



Editorial

Inflammation in Health and Disease: New Insights and Therapeutic Avenues

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The inflammatory response is an adaptive mechanism that evolved to fight against infections and tissue damage. This complex mechanism is vital for the proper function of the organism, and because of that, is under tight regulation involving a complex network of factors, cells, and systems. Physiological inflammation is perfectly orchestrated to allow the mobilization of leukocytes from the circulation to the injured tissues for the removal of pathogens, tissue repair, and return to homeostasis. However, when the self-limited nature of the inflammatory response and the mechanisms of resolution fail, inflammation might become chronic, leading to the development of many disabling serious diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), or psoriasis.

Knowledge of the molecular and cellular processes underlying chronic inflammation has substantially increased in recent decades. This resulted in enormous improvements in the treatments for immune-mediated inflammatory diseases, but also revealed the complexity of the cytokine networks and immune cell subtypes involved in non-resolving inflammatory responses. This fact could explain, in part, why certain groups of patients are totally or partially refractory to current therapies. Therefore, we cannot be satisfied with the available drugs, and more research focusing on deciphering the precise molecular pathways behind uncontrolled inflammation is mandatory for developing novel therapeutic approaches.

The 34 original and review articles included in this Special Issue contributed to the aim of describing and understanding new mechanisms that trigger inflammation and highlighted new putative treatments for different inflammatory conditions.

Neuroinflammation is a perfect example of the two faces of inflammation. While an acute inflammatory response is protective, chronic neuroinflammation leads to inflammatory conditions such as multiple sclerosis, and it also contributes to other neurological [1] and psychiatric disorders such as Alzheimer's or Parkinson's disease [2]. Microglia is pivotal for regulating central nervous system inflammation. Therefore, it would be interesting to develop therapeutic strategies conducted to mitigate their hyperactivation. Following that aim, Saliba et al. synthesized a new antagonist for the orphan G-protein coupled receptor 55, which decreased the production of prostaglandin E₂ and reduced the activation of pro-inflammatory signalling pathways [3]. In line with this, other receptors regulating microglia function are being explored. This is the case for some purinergic receptors such as P2Y receptors, whose actions on microglia and neuroinflammation were elegantly reviewed by Gómez Morillas et al. [4]. These data highlight that the isolation of new receptors that can be pharmaceutically targeted might be relevant for treating neuroinflammatory disorders. Actually, a similar approach is followed for other immune-mediated pathologies, in which the inhibition of various receptors such as sodium-glucose co-transporter 2 [5], angiotensin receptor [6], or toll-like receptors [7] is being tested for controlling the



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exacerbated inflammatory response during acute kidney injury, COVID-19 infection, heart failure, etc.

Focusing on autoimmune responses, Amend et al. [8] and Carvalheiro et al. [9] investigated the effects of IL-10 and angiopoietin-2 in the context of lupus and systemic sclerosis, respectively. The former shed light on the poorly understood role played by IL-10 in the development of lupus, revealing that IL-10 outcome depends on the complex interplay among the different immune cells and the inflammatory microenvironment. The latter investigated, for the first time, how angiopoietin-2 can increase the production of pro-inflammatory mediators by monocytes from systemic sclerosis patients, which could contribute to the development of fibrotic processes in the skin of those patients. Fibrosis is also a key feature in chronic kidney injury, and Leong et al. [10] functionally demonstrated in experimental acute kidney injury mouse models that cyclophilin inhibition protects from renal injury and fibrosis, an observation that is accompanied by reduced innate immune cell infiltration.

Inflammation significantly contributes to skin malignancies, as reviewed by Ansary et al. [11] and Razib Hossain et al. [12]. Interestingly, Yang et al. [13] demonstrated *in vitro* and *in vivo* the therapeutic potential of the natural small molecule neferine as an anti-inflammatory drug for atopic dermatitis. Moreover, Hathaway-Schrader et al. [14] showed new insights for a better comprehension of the immune evasion in melanoma cells.

Historically, inflammation-related research mainly comprised studies related to immune cells and inflammatory mediators. However, in recent years, more multidisciplinary and integrative approaches have been applied for the dissection of the inflammatory process [15]. This is the case for the article by Weiss et al. [16], which showed an interesting view of the participation of histone deacetylases in the activation of pro-inflammatory signalling cascades and mediators in cultured macrophages. Moreover, another work explored the methylation status of specific promoters for their participation in neuronal inflammatory diseases. Hypermethylated O⁶-methylguanine-DNA methyltransferase is commonly observed in brain tumours. However, Teuber-Hanselmann et al. [17] reported an original hypermethylation of that gene in inflammatory conditions affecting the central nervous system. Likewise, the participation of adipokines and obesity in regulating inflammation and cardiovascular disease [18,19] and the impact of the YAP/TAZ signalling in the immunomodulatory responses of tumours [20] have also been discussed. Of note, Götz et al. [21] demonstrated *in vivo* the relevance of the complement system in the recruitment of neutrophils and M2-polarised macrophages to ischemic tissues, which, most likely, are the most relevant players in the observed improvement of angiogenesis.

The impact of environmental factors such as pollutants, microparticles, or endocrine disruptors is gaining interest. The latter is not only relevant for their interference with the normal function of the endocrine system, but endocrine disruptors can also participate in the pathophysiology of non-alcoholic fatty liver disease (NAFLD) (as reviewed by Cano et al.) by modulating liver metabolism [22]. In the same way, the food additive titanium dioxide worsened experimental colitis in mice carrying IBD genetic risk mutations [23], suggesting that the ingestion of industrial compounds can be detrimental to patients with IBD with an increased genetic predisposition. Silicon dioxide is well-known for causing lung silicosis, and novel pathophysiological mechanisms and treatment options were reviewed by Adamcakova et al. [24]. Interestingly, Wang et al. [25] demonstrated the efficacy of a novel class of pharmacological compounds, namely SUL-151, in decreasing neutrophilia after cigarette smoke exposure in mice.

This Special Issue also contains translational studies demonstrating the association between high concentrations of IL-6 receptor antagonist and reduced carbohydrate disorders and NAFLD progression in obese individuals [26], the impairment of circulating monocytes and the aberrant production of pro-inflammatory mediators in spinal cord injury patients [27], and the existence of a fibroinflammatory signature in human follicular fluid of the female reproductive system [28]. Furthermore, Di Paola et al. [29] showed the effects of the thrombopoietin receptor agonist Eltrombopag in the differentiation of

macrophages obtained from children with immune thrombocytopenia. Altogether, these data show, in the human setting, how inflammation can also be at play in conditions not typically recognised as immune-mediated diseases.

Finally, in this compilation of articles, we find very interesting reviews updating a wide variety of topics such as hypoalbuminemia as a surrogate of infections [30], the resolution of inflammation in IBD or pain [31,32], the impact of inflammation in liver tumorigenesis and alcohol disease [33,34], and nutraceutical supplementation in obesity-associated disorders [35]. Moreover, Rafael-Vidal et al. reviewed the potential use of calcineurin inhibitors to treat lupus nephritis [36], and the molecular and cellular mechanisms regulating osteoporosis after spinal cord injury were described by Shams et al. [37].

We hope the lectors will appreciate reading these papers. We thank all the authors and reviewers for their dedication and proactive participation that made the realisation of this remarkable Special Issue possible.

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