The regulation of IL-10 production by immune cells

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Abstract | Interleukin-10 (IL-10), a cytokine with anti-inflammatory properties, has a central role in infection by limiting the immune response to pathogens and thereby preventing damage to the host. Recently, an increasing interest in how IL-10 expression is regulated in different immune cells has revealed some of the molecular mechanisms involved at the levels of signal transduction, epigenetics, transcription factor binding and gene activation. Understanding the specific molecular events that regulate the production of IL-10 will help to answer the remaining questions that are important for the design of new strategies of immune intervention.

The immune response has evolved to protect the host from a wide range of potentially pathogenic microorganisms, but parallel mechanisms to control over-exuberant immune responses and prevent reactivity to self are required to limit host damage. Interleukin-10 (IL-10) is an anti-inflammatory cytokine with a crucial role in preventing inflammatory and autoimmune pathologies•. IL-10-deficient mice• develop inflammatory bowel disease following colonization of the gut with particular microorganisms• (BOX 1) and show other exaggerated inflammatory responses to microbial challenge. Although the absence of IL-10 leads to better clearance of some pathogens with no enhanced immunopathology•, during other infections the absence of IL-10 can be accompanied by an immunopathology that is detrimental to the host but does not necessarily affect the pathogen load•. This suggests that an absence of IL-10 is not always compensated by other regulatory mechanisms and thus that there is a non-redundant role for IL-10 in limiting inflammatory responses in vivo.

To inhibit inflammatory pathologies, IL-10 functions at different stages of an immune response and possibly at different anatomical locations. IL-10 was initially described as a T helper 2 (Th2)-type cytokine•, but further evidence suggested that the production of IL-10 was associated with tolerant or regulatory T (Treg) cell responses•. It is now known that the expression of IL-10 is not specific to Treg cells but instead that it is a much more broadly expressed cytokine (FIG. 1). IL-10 is expressed by many cells of the adaptive immune system, including Treg, Th2 and Th17 cell subsets, Treg cells, CD8+ T cells and B cells (reviewed in REFS 3,10,11,14–16). It is also expressed by cells of the innate immune system, including dendritic cells (DCs), macrophages, mast cells, natural killer (NK) cells, eosinophils and neutrophils• (FIG. 1). Thus, IL-10 production seems to be associated with many immune cells, affirming its crucial role as a feedback regulator of diverse immune responses, not only Th1 cell responses• but also Th2 cell responses to schistosome parasites•, Aspergillus spp.• and allergens• (reviewed in REF. 1).

Much is known about the function of IL-10. For example, the induction of the anti-inflammatory response mediated through the IL-10 receptor (IL-10R) and activation of signal transducer and activator of transcription 3 (STAT3) is reviewed in REF. 3.20. By acting on DCs and macrophages, IL-10 inhibits the development of Th1-type responses (reviewed in REF. 3) but also leads to the suppression of Th2 cell and allergenic responses (reviewed in REF. 1). In addition to an autocrine inhibitory effect of IL-10 on macrophages and DCs, and because IL-10 can be produced by Treg, Th2 and Th17 cells, an additional feedback loop exists to limit the innate effector functions of macrophages and DCs and their subsequent activation of T cells. However, IL-10 enhances the differentiation of IL-10-secreting Treg cells, thus providing a positive regulatory loop for its induction• (reviewed in REFS 1,14). In some situations, IL-10 also activates mast cells and enhances the functions of CD8+ T cells, NK cells and B cells (reviewed in REFS 2,3), although these effects have yet to be tested in infection models.

So, IL-10 is a cytokine with important effects on the development of an immune response. An understanding of how IL10 expression is regulated in different innate...
Box 1 | IL-10 expression and gut homeostasis

The intestine is continuously exposed to bacterial flora, dietary antigens and potential pathogens. To prevent chronic intestinal inflammation, various regulatory lymphocyte populations keep the immune response in check. These populations use several regulatory mechanisms, the best characterized of which involves interleukin-10 (IL-10) and transforming growth factor-β (TGFβ)\(^{15,155}\). IL-10- or TGFβ-receptor-deficient mice do not develop severe autoimmune disorders but develop colitis in the presence of microorganisms\(^{156}\). Many studies unequivocally identify CD4+ T cell-derived IL-10 as a key mediator of intestinal immune homeostasis\(^{157-161}\). Coeliac disease and inflammatory bowel disease (IBD) are the most common causes of non-infectious intestinal inflammation in humans, with recent reports identifying IL10 as a susceptibility locus for the development of IBD\(^{162}\). Polymorphisms in nucleotide-binding oligomerization domain 2 (NOD2) have also been associated with IBD in humans\(^{163}\), which is interesting considering that NOD2 has been associated with IL-10 production\(^{11}\). IL-10 seems to function not directly on T cells, but instead on myeloid cell populations in a similar manner to that observed in the immune response to pathogens\(^1\). In vivo IL-10 production by forkhead box P3 (FOXP3) regulatory T (T\(\text{Reg}\)) cells and FOXP3+ regulatory T cells in the gut seems to be mediated by TGFβ, independently of endogenous IL-10 (REF. 97). This IL-10 independence is in contrast to that reported in vitro for human IL-10-producing regulatory T cells\(^{164}\). Retinoic acid was identified as a cofactor for TGFβ in the induction of FOXP3+ T\(\text{Reg}\) cells, although retinoic acid itself downregulates the expression of IL-10 by inducible FOXP3+ regulatory T cells\(^{165}\). Although the exact mechanisms of IL-10 induction in the intestine remain elusive, the protective role of intestinal T\(\text{Reg}\) cells mostly depends on their expression of IL-10, suggesting that local IL-10 expression might be a therapy for IBD\(^2\).

