ANTI-INFLAMMATORY LIPID MEDIATORS AND INSIGHTS INTO THE RESOLUTION OF INFLAMMATION

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The pro-inflammatory signalling pathways and cellular mechanisms that initiate the inflammatory response have become increasingly well characterized. However, little is known about the mediators and mechanisms that switch off inflammation. Recent data indicate that the resolution of inflammation is an active process controlled by endogenous mediators that suppress pro-inflammatory gene expression and cell trafficking, as well as induce inflammatory-cell apoptosis and phagocytosis, which are crucial determinants of successful resolution. This review focuses on this emerging area of inflammation research and describes the mediators and mechanisms that are currently stealing the headlines.

Inflammation is a beneficial host response to foreign challenge or tissue injury that leads ultimately to the restoration of tissue structure and function[1,2]. This response requires innate immunity and, in some cases, an adaptive immune response, which are the two main integral components of the host's defence system. Innate immunity not only acts as the first line of defence against noxious material, but after recognition of an appropriate stimulus, it provides the necessary signals to instruct the adaptive immune system to mount a response. In turn, the adaptive response relies on the innate immune system to provide the necessary effectors, in the form of phagocytes and granulocytes, to deal with the initiating stimulus. However, prolonged inflammation can cease to be a beneficial event and it contributes to the pathogenesis of many disease states. The chronic inflammatory disease rheumatoid arthritis is characterized by the accumulation and persistence of inflammatory cells in synovial joints, which results in joint damage. This loss of tissue or organ function as a result of an inappropriate inflammatory response is also seen in various other diseases, such as chronic bronchitis, emphysema, asthma, glomerulonephritis, myocardial infarction and ischaemia reperfusion injury. By contrast, certain inflammatory diseases have an intrinsic capacity for complete resolution without tissue injury — for example, lobar streptococcal pneumonia, which involves the extensive accumulation of neutrophils, monocytes and macrophages in the lungs. Studies of patients who have lobar pneumonia show that most of the lesions resolve without any evident tissue destruction. Experiments in animal models of streptococcal pneumonia show resolution of tissue pathology in 3–4 days[3–5]. Therefore, this type of self-limiting inflammatory response is under the strict control of endogenous mechanisms. As continual activation of the adaptive immune system is the driving force behind chronic inflammation, it is crucial to identify the STOP SIGNALS that are present in self-limiting, self-resolving inflammatory lesions. These signals might be used therapeutically to control the activation of the adaptive immune response and the transition from acute to chronic inflammation, when these signals might be absent or become dysregulated. In pursuit of this goal, recent studies have shown that certain lipid mediators might have a crucial role in the resolution of inflammation as endogenous anti-inflammatory mediators. This review will focus on an important and largely ignored issue regarding the regulation of the inflammatory response — that the

STOP SIGNALS
This term was coined to introduce the concept of a cellular agonist that acts as an inhibitor of inflammation.

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doi:10.1038/nri915

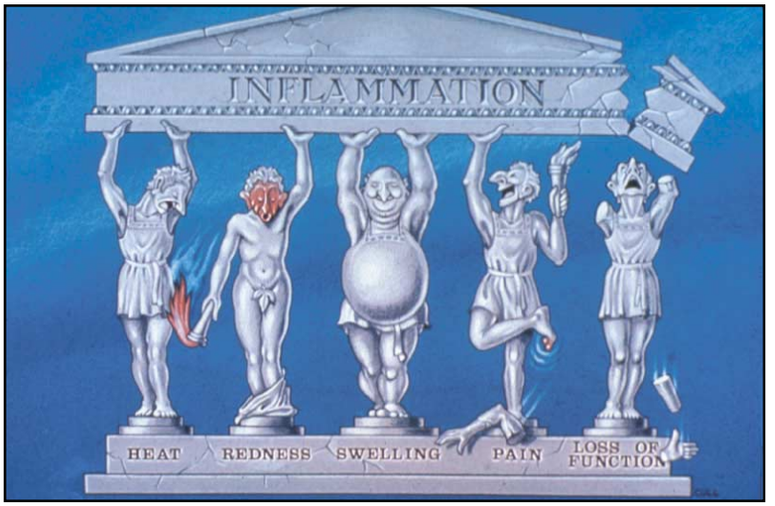

Figure 1 | **Cardinal signs of inflammation.** This cartoon depicts five Greeks representing the cardinal signs of inflammation — heat, redness, swelling, pain and loss of function — which are as appropriate today as they were when first described by Celsus more than 2000 years ago. This figure was commissioned by D.A.W. and drawn by P. Cull for the Medical Illustration Department at St Bartholomew's Medical College.

resolution of inflammation is a highly controlled and coordinated process that involves the suppression of pro-inflammatory gene expression, leukocyte migration and activation, followed by inflammatory-cell clearance by apoptosis and phagocytosis. We highlight the role of new endogenous anti-inflammatory mediators, such as CYCLOPENTENONE PROSTAGLANDINS (cyPGs) and LIPOXINS, that might regulate these events.

Acute inflammation: a salutary response

Inflammation is a reaction of the microcirculation that is characterized by the movement of serum proteins and leukocytes from the blood to the extravascular tissue. This movement is regulated by the sequential release of vasoactive and chemotactic mediators, which contribute to the cardinal signs of inflammation — heat, redness, swelling, pain and loss of tissue function (FIG. 1). Local vasodilation increases regional blood flow to the inflamed area and, together with an increase in microvascular permeability, results in the loss of fluid and plasma proteins into the tissues. Concomitantly, there is an upregulation of expression of adhesion molecules on endothelial cells and the release of chemotactic factors from the inflamed site, which facilitate the adherence of circulating cells to the vascular endothelium and their migration into the affected area. These tightly regulated events result in a predominance of neutrophils in the inflamed area at the onset of the lesion, which are later gradually replaced by mononuclear cells — mainly monocytes, which then differentiate into macrophages. These phagocytic cells ingest foreign material and cell debris. They also release hydrolytic and proteolytic enzymes, and generate reactive oxygen species that eliminate and digest invading organisms. Finally, the injurious stimulus is cleared and normal tissue structure and function is restored. The mediators and mechanisms of this largely ignored process of resolution have begun to be elucidated only recently. It has become clear that endogenous anti-inflammatory mediators reverse vascular changes and inhibit leukocyte migration and activation, while promoting the safe removal of inflammatory cells by apoptosis and subsequent phagocytosis.

There are many mediators that coordinate the initial events of acute inflammation (TABLE 1, FIG. 2). Vasoactive amines, lipid-derived EICOSANOIDS, cytokines and chemokines coordinately regulate vascular changes and inflammatory-cell recruitment[6]. Cell-adhesion molecules facilitate the movement of inflammatory cells from the peripheral circulation to the inflammatory site. Pro-inflammatory cytokines, such as tumour-necrosis factor (TNF) and interleukin-1β (IL-1β), activate signalling pathways in endothelial cells that regulate the expression of these adhesion molecules to initiate the capture of circulating leukocytes[7].

