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THEMED SECTION: MEDIATORS AND RECEPTORS IN THE RESOLUTION OF INFLAMMATION

EDITORIAL

Mediators and receptors in the resolution of inflammation: drug targeting opportunities

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The active resolution of inflammation is recognized as offering new opportunities to generate novel anti-inflammatory agents. The emerging appreciation of the importance of active resolution in regulation of inflammation also creates an imperative to examine developing and existing agents for their potential to influence these pathways. This themed issue of the *British Journal of Pharmacology* contains papers that discuss the roles of annexin-1, lipoxins and related lipid products of fish oils as well as other mechanisms involved in active resolution and their receptor targets.
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The complexity of regulation of inflammation, and particularly of the redundancies among different mediator systems, is well established. This complexity presents challenges to the development of highly effective, tolerable and safe therapeutics. Allergic and non-allergic inflammatory conditions are often only partly controlled, even by cocktails of receptor antagonists, synthesis inhibitors and functional antagonists. It is reasonable then to expect that pleiotropic anti-inflammatory agents would be required to adequately control these conditions. A high level of selectivity, the aspiration of successful drug development programmes, may actually limit the impact of anti-inflammatory agents targeting single mediators.

The most effective functional antagonists of inflammation, the glucocorticoids, have the potential to impact on the expression of no fewer than 6500 genes (Galliher-Beckley *et al.*, 2008); their non-steroidal counterpart, aspirin has a narrower, but nonetheless broad impact, in part by virtue of the range of cyclo-oxygenase products that are affected. However, both the efficacy and the adverse effect profile of glucocorticoids are related to their breadth of activity. Debate continues as to which of the general effector systems of glucocorticoid receptor binding, namely transactivation or transrepression (Buckingham, 2006), are dominant in regulating inflammation (Perretti, 2007; Schacke *et al.*, 2007). Attempts to separate such activities have not yet provided an improved glucocorticoid receptor ligand for clinical use, although advances are being made towards this goal (Schäcke *et al.*, 2009).

The cytokine/mediator networks that initiate and perpetuate inflammatory conditions are characterized by diverse, non-linear features, and the system behaviours cannot currently be predicted (Vodovotz *et al.*, 2008). An increasing number of studies suggest that the active resolution of inflammation contributes to this complexity and may be affected by multiple mediators acting through a variety of potentially parallel and/or redundant pathways. However, these features of parallel and redundant pathways that thwart well-conceived attempts to selectively inhibit the development of inflammation are the same features that render approaches to harness active resolution more likely to succeed. The series of reviews in this issue of the *Journal* was commissioned to provide readers with a perspective on the routes being taken to identify strategies for exploiting active inflammation resolving mechanisms. Mauro Perretti and Jesmond Dalli introduce the complexity of annexin-1, a mediator of many

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of the beneficial anti-inflammatory glucococortioid actions (D'Acquisto *et al.*, 2008), as an active inflammation-resolving protein that acts either directly, or via a proteolytic cleavage product of its N-terminus (Perretti and Dalli, 2009). This alignment of the activity of glucocorticoids with inflammation resolution should perhaps come as no surprise. It does highlight the increasingly recognized need to evaluate new agents for their impact on inflammation-resolving mechanisms (Serhan *et al.*, 2007), a potential referred to as 'r*esolution-toxic*' (Perretti and Dalli, 2009). It seems reasonable to consider whether this new element to safety pharmacology of emerging and established anti-inflammatory agents should be extended to all new therapeutics. It has been found that agents unrelated to inflammation, such as local and volatile general anaesthetics, can differentially compromise the production and actions of endogenous inflammation-resolving pathways (Chiang *et al.*, 2008). Inflammation-related drug safety does not feature prominently in contemporary discussions of the principles of safety pharmacology (Pugsley *et al.*, 2008). Paolo Maderna and Catherine Godson discuss the role of lipoxins in the resolution pathway (Maderna and Godson, 2009) and highlight the activation the formyl peptide-related receptor (FPRL-1), which is also activated by annexin-1 and its N-terminal peptides. The convergence in resolution pathways is brought into even sharper focus by the discovery that aspirin acetylation of COX-2 yields an enzyme that retains catalytic activity and is able to produce epimers of lipoxin A that also have agonist activity at FPRL-1 receptors, as highlighted in an earlier review from Serhan and Chiang (2008). This discussion is extended by Payal Kohli and Bruce Levy in an article that focuses on newer members of the resolution pathway, the resolvins and protectins that are generated from polyunsaturated free fatty acids (PUFA) eicosapentaenoic (C20:5) and docosahexaenoic (C22:6) acids respectively (Kohli and Levy, 2009). Unlike the lipoxins, annexin-1 and its N-terminal cleavage products, the resolvins and protectins act on distinct receptors, including a novel receptor chemR23, and the leukotriene B_4 receptor, BLT1. Kohli and Levy discuss how these products may explain the anti-inflammatory benefits of dietary loading with the omega 3 C20:5 and C22:6 PUFAs.