and adaptive immune cells is therefore of importance for the development of immune intervention strategies in various pathologies. Several layers of regulation of IL-10 expression exist, and this is a main focus of this Review. First, regulation of IL-10 production involves changes in the chromatin structure at the IL10 locus. A second layer of regulation involves the enhancement or silencing of IL10 transcription and is controlled by specific transcription factors activated by discrete signal-transduction pathways. In addition, post-transcriptional mechanisms exist. Many of the molecular events leading to IL10 expression are common to various IL-10-producing immune cells. However, there are also cell-specific signals and molecular mechanisms that allow IL-10 production by particular immune cells and not by others.

In this Review, we discuss our current understanding of the regulation of IL10 expression at the molecular level in different cell types, from signal transduction pathways to epigenetic regulation and the activation of specific transcription factors involved in IL-10 production. Throughout, we highlight the common and distinct mechanisms of IL-10 regulation that exist in different IL-10-producing immune cells.

**IL-10 production by immune cells**

**Induction by pathogen-derived products.** Pathogen activation of DCs and macrophages involves the recognition of pathogen-derived products by pattern recognition receptors (PRRs), which triggers the expression of cytokines and other factors\(^2\). Both macrophages\(^3\)–\(^27\) and DCs\(^28\)–\(^35\) can express IL-10 in vitro following activation of specific PRRs (FIG. 2a). In addition, DCs\(^31,34\), macrophages\(^35\) and neutrophils\(^36\) have been reported to express IL-10 in vivo.

It has been suggested that Toll-like receptor 2 (TLR2) agonists are specialized in inducing IL-10 expression by antigen-presenting cells (APCs)\(^29\)–\(^37\)–\(^38\). For example, TLR2 signalling is crucial for the induction of IL-10 production by macrophages (M. Teixeira-Coelho, J. Carmona, A. G. Castro and M.S., unpublished observations) or by DCs\(^39\) stimulated with Mycobacterium tuberculosis or with lipopeptides and the LcrV antigen of Yersinia pestis\(^40\). IL-10 production by macrophages following pneumococcal cell wall stimulation mainly depends on TLR2; however, in this case a role for nucleotide-binding oligomerization domain 2 (NOD2) signalling, independent of TLR2, has also been described\(^41\). Significant amounts of IL-10 are also produced by macrophages and myeloid DCs following stimulation with TLR4 and TLR9 ligands\(^26\). Of note, IL-10 production following TLR3 stimulation was only observed in macrophages\(^26\). Interestingly, activation of macrophages through TLRs results in high levels of IL-10 production, whereas myeloid DCs only produce intermediate amounts and plasmacytoid DCs (pDCs) do not produce detectable levels of IL-10 (REF. 26) (FIG. 1).

In addition, IL-10 can be induced by TLR-independent stimuli, such as the C-type lectins DC-specific ICAM3-grabbing non-integrin (DC-SIGN; also known as CLEC4M)\(^42\) and dectin 1 (also known as CLEC7A)\(^42\) (FIG. 2a). Ligation of CD40 enhances IL-10 production by TLR-stimulated\(^43\) or dectin 1-stimulated DCs\(^42\) and ligation of Fc receptors (FcRs) enhances IL-10 production by TLR-stimulated macrophages\(^45\).

**Signalling pathways for innate IL-10 production.** Following TLR ligation, signalling cascades are activated through Toll/IL-1 receptor (TIR)-domain-containing adaptor molecules, such as myeloid differentiation primary-response protein 88 (MYD88) and TIR-domain-containing adaptor protein inducing IFNβ (TRIF; also known as TICAM1), leading to the production of IL-10 and pro-inflammatory cytokines\(^29\)–\(^30\),\(^42\). TLR signalling through MYD88 leads to the activation of mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) (FIG. 2a).

In addition, signals that are required for IL-10 production by macrophages have also been reported. Of note, optimal lipopolysaccharide (LPS)-induced IL-10 production by macrophages requires both the activation of the TRIF- and MYD88-dependent pathways\(^29\),\(^27\) and the production of and signalling by type I interferons (IFNs)\(^37\). This secondary induction of IL-10 by type I IFNs has important implications for the use of type I IFNs as potential anti-inflammatory drugs. Moreover, this study is in line with the observation that TNF-α receptor factor 3 (TRAF3), an important component of the type I IFN production pathway, is also involved in LPS-induced upregulation of IL-10 expression\(^42\).