Endogenous anti-inflammatory mediators

It is well known that the inflamed tissue generates local pro-inflammatory stimuli to drive acute inflammation, but there is also systemic and local production of endogenous mediators that counterbalance these pro-inflammatory events. Studies in the 1950s and 1960s identified endogenous anti-inflammatory mediators that counteract vascular leakage — namely, adrenaline, noradrenaline and 5-hydroxytryptamine[8–10] — and intracellular cyclic AMP, a second messenger induced by several hormones, inflammatory mediators and cytokines, which dampens leukocyte activation[11]. Elevation of the level of intracellular cAMP — by inhibiting the enzyme system that is responsible for its catabolism (phosphodiesterase) — ameliorates immune and non-immune inflammation *in vivo* and suppresses various cellular processes *in vitro*, including the immunological release of histamine and leukotrienes from mast cells, monocytes and neutrophils; lysosomal enzymes and reactive oxygen species from neutrophils; and cytokines and nitric oxide (NO) from macrophages[12]. These data further indicate that cAMP has a central role in the resolution of inflammation. Perhaps the most powerful endogenous anti-inflammatory agents to be described so far are the glucocorticoids. Glucocorticoids and their synthetic mimetics are used for the treatment of several chronic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, asthma, psoriasis and vasculitis. Most of the actions of glucocorticoids require binding to cytoplasmic steroid hormone receptors that migrate to the nucleus and antagonize pro-inflammatory gene transcription[13]. However, glucocorticoids also induce the expression of regulatory proteins that have anti-inflammatory actions, of which the peptide annexin 1 (previously known as lipocortin 1) has been well described *in vitro* and *in vivo*. Annexin 1 has been shown to inhibit the production of prostaglandins, as well as neutrophil and monocyte migration, *in vivo*[14–16].

Anti-inflammatory lipid mediators

Research in recent years has uncovered new endogenous anti-inflammatory lipid mediators that have potent

CYCLOPENTENONE PROSTAGLANDINS
Prostaglandin metabolites that are characterized by the presence of a highly reactive electrophilic carbon atom in the unsaturated carbonyl group of the cyclopentane ring.

LIPOXINS
Leukocyte-derived eicosanoids generated during the inflammatory response that act as downregulatory signals.

EICOSANOIDS
A class of lipid mediator that have twenty-carbon fatty-acid derivatives; from the Greek eicosa, meaning 20. Eicosanoids are fatty-acid derivatives, primarily derived from arachidonic-acid precursors, that have a wide variety of biological activities. There are four main classes of eicosanoid — the prostaglandins, prostacyclins, thromboxanes and leukotrienes — derived from the activities of cyclooxygenases and lipoxygenases on membrane-associated fatty-acid precursors.

Table 1 | **Mediators that regulate the acute inflammatory response**

Mediator class	Pro-inflammatory	Anti-inflammatory
Amines	Histamine, bradykinin	Adrenaline, noradrenaline
Lipid mediators	PGE_2, PGI_2, LTB_4, LTC_4	PGJ_2, $PGA_{1/2}$, lipoxins
Complement	C3a, C5a	C1q receptor
Cyclic nucleotides	cGMP	cAMP
Adhesion molecules	E-selectin, P-selectin, ICAM1, VCAM1	$\alpha_v\beta_3$ integrin, TSP receptor, PS receptor
Cytokines	TNF, IL-1β, IL-6	TGF-β1, IL-10
Chemokines	IL-8 (CCL8), GRO/KC, MIP1α (CCL3), MCP1 (CCL2)	-
Steroid hormones	-	Glucocorticoids

cAMP, cyclic adenosine 3,5 monophosphate; cGMP, cyclic guanosine 3,5 monophosphate; ICAM1, intercellular adhesion molecule 1; IL, interleukin; LT, leukotriene; MCP1, monocyte chemotactic protein 1; MIP1α, macrophage inflammatory protein 1α; PG, prostaglandin; PS, phosphatidylserine; TGF-β1, transforming growth factor-β1; TNF, tumour-necrosis factor; TSP, thrombospondin; VCAM1, vascular cell adhesion molecule 1.

LIPOXYGENASE
A nonheme iron dioxygenase that is the key enzyme in leukotriene production.

TRANSCELLULAR BIOSYNTHESIS
A biosynthetic pathway that is dependent on molecules transferred from one cell to another.

immunomodulatory and anti-inflammatory effects. These can be divided into two classes: the lipoxins and the cyPGs. The lipoxins are generated *in vivo* by the action of LIPOXYGENASE or the concerted action of lipoxygenase and cyclooxygenase enzymes, whereas the cyPGs are spontaneous prostaglandin metabolites that are formed by the action of cyclooxygenase (ONLINE FIGS 1–3). Recent research indicates that these two classes of lipid metabolite are endogenous anti-inflammatory mediators that promote the resolution of inflammation *in vivo*.

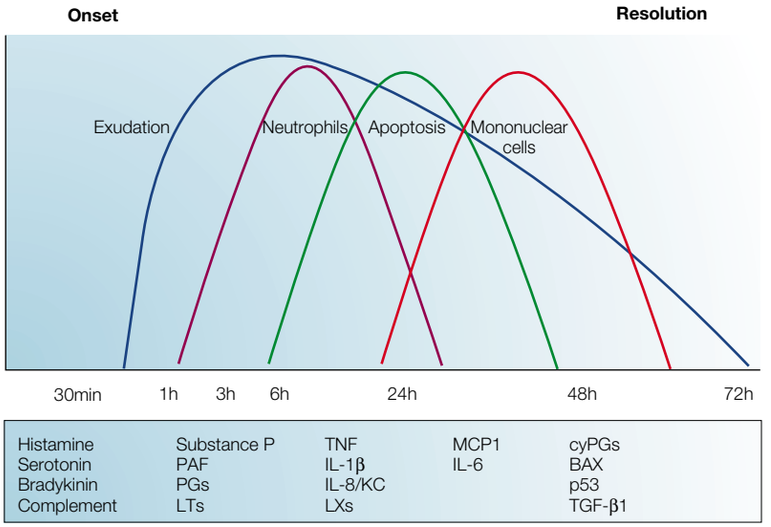

Figure 2 | **Theoretical time course of acute inflammation and associated mediators.** This schematic illustrates the cellular kinetics of inflammation and sequential release of mediators, based on studies of animal models of acute inflammation. Vasoactive amines and lipid mediators promote exudate formation and oedema; this is followed by the expression of cytokines and chemokines that activate the endothelium and mediate leukocyte (neutrophil) migration. Finally, anti-inflammatory mediators, such as lipoxins (LXs) and cyclopentenone prostaglandins (cyPGs), attenuate cell migration and promote the apoptosis and clearance of leukocytes from the inflammatory site. The phagocytosis of apoptotic cells by mononuclear cells promotes the further release of anti-inflammatory mediators, such as transforming growth factor-β1 (TGF-β1). BAX, BCL-2-associated X protein; IL, interleukin; LTs, leukotrienes; MCP1, monocyte chemotactic protein 1 (CCL2); PAF, platelet-activating factor; PGs, prostaglandins; TNF, tumour-necrosis factor.

Lipoxins. In contrast to prostaglandins and leukotrienes, which are generated by intracellular biosynthesis, lipoxins are generated through cell–cell interactions by a process known as TRANSCELLULAR BIOSYNTHESIS[17]. Nanomolar concentrations of lipoxins inhibit neutrophil and eosinophil chemotaxis[18,19]; lipoxin A_4 (LXA_4), for example, blocks neutrophil migration across postcapillary venules and inhibits neutrophil entry into inflamed tissues in animal models[20]. Owing to the very short half-life of the lipoxins, a range of stable, biologically active analogues have been designed and tested for their anti-inflammatory effects in animal models. The LXA_4 analogue 16-phenoxy-LXA_4 markedly reduced leukotriene B_4 (LTB_4)-induced ear swelling in the mouse, by preventing neutrophil infiltration and reducing the increased vascular permeability[21]. In contrast to their inhibitory effects on neutrophil and eosinophil recruitment, lipoxins are potent chemoattractants for monocytes[22]; LXA_4 and LXB_4 stimulate monocyte adherence to vascular endothelium and chemotaxis. However, lipoxin-recruited monocytes do not generate superoxide anions or degranulate in the presence of lipoxins.

