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Themed Section: Inflammation: maladies, models, mechanisms and molecules

EDITORIAL

Inflammation: maladies, models, mechanisms and molecules

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The continued focus of attention on the diversity of mechanisms underpinning inflammation has improved our understanding of the potential to target specific pathways in the inflammatory network to achieve meaningful therapeutic gains. In this themed issue of the British Journal of Pharmacology our scope was deliberately broad, ranging across both acute and chronic disease in various organs. Pro- and anti-inflammatory mechanisms receive attention as does the phenotype of macrophages. Whilst the manifestations of neuro-inflammation are less obvious than those in peripheral tissues, central innate and adaptive immunity in brain and the M1/M2 phenotypes of microglia are topics of special interest. The contributions to the inflammatory milieu of cytokines, chemokines and associated signalling cascades are considered. Overall, the coverage herein advances the basic science underpinning our understanding of inflammation and emphasizes its importance in different pathologies.

LINKED ARTICLES

This article is part of a themed section on Inflammation: maladies, models, mechanisms and molecules. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2016.173.issue-4

Abbreviations

HDL, high-density lipoprotein; NSAID, non-steroidal anti-inflammatory drug; SAA, serum amyloid A

Tables of Links

TARGETS	
GPCRs[a]	**Catalytic receptors**[b]
AT2 receptor	NLRP3
FPR2	PYCARD (ASC)
NK1 receptor	**Enzymes**[c]
PAR2	Caspase 1
	Neutrophil elastase

LIGANDS	
Deoxycorticosterone	IL-17A
ICAM-1	Interferon-α
IL-1β	Lipoxin A4
IL-6	Serum amyloid A
IL-8	Substance P
IL-10	TNF-α

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c] Alexander *et al.*, 2013a,b,c).

Inflammation is indeed an extremely diverse topic, but relevant to the function of every organ in the body. It is derived from the Latin *inflammo* meaning 'I ignite, set alight'. The Concise English Dictionary describes *inflammation* as a state of being in flame; morbid heat of a part of the body with pain, redness and swelling; or kindling of the passions. In some organs, such as the CNS, these signs may be difficult to detect. The signposts of inflammation were described by

Celsus as pain, heat, redness and swelling to which was later added, loss of function. The Scottish surgeon, John Hunter, recognised these in his treatise on gunshot wounds in 1794, which also emphasized fever. In identifying tumours as wounds that do not heal, Dvorak established the broader reach of inflammatory processes, to the current day when these processes are seen as integral to the pathophysiology of most chronic diseases.

Here, our scope was deliberately broad, ranging across diverse tissues and addressing mechanisms, models and disease to capture the great contemporary interest in inflammation. This themed issue brings together contributions from established and emerging workers in the field to provide an up-to-date account of how and why inflammation is such an attractive area for drug development. The themed issue provides a timely overview of many aspects of this critical field and maps future directions for research relevant to the pharmacology of inflammation and its relevance to tissue damage and pathophysiology. Importantly, the articles contained within this volume address inflammation in various organs (airways, heart, liver and brain), illustrating just how important this topic is to pharmacology and therapeutics.

The pervasive influence of inflammation on chronic disease is well exemplified by the new findings of Sampson *et al.* (2016) in the anti-atherogenic actions of the selective non-peptide AT_2 receptor agonist, compound 21. The link to inflammation is suggested to involve a suppressant action on reactive oxygen species resulting in diminished signalling via the NF-κβ transcription factor pathway, thereby reducing the expression of pro-inflammatory cytokines, such as IL-6. The current work describes two further mechanisms involving suppression of monocyte recruitment by decreasing the expression of chemokines and intercellular adhesion molecule-1 (ICAM-1) on vascular endothelial cells, the latter linked to a diminished area of atherosclerotic plaque in apolipoprotein E (Apo E) −/− mice fed a high-fat diet. Investigations of human monocyte/macrophage phenotypic modulation did not reveal any detectable effect of compound 21, but equivalent murine studies were not undertaken. A study from the same group has identified high-density lipoprotein (HDL) as an inhibitor of the phenotypic modulation of human monocyte-derived macrophages to the M1 phenotype, preferentially directing to the M2 phenotype, which is regarded as having a wound healing profile, promoting cell growth and angiogenesis (Lee *et al.*, 2016). The macrophage differentiation effects of HDL were shown to depend on caveolin-1 expression in studies using bone marrow-derived macrophages from wild-type or caveolin-1 −/− mice.

