of how nuclear receptors may control macrophage development in some of the tissue-resident macrophage pools.

A highly specialized bone-resident macrophage pool is formed by osteoclasts, which are bone degrading cells important for physiological remodeling of the bone architecture. The review by Bae *et al.* [14] from the laboratory of *Kyung-Hyun Park-Min* in New York, USA, examines how osteoclast dysfunction can cause diseases such as osteoporosis, bone metastasis, and inflammatory bone erosion, and provides an overview of the molecular mechanisms underlying the action of nuclear receptors in osteoclasts that block these pathological processes.

The molecular mechanisms that enable nuclear receptors to control gene transcription are complex, as exemplified by the transcriptional machinery of the glucocorticoid receptor (GR). In their review, Syed *et al.* [15] from the laboratory of *Henriette Uhlenhaut* in München, Germany summarize the known molecular mechanisms that underpin the anti-inflammatory effects of GR signaling. Factors influencing the anti-inflammatory actions of GR — including different chromatin states such as DNAse hypersensitive regions and histone marks — are discussed, together with the relevant transcriptional co-regulators and promoter/enhancer features. The authors further address the involvement of non-coding RNAs such as lncRNAs, miRNAs and eRNAs, which adds another level of complexity to nuclear receptor signaling, as exemplified by the post-transcriptional regulation of GR. The immunomodulatory function of GR is reviewed by Van Looveren *et al.* [16] from the laboratory of *Claude Libert* in Ghent, Belgium. Activation of GR by glucocorticoid steroid hormones has well known anti-inflammatory effects in many clinical settings; however, glucocorticoid resistance and unwanted side effects remain a major barrier to treatment. Van Looveren *et al.* examine the recent findings suggesting that GR dimerization is essential to induce anti-inflammatory effects of glucocorticoids, and discuss the concept that pharmacological intervention to selectively trigger GR dimerization can have utility in life-threatening inflammatory conditions such as sepsis.

It is increasingly evident that intestinal microbiota produce metabolites that can engage nuclear receptors, with the potential to shape immunity and metabolism. In their review, *Stefano Fiorucci et al.* [17] from Perugia, Italy, describe how steroids produced during cholesterol and bile acid metabolism in the liver and by intestinal microbiota are ligands for bile acid receptors (BARs). The two best characterized members of this family are the nuclear receptor farnesoid-X-receptor (FXR) and the G protein-coupled receptor bile acid receptor 1. Both receptors are expressed by cells of innate immunity including liver-resident and intestinal-resident macrophages and monocyte-derived macrophages. Fiorucci *et al.* provide insights into the role of BARs in the possible interface between immune response and metabolic performance. For example, BARs might have a role in the development and maintenance of a tolerogenic phenotype, and BAR ligands have proved effective in the treatment of inflammatory and metabolic disorders. Accordingly, agonists of these receptors are currently under development for the treatment of non-alcoholic steato-hepatitis and diabetes.

As mentioned earlier, innate immune signaling determines metabolic performance. Indeed, the interplay

between innate immune cells and metabolically active cells begins soon after birth, and has a key role in the development of diabetes and obesity-associated metabolic diseases [18]. While metabolic deterioration is primarily a consequence of hyperinflammation within metabolic organs, it has recently been shown that inflammatory signaling is important for the physiological development of metabolism [18–20]. The final review in this section by Molocea *et al.* [21] from the laboratory of *Stephan Herzig*, in München, Germany focuses on the role of inflammatory signaling in opposing metabolic settings, cachexia and obesity, and summarizes existing therapies and discusses potential novel strategies that could emerge by bridging the mechanistic commonalities between the syndromes.

As the Guest Editor of this Section, I hope that this collection of review articles will be useful references for teaching and research to stimulate discussion, and to open up new avenues of research in the understanding of immune signaling. I thank all of my colleagues who enthusiastically accepted the invitation to participate in the 2020 Section, as authors and reviewers. I also appreciate the editorial assistance provided by the *Current Opinion in Pharmacology* Editorial Office.

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