The acute inflammatory response is characterized by the initial recruitment of neutrophils, followed by the recruitment of monocytes that differentiate into macrophages. Activated neutrophils that have degranulated are subsequently phagocytosed by monocyte-derived macrophages, which eventually exit the inflamed site in the draining lymphatics. Whether the acute inflammatory lesion resolves depends, in part, on the activation state of the monocytes. It seems that lipoxins might have a crucial role in resolving inflammation, not only by recruiting monocytes to clear the inflamed site of necrotic and apoptotic neutrophils, but also by regulating their level of activation and capacity to cause tissue damage by the uncontrolled generation of reactive oxygen species[22]. As discussed later, it seems that lipoxins might share this role with cyPGs. Lipoxins also promote the phagocytic clearance of apoptotic cells by macrophages, which might contribute further to the resolution of inflammation[23].

Cyclopentenone prostaglandins. Recent studies in our laboratory, which have been confirmed by others, indicate that products of CYCLOOXYGENASE 2 (COX2) have an important role in the resolution of acute inflammation[24–26]. These studies show that although COX2 drives the onset of inflammation through the production of pro-inflammatory prostaglandin E_2 (PGE_2), it also brings about the resolution of inflammation through the preferential synthesis of the anti-inflammatory cyPG 15deoxy$\Delta^{12,14}PGJ_2$ ($15dPGJ_2$). These studies highlight several important findings. First, there is a switch in prostaglandin synthesis from pro-inflammatory prostaglandins at the onset of inflammation to anti-inflammatory prostaglandins at the resolution of inflammation. This has also been shown by Levy and colleagues[27], who described a switch from the pro-inflammatory prostaglandins and leukotrienes that are produced during the initiation of inflammation to the

Box 1 | **Anti-inflammatory properties of lipoxins and prostaglandins**

Lipoxins
- ↑ Phagocytosis of apoptotic neutrophils
- ↓ Neutrophil and eosinophil migration
- ↓ Adhesion-molecule activation and gene expression
- ↑ Monocyte adhesion and chemotaxis
- ↓ Interleukin-8 (CCL8) release by epithelial cells
- ↓ Superoxide production by neutrophils

Cyclopentenone prostaglandins
- ↓ Expression of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 on endothelium
- ↓ Monocyte migration
- ↓ Expression of inducible nitric oxide synthase by macrophages
- ↑ Myeloid-cell apoptosis
- ↓ Nuclear factor-κB activation

anti-inflammatory lipoxins that are produced during resolution. Second, COX2 is essential for the resolution of inflammation. Finally, $15dPGJ_2$ is a new endogenous mediator that has potent anti-inflammatory properties. Since then, several studies in animal models of autoimmune and inflammatory diseases have indicated that cyPGs, such as $15dPGJ_2$, have potent immunomodulatory and anti-inflammatory properties[28–32].

The anti-inflammatory properties of cyPGs, similar to the lipoxins, might relate to effects on cell trafficking and activation[33,34]. $15dPGJ_2$ has been shown to inhibit TNF-stimulated expression of the adhesion molecules vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) by primary human endothelial cells. However, the expression of E-selectin and platelet/endothelial cell adhesion molecule 1 (PECAM1) was unaltered. Furthermore, $15dPGJ_2$ inhibited phorbol 12-myristate-13-acetate (PMA)- and lipopolysaccharide (LPS)-stimulated VCAM1 expression and monocyte binding to human aortic endothelial cells. Interestingly, $15dPGJ_2$ had no effect on neutrophil adhesion to PMA-activated endothelial cells; this might be due to the selective inhibition of adhesion-molecule expression described above. However, $15dPGJ_2$ blocked the adhesion-dependent oxidative burst of neutrophils *in vitro*[35]. Also, $15dPGJ_2$ has been shown recently to suppress chemokine expression selectively *in vitro*; expression of the mononuclear-cell chemokine monocyte chemotactic protein 1 (MCP1; also known as CCL2), but not of the neutrophil-selective IL-8 (CXCL8), was inhibited by $15dPGJ_2$[36]. We and others have shown the potent inhibitory effects of cyPGs on macrophage activation *in vitro*[37–42]. Ricote *et al.*[38] described the suppression of pro-inflammatory signalling pathways, including nuclear factor-κB (NF-κB), AP1 and signal transducers and activators of transcription (STATs), in macrophages by $15dPGJ_2$. Other studies have shown the inhibition of pro-inflammatory gene expression by $15dPGJ_2$ and other cyPGs in mouse macrophages *in vitro*[40–42]. These effects of cyPGs on monocyte migration and macrophage activation are in contrast to the potent inhibitory effects of lipoxins on neutrophil recruitment and activation. This might indicate that lipoxins are early braking signals for the neutrophil response in acute inflammation, whereas cyPGs promote the resolution of inflammation through the suppression of pro-inflammatory macrophage function (BOX 1).

Apoptosis and phagocytosis

The accumulation and persistence of leukocytes is a hallmark of chronic inflammation. Apoptosis and the clearance of apoptotic cells have been recognized as important mechanisms for the resolution of inflammation *in vivo*[43,44]. Apoptosis is a physiological process for the non-inflammatory removal of cells, and the apoptotic programme is a conserved feature of all eukaryotic cells. During apoptosis, cells retain an intact membrane and, therefore, do not release potentially pro-inflammatory intracellular components. During the inflammatory response, recruited granulocytes that undergo apoptosis retain their granules and lose the ability to degranulate in response to pro-inflammatory stimuli[43]. Apoptotic cells express specific surface molecules that allow their recognition and phagocytosis by macrophages[44]. Leukocyte apoptosis and ingestion by phagocytes such as macrophages allows the non-inflammatory clearance of dead and dying cells from sites of inflammation (FIG. 3). In animal models of resolving inflammation, we have shown that leukocyte apoptosis coincides with the production and release of cyPGs and other anti-inflammatory mediators, such as transforming growth factor-β1 (TGF-β1)[45]. *In vitro* studies have shown the ability of $15dPGJ_2$ to promote cell apoptosis[46–48]. Furthermore, the therapeutic effects of $15dPGJ_2$ in a rat model of arthritis are associated with the induction of synoviocyte apoptosis[28]. These studies, and work from our laboratory (T.L. and D.W.G., unpublished observations), indicate that endogenous PGD_2 metabolites (such as $15dPGJ_2$) might regulate leukocyte apoptosis during the resolution of inflammation *in vivo*. This might account for the anti-inflammatory properties of these prostaglandin metabolites.