The connections between inflammation and vascular disease continue to strengthen, with studies such as that by Krishnan *et al.* (2016) showing that hypertension induced in the unilateral nephrectomy and deoxycorticosterone acetate (known as 1K/DOCA) model requires inflammasomes, suggesting an inflammatory in addition to a mechanical action. Hitherto, this model has been considered to involve uncompensated fluid retention reinforcing the endocrine/neural-related hypertensive actions of DOCA. The current work implicates the inflammasome subunits, cryopyrin (NLR family, pyrin domain containing 3; NLRP3), the PYCARD (ASC) gene product and pro-caspase-1, linking them to activation of IL-1β and additional cytokines and adhesion molecules, which facilitate macrophage accumulation in the remaining kidney. The link to fibrosis raises the intriguing prospect of an anti-inflammatory approach to renal fibrosis and hypertension.

Joint inflammation in rheumatoid arthritis limits function and quality of life. Disease-modifying anti-rheumatic drugs, methotrexate and biologicals targeting TNF-α complement conventional non-steroidal anti-inflammatory agents (NSAIDs) in the management of this condition, and the NSAIDs are also important in treating osteoarthritis. However, there is ongoing interest in adding to the therapeutic repertoire, as amongst the affected populations of patients, there remain subsets with poorly controlled disease or those intolerant of important components of the therapeutic regimen. In the study by Muley *et al.* (2016), neutrophil elastase has been shown to mimic the features of inflammation and pain in mouse knee. Interestingly, the vasodilatation and knee swelling effects of the intra-articular enzyme are attenuated in protease-activated receptor-2 (PAR2) −/− mice or by co-treatment with the PAR2 antagonist, silvestat, in wild-type mice, suggesting that degradation of extracellular matrix is less important than activation of pro-inflammatory signalling through the PAR2 receptor. Leukocyte recruitment and sensitization of pressure responses are also mediated by PAR2 activation. Such findings signify the potential for PAR2 to drive pain and inflammation in joints, but further exploration in more complex and chronic models is needed to understand the relative importance of this and other pathways as targets.

The airways, including the nasal epithelium, are sites of interaction with the external environment that brings pathogens, particulates and noxious gases to the barrier. Thus, epithelial cells require the dual capacity to serve as a barrier to the exposure of deeper structures to such stimuli and also to signal an innate and rapid response that limits the potential of the stimulus to damage the airways. Reihill *et al.* (2016) show that the plant-derived diterpenoid, gibberellic acid, has anti-inflammatory activity on primary nasal epithelial cell cultures, as measured by suppression of IL-6 and IL-8. This anti-inflammatory effect depends on the expression of the zinc finger protein A20, leading the authors to speculate that agents increasing A20 expression could be useful for chronic inflammatory disease.

The link between airway inflammation and lung cancer is explored in a review by Bozinovski *et al.* (2016). Their principal messages, encapsulated diagrammatically, are that reactive molecules in, or triggered by, tobacco smoke increase genomic instability; serum amyloid A (SAA) in conjunction with IL-10 acting on neutrophils and M2 phenotype macrophages impair cell function, leading to reduced tumour immune surveillance, whilst increased IL-17A expression activates macrophages and neutrophils with the release of inflammatory proteases and growth factors that promote tumour inflammation. They speculate on biased signalling from the formyl peptide receptor 2 (FPR2), with activation by serum amyloid A, leading to pro-inflammatory responses, whereas other ligands such as lipoxin A_4 influence the tumour microenvironment by promoting inflammation resolution by activation of macrophage efferocytosis. The role of the FPR2 system in different tumour types may be difficult to predict, as the balance of pro-tumour and anti-tumour actions may not be limited to actions on macrophages, but also be influenced by actions on epithelial cells, as evidenced in breast tumour epithelium (Al-Zaubai *et al.*, 2014; Khau *et al.*, 2011) and other stromal elements, including fibroblasts (Jia *et al.*, 2013).

Brain inflammation is now a huge topic of study internationally despite being recognised much later than peripheral inflammation where obvious signs such as dilation of blood vessels, itchiness and pain have been noted since time immemorial. Whilst both acute and chronic brain inflammation are now well documented, historically, the CNS was considered to be immune privileged in that it lacked resident NK cells, T- and B-lymphocytes and a lymphatic system. This scenario has now been transformed, with the existence of central innate and adaptive immunity well established and crosstalk between the nervous and immune systems fully accepted. Phenomena such as oedema and breakdown of the blood–brain barrier receive attention here, as do the involvement of various chemical mediators and both of the key cell types, microglia and astrocytes. For decades, the view prevailed that microglia were 'nasty' brain cells only causing toxic events during inflammation, but their different states, or continuum of states between the M1 and M2 phenotypes, are the centre of great contemporary interest with these inflammatory cells also contributing to minimization of injury and repair. Workers also now realize that astrocytes should be appraised from a similar perspective (Lau *et al.*, 2012; Khakh and Sofroniew, 2015).