The hepoxilins are a further class of lipids mobilized in inflammation and having the potential to perpetuate inflammatory responses. In the review by Cecile Pace-asciak hepoxilin analogues with anti-inflammatory and anti-fibrotic effects are discussed, although the receptor mediating these effects is as yet not fully identified (Pace-Asciak, 2009). The receptor mechanisms of the sphingolipid-derivatives discussed by Graeme Nixon are better delineated and antagonists of the GPCR S1P receptors are being evaluated for their potential as anti-inflammatory agents (Nixon, 2009). Endogenous lipids are also among the characterized ligands for the multiple members of the peroxisome proliferator receptor (PPAR) family discussed by Maria Belvisi and Jane Mitchell. The PPARγ subtype is of particular interest, as it has been implicated in anti-inflammatory and anti-remodelling activities observed with the insulin-sensitizing agent, rosiglitazone (Belvisi and Mitchell, 2009). Moreover, the pleiotropic nature of PPARγ actions fits the mould of successful anti-inflammatory strategies.

The actions of lipid and peptide mediators of resolution in terminating neutrophil recruitment and promoting their phagocytosis by macrophages are reasonably well understood, but there are many additional mechanisms discussed in the pages of this issue. The survival of inflammatory cells at sites of chronic inflammation has long been recognized as a determinant of duration and intensity of inflammation. Leitch *et al.* discuss a novel approach to accelerating clearance of neutrophils using cyclin-dependent kinase inhibitors (CDKI) to trigger neutrophil apoptosis (Leitch *et al.*, 2009).

The role of proteases and the potential of targeting their effectors as anti-inflammatory strategies have been examined in three papers in the issue. Terence Peters and Peter Henry argue that activation protease-activated receptor 2 (PAR2) provides cytoprotective PGE_2 production by the respiratory epithelium, but acknowledge that the PAR2 pharmacology is complex and highly context dependent (Peters and Henry, 2009). The successful clinical use of activated protein C (APC) provides an example of an agent that has, among a breadth of activities, the capacity to diminish inflammation. Michael Matthay *et al.* discuss how APC evokes a distinct anti-inflammatory response that together with its anti-thrombotic effects confers a therapeutic effect on APC in the treatment of severe sepsis (Neyrinck *et al.*, 2009). It appears that APC interacts with the PAR1 receptor to redirect signalling to pathways that evoke anti-inflammatory effects, whereas normally, PAR1 responds to ligands such as thrombin, with the production of pro-inflammatory mediators. Catherine Greene and Noel McElvaney discuss the potential of anti-proteases to resolve inflammation, identifying the protease/anti-protease balance, as well more direct anti-inflammatory effects independent of protease inhibition, that could be harnessed (Greene and McElvaney, 2009).

Ultimately, the conceptual picture that emerges from inflammation resolution provides further insights into the limitations on the efficacy of anti-inflammatory strategies. It appears that pro-inflammatory networks are responsible for triggering the resolution pathways. Thus, inopportune timing or extent of inhibition of such triggering mechanisms may, during certain stages of the evolving inflammatory response, lead to an increase in either the intensity or the duration of response. This analysis is, of course, overly simplistic, in that it invokes a discrete beginning and end to the inflammatory episode, whereas for many chronic diseases, there is good evidence to suggest that the underlying inflammation never fully resolves. In such chronic inflammatory conditions, the chronic anti-inflammatory treatment could conceivably also provide a chronic suppression of resolution.

Regardless of the need to carefully consider the interactions between anti-inflammatory and pro-resolving strategies, the field is entering an exciting period of development during which it seems likely that many novel therapeutic approaches to inflammation will be evaluated.

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