The signals that promote leukocyte apoptosis are important for the resolution of inflammation; however, apoptotic cells themselves can also promote the resolution of inflammation. Studies by Fadok and colleagues[49] have shown that the phagocytic clearance of apoptotic cells by macrophages promotes the release of TGF-β1 and suppresses the pro-inflammatory activity of the macrophages (FIG. 3). These *in vitro* studies have now been extended to *in vivo* models of inflammation. The transfer of apoptotic cells to LPS-stimulated lungs reduced the release of pro-inflammatory mediators and leukocyte recruitment; this effect could be reversed by the administration of TGF-β1-neutralizing antiserum[50]. Also, the uptake of apoptotic cells by synovial macrophages has been shown to ameliorate immune-complex-induced arthritis in mice[51]. Therefore, it is proposed that intrinsic defects in apoptosis and the clearance of apoptotic cells might lead to chronic inflammatory

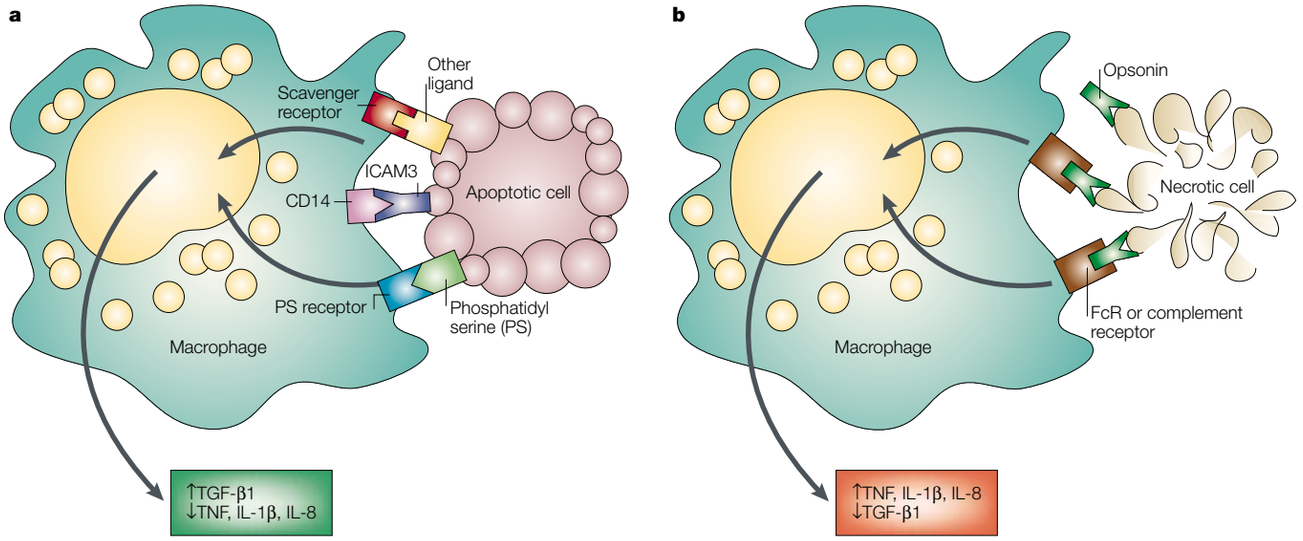

Figure 3 | **The two faces of phagocytosis.** The non-inflammatory clearance of apoptotic cells (**a**) compared with the pro-inflammatory ingestion of necrotic cells and debris (**b**). **a** | Macrophages recognize apoptotic cells through specific cell-surface receptors; subsequent phagocytosis promotes the release of anti-inflammatory mediators, such as transforming growth factor-β1 (TGF-β1), and suppresses the production of pro-inflammatory mediators. **b** | However, necrotic-cell debris does not express specific receptors and is phagocytosed through alternative mechanisms, such as Fc receptors (FcR), that promote the release of pro-inflammatory mediators, such as tumour-necrosis factor (TNF). IL, interleukin; ICAM3, intercellular adhesion molecule 3.

diseases. In support of this hypothesis, cytokine-mediated suppression of apoptosis has been shown in sputum from patients with neutrophilic lung diseases, including cystic fibrosis, idiopathic fibrosis and pneumonia[52]. A recent study has also described the impaired clearance of apoptotic cells in patients with cystic fibrosis and bronchiectasis[53]. In addition, the impaired uptake of apoptotic cells has been linked to the pathogenesis of systemic lupus erythematosus (SLE)[54].

The promotion of leukocyte apoptosis by cyPGs and the enhanced uptake of apoptotic cells induced by anti-inflammatory lipoxins (BOX 1) indicate that these endogenous lipid mediators might coordinately regulate the resolution of inflammation. Therefore, defects in the production of these mediators might predispose to chronic inflammation, and their exogenous application might promote the resolution of inflammatory diseases.

NF-κB and the resolution of inflammation

The molecular mechanism of the anti-inflammatory action of cyPGs has been the subject of much debate. The PGD_2 metabolites of the J_2 series are thought to be endogenous ligands for peroxisome proliferator-activated receptor γ (PPARγ). PPARs have been proposed to negatively regulate inflammation through various mechanisms[55,56]. However, many of the reported effects of PPARγ agonists occur at doses far in excess of those that are required for the activation of the receptor. Studies that evaluated the PPARγ-dependent inhibition of macrophage activation *in vitro* have shown that $15dPGJ_2$ is significantly more effective at inhibition than synthetic PPARγ ligands, despite the fact that it has a relatively low binding affinity for PPARγ[38]. Similarly, experiments with PPARγ-negative cell lines have shown that PGD_2 metabolites have modulatory effects that are independent of PPARγ[42]. The possible anti-inflammatory roles of PPARs have been reviewed elsewhere and are not discussed further here.

How might cyPGs regulate inflammation independent of PPARs? The cyPGs are characterized by the presence of a highly reactive electrophilic carbon atom in the unsaturated carbonyl group of the cyclopentane ring (ONLINE FIG. 3). Through Michael addition reactions, this carbon atom can react with nucleophiles, such as the free sulphydryl groups of glutathione (GSH) and cysteine residues that form disulphide bonds in proteins. Cyclopentenone prostaglandins have been shown to modify conserved cysteine residues that are found in both the *trans*-acting DNA-binding proteins of NF-κB and elements of the upstream kinase complex — inhibitor of NF-κB (IκB) kinase (IKK) — that activates NF-κB[42,57,58].

NF-κB is thought to have a pivotal role in immune and inflammatory responses through the regulation of genes that encode pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors and inducible enzymes, such as COX2 and inducible nitric oxide synthase (iNOS). NF-κB also has a pivotal role in the regulation of cell apoptosis. The consensus pathway for the activation of NF-κB in response to pro-inflammatory stimuli such as TNF and IL-1β has been characterized extensively (FIG. 4).

Many of the target genes that are suppressed by cyPGs are regulated by the NF-κB pathway. These include the genes that encode the adhesion molecules ICAM1 and VCAM1, and the inducible enzymes iNOS and COX2. Ricote *et al.*[38] showed that the inhibitory effects of $15dPGJ_2$ on macrophage gene expression are mediated at

CYCLOOXYGENASE 2 (COX2). An inducible cyclooxygenase enzyme that is thought to be the main producer of prostaglandins during the inflammatory response.