Linking the terms microglia, M1 and M2, in PubMed identifies only 210 articles of which some 60% were published from 2014 onwards, although there are >20 000 published papers on microglia. Whilst there is a growing set of molecular descriptors that have been employed to define M1 and M2 phenotypes, there is increasing evidence for metabolic reprogramming in the regulation of the inherent inflammatory response. The application of the relatively new Seahorse technology for studying mitochondrial bioenergetics allowed Orihuela *et al.* (2016) to explore the possible relationship to the polarization states of microglia, and they demonstrated a unique pattern of metabolic shifts. This work is at an early stage, but new understanding of links to morphological and functional parameters will advance attempts to better understand the regulation of these dynamic cells. Indeed, an improved understanding of the functional involvement of microglial M1/M2 phenotypes, including advances in markers reflecting different activation states, would greatly advance our understanding of their association with macro-scale structural changes in schizophrenia where inflammation maybe an underlying mechanism. Synaptic pruning is critical in neurodevelopment and microglial abnormalities may be linked to functional dysconnectivity in related animal models, which possess some of the behavioural abnormalities of psychiatric disorders (Laskaris *et al.*, 2016).

Faden *et al.* (2016) continue the concept of the M1/M2 paradigm and its relationship to immunopathogenesis, emphasizing the growing awareness that the M2-like phenotype possesses anti-inflammatory and neuro-restorative actions. Here, the focus is upon traumatic brain and spinal cord injury where the persistent activation of microglia towards the M1-like neurotoxic phenotype may contribute to the progressive neuronal loss in brain trauma. These conditions should be viewed as both acute and chronic neurodegenerative disorders, which are treatable with new therapeutic approaches. Karve *et al.* (2016) adopt a different approach when considering inflammation after traumatic brain injury focusing on resident astrocytes and microglia and the chemical mediators (e.g. cytokines, chemokines and growth factors) they may be secreted to facilitate both inflammation resolution and exacerbation. Astrocytes play key roles in the glial scar and in the maintenance of the integrity of the blood–brain barrier, while diverse responses of microglia depend upon their activation state. Microglial responses involve expression and secretion of a variety of molecules, and we should note that the M1/M2 polarization is an evolving story with emergence of new insights into the microglial transcriptome. Thus, therapies targeting CNS injuries must take into account the multifaceted nature of cellular responses exhibited by resident inflammatory cells.

One possible target for managing inflammation in traumatic brain injury appears to be receptors for substance P – not only is this neuropeptide associated with increased blood–brain barrier permeability, vasogenic oedema and consequent functional outcomes linked to neuronal injury, but it also activates both microglia and astrocytes (Corrigan *et al.*, 2016). Neurokinin 1 (NK_1) receptor antagonists attenuate blood–brain permeability and represent a promising approach for the management of traumatic brain injury and other forms of acute brain injury. Hofer and Campbell (2016) provide yet another perspective where cytokines are crucial mediators of inflammatory and immune-mediated diseases in the brain. Local production of cytokines in brain increases greatly following infection and injury and in autoimmune disorders as diverse as multiple sclerosis, neuromyelitis optica, human immunodeficiency virus (HIV)-associated dementia, Alzheimer's disease and stroke. The authors focus our attention upon two cytokines, interferon-α and IL-6, which have complex roles in different neurological disorders probably involving leukocytes, macrophages and multiple brain cells. However, what is apparent from studies in genetically engineered mice is that astrocytes are a major site of their production in brain and that astrocytosis, their inflammatory activation, is likely to be causative in various neuropathologies. Importantly, there has been appreciable progress towards the clinical usage of therapeutic monoclonal antibodies directed at both interferon-α and IL-6 giving hope that such therapy will be effective in treating some of these neurological disorders.

The articles in 'Inflammation: maladies, models, mechanisms and molecules' reflect not only the dynamic nature of this diverse topic of research but also the enthusiasm of the authors for this rapidly advancing field. The articles contained herein will be of interest to academic and industry-based researchers and students alike. The editors thank the authors and reviewers for their efforts in making the themed issue a highly contemporary assembly.

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