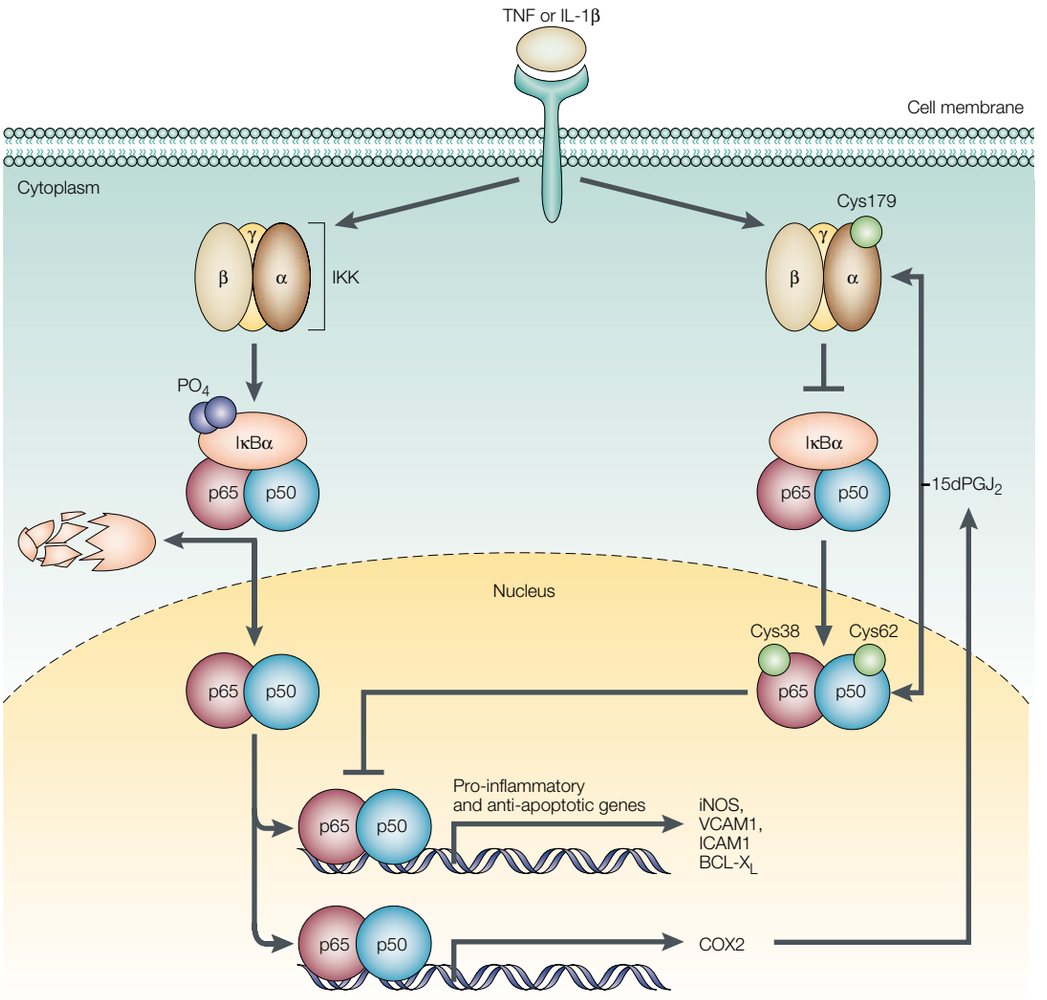

Figure 4 | **NF-κB activation in response to pro-inflammatory stimuli.** Tumour-necrosis factor (TNF) and interleukin-1β (IL-1β) stimulate the phosphorylation, ubiquitylation and subsequent degradation of inhibitor of nuclear factor-κB, α (IκBα). This allows the NF-κB p65–p50 heterodimer to migrate to the nucleus and upregulate the expression of pro-inflammatory and anti-apoptotic genes. TNF and IL-1β act through distinct cell-surface receptors and signalling pathways that converge on the activation of IκB kinase (IKK), which consists of three subunits — IKKα, IKKβ and IKKγ. IKKβ is responsible for the activation of NF-κB in response to TNF and IL-1β through the phosphorylation of IκBα. The cyclopentenone prostaglandin 15deoxyΔ^{12,14}PGJ$_2$ (15dPGJ$_2$) inhibits the NF-κB pathway at many levels through the covalent modification of crucial cysteine residues in the IKK complex (Cys179) and the DNA-binding subunits of NF-κB (Cys38 and Cys62 of p65 and p50, respectively). NF-κB target genes include the *COX2* gene; therefore, 15dPGJ$_2$ generated through COX2 might act as a negative-feedback loop for the expression of COX2 enzyme. This might promote the resolution of inflammation through the inhibition of pro-inflammatory and anti-apoptotic gene expression. COX2, cyclooxygenase 2; ICAM1, intercellular adhesion molecule 1; iNOS, inducible nitric oxide synthase; VCAM1, vascular cell adhesion molecule 1.

the gene promoter level. Later, it was shown that in macrophage and lymphocyte cell lines, 15dPGJ$_2$ inhibited the activation of IKKβ, which regulates the activation of NF-κB in response to pro-inflammatory stimuli[41,42,57]. 15dPGJ$_2$ was shown to alkylate Cys179 of IKKβ, which is located in the kinase activation loop[57]. The DNA-binding subunits of NF-κB — p50 (NF-κB1) and p65 (RELA) — have also been shown to be alkylated at Cys62 and Cys38, respectively, by 15dPGJ$_2$[42,58]. These residues are located in the DNA-binding domains of the proteins and their alkylation prevents the activation of gene expression. These studies indicate that 15dPGJ$_2$ might inhibit activation of the NF-κB pathway at many levels (FIG. 5).

Besides the role of NF-κB in pro-inflammatory gene expression, the NF-κB pathway also regulates protection from cytokine-induced apoptosis[59,60]. This might underpin the pro-apoptotic action of cyPGs and contribute to their anti-inflammatory and immunoregulatory properties *in vivo*. For example, expression of the anti-apoptotic protein BCL-X$_L$ is regulated by the NF-κB pathway. 15dPGJ$_2$ inhibits activation of the BCL-X$_L$ promoter by NF-κB and promotes the apoptosis of CD28-co-stimulated primary human CD4$^+$ T cells *in vitro*[47]. Recently, Ward *et al.*[48] described the induction of caspase-dependent apoptosis in both neutrophil and eosinophil granulocytes by 15dPGJ$_2$ through the

TRANSACTIVATION
The activation of gene transcription by *trans*-acting factors, such as protein transcription factors, as opposed to *cis*-acting DNA elements, such as enhancers/promoters.

inhibition of IκBα degradation, independent of PPARγ. Previous studies from this laboratory have shown that the specific inhibition of NF-κB can induce granulocyte apoptosis directly and prevent the delay of apoptosis in stimulated granulocytes[60]. It should be noted that a direct causal link between $15dPGJ_2$-mediated inhibition of NF-κB and the resolution of inflammation has yet to be proven. However, the specificity of $15dPGJ_2$ for IKKβ and the activation of NF-κB in response to pro-inflammatory stimuli indicates that $15dPGJ_2$ might be particularly attractive as a pharmacological agent.

In contrast to the well-documented pro-inflammatory role of NF-κB, we have described an active role for NF-κB in the resolution of inflammation recently[45]. This involves the recruitment of alternative DNA-binding complexes that lack transactivation domains, such as p50–p50 homodimers. Broad-spectrum inhibitors of the NF-κB pathway, such as antioxidants and proteasome inhibitors, had the expected anti-inflammatory actions during the initiation of inflammation; however, when they were administered after the onset of inflammation, these inhibitors prevented the resolution of inflammation, which was associated with the inhibition of leukocyte apoptosis. We hypothesize that this alternative NF-κB pathway promotes leukocyte apoptosis by the TRANSACTIVATION of pro-apoptotic target genes with co-activating factors. Alternatively, active NF-κB DNA-binding complexes that lack transactivation domains might act as dominant-negative inhibitors of anti-apoptotic gene expression (FIG. 5). Cyclopentenone prostaglandins might repress the activation of IKKβ, leading to a predominance of anti-inflammatory signalling pathways that are regulated independently of IKK or by an alternative IKK complex that is not sensitive to inhibition by cyPGs.

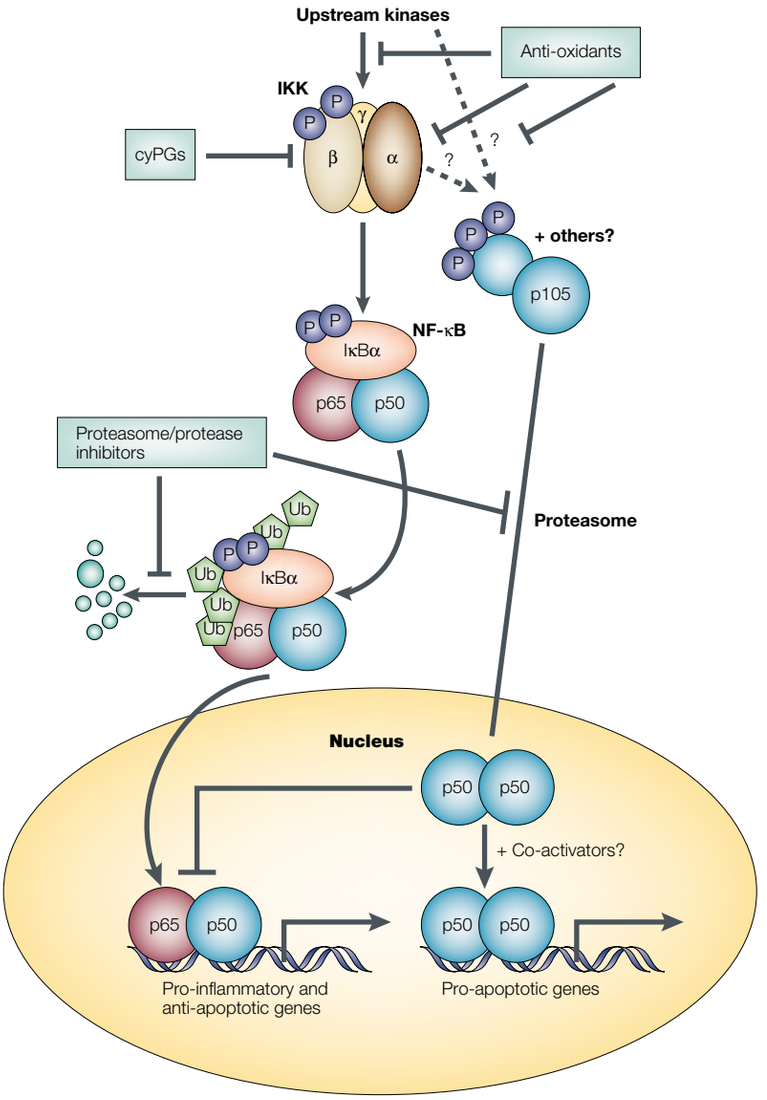

Figure 5 | **Hypothetical model of an alternative anti-inflammatory pathway of NF-κB activation.** Broad-spectrum nuclear factor-κB (NF-κB) inhibitors that target the proteasome or undefined upstream signalling events could block potentially beneficial anti-inflammatory pathways of NF-κB activation. For example, they might block the processing of p105 to p50 and the assembly of p50–p50 homodimer complexes, which negatively regulate pro-inflammatory gene expression and might coordinate the expression of an alternative set of NF-κB target genes through interaction with distinct co-activators. The specificity of cyclopentenone prostaglandins (cyPGs) for inhibitor of NF-κB kinase-β (IKKβ) might prevent undesirable side effects of inhibitors through the inhibition of other IKKs or IKK-independent pathways for NF-κB activation. Anti-oxidants have been shown to inhibit many stages of the NF-κB pathway, including the activation of upstream IKK kinases and IκB kinase activity. P, phosphate; Ub, ubiquitin.

Therapeutic implications

Synthetic lipoxin analogues have shown promise as therapeutic agents in several disease models[61]. For example, lipoxin analogues prevent allergen-induced expression of CCL11 (eotaxin) *in vivo*, and inhalation of LXA_4 by asthmatic patients inhibits LTC_4-induced airway obstruction. Several studies in animal models of autoimmune and inflammatory diseases have indicated that the administration of cyPGs, such as $15dPGJ_2$, might offer a new approach to anti-inflammatory therapy. The intra-peritoneal administration of $15dPGJ_2$ was shown to ameliorate adjuvant-induced arthritis (AIA) in the rat[28]. These effects were associated with the suppression of pannus formation and of mononuclear-cell infiltration into the joint. We have shown similar effects of both $15dPGJ_2$ and PGA_2 in mouse collagen-II-induced arthritis, which has a different aetiology to that of AIA in the rat (P. R. Colville-Nash, T.L., D.A.W. and D.W.G., unpublished observations). A recent study by Diab *et al.*[29] has shown that $15dPGJ_2$ significantly attenuates clinical signs of disease in experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis. *Ex vivo* culture with $15dPGJ_2$ reduced the ability of encephalitogenic T cells to adoptively transfer disease. $15dPGJ_2$ was also shown to inhibit the proliferation and cytokine production of antigen (myelin basic protein)-specific T cells isolated from the spleen. These data agree with previous studies that showed reduced proliferation and IL-2 secretion of T-cell clones and splenocytes after treatment with $15dPGJ_2$[30]. Endogenous PGJ_2 has also been proposed to modulate lupus nephritis *in vivo*. Renal glomerular mesangial cells are an important source of inflammatory mediators and cytokines that drive the inflammatory response in lupus

CYCLOOXYGENASE PATHWAY
A biochemical pathway for the intracellular production of prostaglandins from arachidonic acid.

nephritis. Reilly *et al.*[31] have shown that mesangial cells from lupus-prone MRL/lpr mice are defective in PGJ_2 production when stimulated *ex vivo*, and that this is associated with exacerbated NO production. The production of NO could be blocked by the addition of exogenous PGJ_2. The suppressive effects of PGJ_2 on the production of pro-inflammatory mediators are not confined to the immune system. PGJ_2 has also been shown to inhibit the β-amyloid-stimulated expression of IL-6 and TNF by microglia *in vitro*[32]. Alzheimer's disease is characterized by the deposition of β-amyloid in the brain and the activation of microglia that are associated with the amyloid plaque, so PGJ_2 might also counteract inflammation in the central nervous system.

The specificity of cyPGs for the IKKβ–NF-κB pathway makes them particularly attractive therapeutic agents. As described above, alternative inhibitors of the NF-κB pathway might prevent leukocyte apoptosis during the inflammatory response[45]. The use of such inhibitors in chronic inflammatory diseases (such as rheumatoid arthritis) might have adverse side effects. However, selective inhibitors of the IKKβ pathway and IκBα degradation would spare other, possibly protective, signalling pathways (FIG. 5).

Concluding remarks

It seems paradoxical that certain families of eicosanoid, particularly those produced by the CYCLOOXYGENASE PATHWAY, might have a crucial role in bringing about the resolution of inflammation. However, there do seem to be circumstances when the 'poacher' might take the role of unlikely 'game-keeper'. The concepts that are discussed in this review highlight an important and largely ignored issue regarding the regulation of the inflammatory response — that the resolution of inflammation is a highly regulated and coordinated process. This process involves the suppression of pro-inflammatory gene expression, leukocyte migration and activation, followed by inflammatory-cell apoptosis, phagocytosis and clearance. We have described experimental evidence both *in vivo* and *in vitro* that these events might be regulated by endogenous anti-inflammatory mediators, such as cyPGs and lipoxins. We speculate that analogous compounds might be used as new anti-inflammatory agents for the treatment of chronic inflammatory diseases. Lipoxin analogues have already shown potential as anti-inflammatory agents in animal models of inflammation. Studies that show the therapeutic activity of the cyPG $15dPGJ_2$ in animal models of autoimmune and inflammatory diseases indicate that $15dPGJ_2$ analogues might also be effective therapeutic agents.

There has been important progress in defining the molecular targets of lipoxins with the cloning of the receptor for lipoxin A_4 and the recent generation of receptor transgenics, which will be an important tool for future studies of the anti-inflammatory roles of these mediators[62]. However, the molecular targets of cyPGs have yet to be defined *in vivo*. The recent generation of antibodies specific for $15dPGJ_2$[63], which have been used to study the production of this prostaglandin *in vitro* and *in vivo*, will allow further studies of the role of $15dPGJ_2$ in pathology and the possibility of developing blocking antibodies to define the endogenous roles of these mediators further. It might also be possible to generate antibodies specific for the adduct that is formed by $15dPGJ_2$ with specific peptide targets, which could be used to confirm the molecular targets of $15dPGJ_2$ *in vivo*.

Further insights into the role of PGD_2 metabolites in the resolution of inflammation will be provided by studies of PGD_2-synthase-knockout and -transgenic mice. It is predicted that the knockout mice might have defects in the resolution of inflammation and would, therefore, be more susceptible to chronic inflammatory and autoimmune diseases. By contrast, the transgenic mice would be resistant to inflammatory irritants and have reduced disease activity in models of chronic inflammation.

Future studies of the resolution of inflammation will no doubt uncover further anti-inflammatory mediators and pathways that might be harnessed for the treatment of inflammatory and autoimmune diseases.

1. Florey, H. W. *General Pathology* (Lloyd–Luke, London, 1970).
2. Majno, G. *The Healing Hand: Man and Wound in the Ancient World* (Harvard University Press, Cambridge, Massachusetts, 1975).
These two historical references give an excellent account of the experimental pathology of inflammation and highlight aspects that are generally ignored in more recent texts that focus on molecular events.
3. Jay, S. J., Johanson, W. G. Jr & Pierce, A. K. The radiographic resolution of *Streptococcus pneumoniae* pneumonia. *N. Engl. J. Med.* **293**, 798–801 (1975).
4. Deepe, G. S. Jr & Eagleton, L. E. Resolution of influenzal pneumonia. *IMJ Ill. Med. J.* **158**, 76–78 (1980).
5. Metlay, J. P., Atlas, S. J., Borowsky, L. H. & Singer, D. E. Time course of symptom resolution in patients with community-acquired pneumonia. *Respir. Med.* **92**, 1137–1142 (1998).
6. Larsen, G. L. & Henson, P. M. Mediators of inflammation. *Annu. Rev. Immunol.* **1**, 335–359 (1983).
7. Shanley, T. P., Warner, R. L. & Ward, P. A. The role of cytokines and adhesion molecules in the development of inflammatory injury. *Mol. Med. Today* **1**, 40–45 (1995).
8. Spector, W. G. & Willoughby, D. A. Local treatment of experimental burns with a monoamine oxidase inhibitor. *Nature* **189**, 489–490 (1961).
9. Spector, W. G., Walters, M. & Willoughby, D. A. Venular and capillary permeability in thermal injury. *J. Path. Bacteriol.* **90**, 635–640 (1965).
10. Spector, W. G. & Willoughby, D. A. Suppression of increased capillary permeability in injury by monoamine oxidase inhibitors. *Nature* **186**, 162–163 (1960).
11. Ottonello, L., Morone, M. P., Dapino, P. & Dallegri, F. Cyclic AMP-elevating agents down-regulate the oxidative burst induced by granulocyte–macrophage colony-stimulating factor (GM-CSF) in adherent neutrophils. *Clin. Exp. Immunol.* **101**, 502–506 (1995).
12. Moore, A. R. & Willoughby, D. A. The role of cAMP regulation in controlling inflammation. *Clin. Exp. Immunol.* **101**, 387–389 (1995).
13. Adcock, I. M. Molecular mechanisms of glucocorticoids actions. *Pulm. Pharmacol. Ther.* **13**, 115–126 (2000).
14. Goulding, N. J. *et al.* Anti-inflammatory lipocortin 1 production by peripheral-blood leucocytes in response to hydrocortisone. *Lancet* **335**, 1416–1418 (1990).
15. Cirino, G. & Flower, R. J. Human recombinant lipocortin 1 inhibits prostacyclin production by human umbilical artery *in vitro*. *Prostaglandins* **34**, 59–62 (1987).
16. Perretti, M. & Flower, R. J. Modulation of IL-1-induced neutrophil migration by dexamethasone and lipocortin 1. *J. Immunol.* **150**, 992–999 (1993).
17. Serhan, C. N. Lipoxin biosynthesis and its impact in inflammatory and vascular events. *Biochim. Biophys. Acta* **1212**, 1–25 (1994).
18. Soyombo, O., Spur, B. W. & Lee, T. H. Effects of lipoxin A4 on chemotaxis and degranulation of human eosinophils stimulated by platelet-activating factor and *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine. *Allergy* **49**, 230–234 (1994).
19. Maddox, J. F. *et al.* Lipoxin B4 regulates human monocyte/neutrophil adherence and motility: design of stable lipoxin B4 analogs with increased biologic activity. *FASEB J.* **12**, 487–494 (1998).
20. Colgan, S. P., Serhan, C. N., Parkos, C. A., Delp-Archer, C. & Madara, J. L. Lipoxin A4 modulates transmigration of human neutrophils across intestinal epithelial monolayers. *J. Clin. Invest.* **92**, 75–82 (1993).
21. Raud, J., Palmertz, U., Dahlen, S. E. & Hedqvist, P. Lipoxins inhibit microvascular inflammatory actions of leukotriene B4. *Adv. Exp. Med. Biol.* **314**, 185–192 (1991).
22. Maddox, J. F. & Serhan, C. N. Lipoxin A4 and B4 are potent stimuli for human monocyte migration and adhesion: selective inactivation by dehydrogenation and reduction. *J. Exp. Med.* **183**, 137–146 (1996).
23. Godson, C. *et al.* Cutting edge: lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages. *J. Immunol.* **164**, 1663–1667 (2000).

24. Gilroy, D. W. *et al.* Inducible cyclooxygenase may have anti-inflammatory properties. *Nature Med.* **5**, 698–701 (1999).
This paper presents experimental evidence that 15deoxy$\Delta^{12,14}$PGJ_2 is an endogenous anti-inflammatory mediator *in vivo*.
25. Bandeira-Melo, C. *et al.* Cyclooxygenase-2-derived prostaglandin E2 and lipoxin A4 accelerate resolution of allergic oedema in *Angiostrongylus costaricensis*-infected rats: relationship with concurrent eosinophilia. *J. Immunol.* **164**, 1029–1036 (2000).
26. Ianaro, A., Ialenti, A., Maffia, P., Pisano, B. & Di Rosa, M. Role of cyclopentenone prostaglandins in rat carrageenin pleurisy. *FEBS Lett.* **508**, 61–66 (2001).
27. Levy, B. D., Clish, C. B., Schmidt, B., Gronert, K. & Serhan, C. N. Lipid mediator class switching during acute inflammation: signals in resolution. *Nature Immunol.* **2**, 612–619 (2001).
28. Kawahito, Y. *et al.* 15-deoxy-$\Delta^{12,14}$-PGJ_2 induces synoviocyte apoptosis and suppresses adjuvant-induced arthritis in rats. *J. Clin. Invest.* **106**, 189–197 (2000).
29. Diab, A. *et al.* Peroxisome proliferator-activated receptor-γ agonist 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 ameliorates experimental autoimmune encephalomyelitis. *J. Immunol.* **168**, 2508–2515 (2002).
30. Clark, R. B. *et al.* The nuclear receptor PPARγ and immunoregulation: PPARγ mediates inhibition of helper T-cell responses. *J. Immunol.* **164**, 1364–1371 (2000).
31. Reilly, C. M. *et al.* Inhibition of mesangial-cell nitric oxide in MRL/lpr mice by prostaglandin J_2 and proliferator activation receptor-γ agonists. *J. Immunol.* **164**, 1498–1504 (2000).
32. Combs, C. K., Johnson, D. E., Karlo, J. C., Cannady, S. B. & Landreth, G. E. Inflammatory mechanisms in Alzheimer's disease: inhibition of β-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARγ agonists. *J. Neurosci.* **20**, 558–567 (2000).
33. Pasceri, V., Wu, H. D., Willerson, J. T. & Yeh, E. T. Modulation of vascular inflammation *in vitro* and *in vivo* by peroxisome proliferator-activated receptor-γ activators. *Circulation* **101**, 235–238 (2000).
34. Jackson, S. M. *et al.* Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leucocyte–endothelial-cell interaction. *Arterioscler. Thromb. Vasc. Biol.* **19**, 2094–2104 (1999).
35. Vaidya, S., Somers, E. P., Wright, S. D., Detmers, P. A. & Bansal, V. S. 15-deoxy-$\Delta^{12,1412,14}$-prostaglandin J_2 inhibits the β_2 integrin-dependent oxidative burst: involvement of a mechanism distinct from peroxisome proliferator-activated receptor-γ ligation. *J. Immunol.* **163**, 6187–6192 (1999).
36. Zhang, X., Wang, J. M., Gong, W. H., Mukaida, N. & Young, H. A. Differential regulation of chemokine gene expression by 15-deoxy-$\Delta^{12,14}$ prostaglandin J_2. *J. Immunol.* **166**, 7104–7111 (2001).
37. Rossi, A., Elia, G. & Santoro, M. G. Inhibition of nuclear factor κB by prostaglandin A1: an effect associated with heat shock transcription factor activation. *Proc. Natl. Acad. Sci. USA* **94**, 746–750 (1997).
38. Ricote, M., Li, A. C., Willson, T. M., Kelly, C. J. & Glass, C. K. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. *Nature* **391**, 79–82 (1998).
39. Jiang, C., Ting, A. T. & Seed, B. PPAR-γ agonists inhibit production of monocyte inflammatory cytokines. *Nature* **391**, 82–86 (1998).
References 38 and 39 were published simultaneously in *Nature* and identify 15deoxy$\Delta^{12,14}$PGJ_2 as a potent modulator of macrophage activation *in vitro*.
40. Colville-Nash, P. R., Qureshi, S. S., Willis, D. & Willoughby, D. A. Inhibition of inducible nitric oxide synthase by peroxisome proliferator-activated receptor agonists: correlation with induction of heme oxygenase 1. *J. Immunol.* **161**, 978–984 (1998).
41. Castrillo, A., Diaz-Guerra, M. J., Hortelano, S., Martin-Sanz, P. & Bosca, L. Inhibition of IκB kinase and IκB phosphorylation by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 in activated murine macrophages. *Mol. Cell. Biol.* **20**, 1692–1698 (2000).
42. Straus, D. S. *et al.* 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 inhibits multiple steps in the NF-κB signaling pathway. *Proc. Natl Acad. Sci. USA* **97**, 4844–4849 (2000).
43. Haslett, C. Granulocyte apoptosis and its role in the resolution and control of lung inflammation. *Am. J. Respir. Crit. Care Med.* **160**, S5–S11 (1999).
An excellent review of the role of granulocyte apoptosis in the resolution of inflammation.
44. Savill, J. & Fadok, V. Corpse clearance defines the meaning of cell death. *Nature* **407**, 784–788 (2000).
This review describes how the recognition and phagocytosis of apoptotic cells might regulate the inflammatory response.
45. Lawrence, T., Gilroy, D. W., Colville-Nash, P. R. & Willoughby, D. A. Possible new role for NF-κB in the resolution of inflammation. *Nature Med.* **7**, 1291–1297 (2001).
46. Bishop-Bailey, D. & Hla, T. Endothelial-cell apoptosis induced by the peroxisome proliferator-activated receptor (PPAR) ligand 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2. *J. Biol. Chem.* **274**, 17042–17048 (1999).
47. Khoshnan, A. *et al.* The NF-κB cascade is important in Bcl-xL expression and for the anti-apoptotic effects of the CD28 receptor in primary human $CD4^+$ lymphocytes. *J. Immunol.* **165**, 1743–1754 (2000).
48. Ward, C. *et al*. Prostaglandin D_2 and its metabolites induce caspase-dependent granulocyte apoptosis that is mediated via inhibition of IκBα degradation using a peroxisome proliferator-activated receptor-γ-independent mechanism. *J. Immunol.* **168**, 6232–6243 (2002).
49. Fadok, V. A. *et al.* Macrophages that have ingested apoptotic cells *in vitro* inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-β, PGE_2 and PAF. *J. Clin. Invest.* **101**, 890–898 (1998).
50. Huynh, M. L., Fadok, V. A. & Henson, P. M. Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF-β1 secretion and the resolution of inflammation. *J. Clin. Invest.* **109**, 41–50 (2002).
51. van Lent, P. L. *et al.* Uptake of apoptotic leucocytes by synovial lining macrophages inhibits immune complex-mediated arthritis. *J. Leukocyte Biol.* **70**, 708–714 (2001).
52. Dibbert, B. *et al.* Cytokine-mediated Bax deficiency and consequent delayed neutrophil apoptosis: a general mechanism to accumulate effector cells in inflammation. *Proc. Natl Acad. Sci. USA* **96**, 13330–13335 (1999).
This paper presents evidence for defects in apoptosis in clinical samples from patients with inflammatory lung disease.
53. Vandivier, R. W. *et al.* Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic-cell clearance in cystic fibrosis and bronchiectasis. *J. Clin. Invest.* **109**, 661–670 (2002).
54. Taylor, P. R. *et al.* A hierarchical role for classical-pathway complement proteins in the clearance of apoptotic cells *in vivo*. *J. Exp. Med.* **192**, 359–366 (2000).
55. Straus, D. S. & Glass, C. K. Cyclopentenone prostaglandins: new insights on biological activities and cellular targets. *Med. Res. Rev.* **21**, 185–210 (2001).
56. Clark, R. B. The role of PPARs in inflammation and immunity. *J. Leukocyte Biol.* **71**, 388–400 (2002).
57. Rossi, A. *et al.* Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IκB kinase. *Nature* **403**, 103–108 (2000).
This study identified IKKβ as a specific target of 15deoxy$\Delta^{12,14}$PGJ_2.
58. Cernuda-Morollon, E., Pineda-Molina, E., Canada, F. J. & Perez-Sala, D. 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 inhibition of NF-κB–DNA binding through covalent modification of the p50 subunit. *J. Biol. Chem.* **276**, 35530–35536 (2001).
59. Karin, M. & Ben-Neriah, Y. Phosphorylation meets ubiquitination: the control of NF-κB activity. *Annu. Rev. Immunol.* **18**, 621–663 (2000).
60. Ward, C. *et al*. NF-κB activation is a critical regulator of human granulocyte apoptosis *in vitro*. *J. Biol. Chem.* **274**, 4309–4318 (1999).
61. Fierro, I. M. & Serhan, C. N. Mechanisms in anti-inflammation and resolution: the role of lipoxins and aspirin-triggered lipoxins. *Braz. J. Med. Biol. Res.* **34**, 555–566 (2001).
62 Levy, B. D. *et al*. Multi-pronged inhibition of airway hyper-responsiveness and inflammation by lipoxin A_4. *Nature Med.* **8**, 1018–1023 (2002).
63 Shibata, T. *et al*. 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2. A prostaglandin D_2 metabolite generated during inflammatory processes. *J. Biol. Chem.* **277**, 10459–10466 (2002).

Acknowledgements

T. L. would like to acknowledge financial support of the Arthritis Research Campaign and The Special Trustees of St Bartholomew's Hospital Joint Research Board. D. W. would like to acknowledge financial support of the William Harvey Research Foundation.

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