The MAPK cascade is composed of three major groups of kinases: extracellular signal-regulated kinases (ERKs) (comprising ERK1 (also known as MAPK3) and ERK2 (also known as MAPK1), which are collectively referred to here as ERK); JUN N-terminal kinases
(JNKs) (comprising JNK1 (also known as MAPK8) and JNK2 (also known as MAPK9)); and p38 (REF. 44). Following TLR stimulation, activation of ERK modulates IL-10 expression,30,43,47, and in the presence of chemical inhibitors of ERK30,45,47 or in ERK-deficient cells46 IL-10 production by TLR-activated DCs is decreased. Furthermore, the differences in IL-10 production by macrophages, myeloid DCs and pDCs have been shown to correlate with the strength of ERK activation in each of these cell types.47 Following TLR stimulation, ERK is most highly activated in macrophages, with lower activation of ERK in myeloid DCs and the lowest amount of activated ERK in pDCs47 (FIG. 1).

Further studies using cells deficient for tumour progression locus 2 (TPL2) or NF-κB1 (also known as p105) support the role of ERK in the induction of IL-10. TPL2 is an upstream activator of ERK and, following TLR stimulation, TPL2 dissociates from the TPL2–NF-κB1 complex and activates ERK. In the absence of NF-κB1, TPL2 is rapidly degraded in the cell and, as a consequence, ERK activation by TPL2 is compromised.44 In TPL2-deficient macrophages and myeloid DCs the amounts of TLR-induced IL-10 were lower than in wild-type cells owing to the absence of ERK activation.45 Similarly, NF-κB1-deficient macrophages have lower levels of IL-10 expression than control cells.

**Figure 1 | Interleukin-10 expression in the immune system.** a | Interleukin-10 (IL-10) is expressed by macrophages and myeloid dendritic cells (DCs), but not by plasmacytoid DCs, in response to microbial products. The extracellular signal-regulated kinase 1 (ERK1) and ERK2 (which are collectively referred to here as ERK) pathway is one of the signalling cascades that is activated in these cells that results in IL-10 expression. For other immune cells, such as B cells, mast cells and eosinophils, the exact signalling pathways that lead to IL-10 production remain elusive. b | In T helper (Tn) cells, the expression of IL-10 is accompanied by the expression of the signature cytokines for each subset, with the exception of Tn1 cells from naive CD4+ T cells requires T cell receptor triggering and the activation of distinct signal transducer and activator of transcription (STAT) pathways, activation of the ERK pathway is a common requirement for IL-10 expression by these cells. High doses of antigen presented by DCs to naive T cells or IL-12 favours the development of Tn1 cells, which normally lose the capacity to express other cytokines. Although the differentiation of Tn4, Tn17 cells and IL-10 production by TLR-activated DCs is decreased. In Tn2 cells, IL-4 and STAT6 signalling pathways are required for IL-10 expression. Induction of IL-10-producing Tn17 cells is not well understood, but transforming growth factor-β (TGFβ), IL-6, IL-21 and/or IL-27 and Stat3 signalling are likely to be involved. c | TGFβ can induce the production of IL-10 by forkhead box P3 (FOXP3)+ Tnreg cells and this cytokine can also promote the development of IL-10-producing FOXP3+ regulatory T cells from naive T cells. Conversely, FOXP3+ IL-10-producing Tnreg cells can differentiate from naive T cells in vitro in the presence of TGFβ and retinoic acid.
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title

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Myeloid DCs

Macrophages and myeloid DCs

Macrophages

DC-SIGN

TLR2

Dectin 1

RAF

NF-κB

SYK

ERK

IL-10

p38

MEK1

MEK2

MSK1

MSK2

CRK

IL-10

Endosome

Cytoplasm

TLR-dependent signal

IFNγ

TLP2

IFNγ

PI3K

AKT

MSK2

GSK3

DUSP1

CREB

AP1

IL-10

Through IL-10R and STAT3

Through IL-10R and STAT3

Figure 2 | Signals that induce interleukin-10 expression by cells of the innate immune response. (a) The expression of interleukin-10 (IL-10) can be induced by Toll-like receptor (TLR) or non-TLR signalling in macrophages and myeloid dendritic cells (DCs). Activation of TLRs and their adaptor molecules — myeloid differentiation primary-response protein 88 (MYD88) and TIR-domain-containing adaptor protein inducing IFNβ (TRIF) — results in the activation of the extracellular signal-regulated kinase 1 (ERK1) and ERK2 (which are collectively referred to here as ERK), p38, and nuclear factor-κB (NF-κB) pathways. Activation of these pathways results in the induction of IL-10 expression, in addition to pro-inflammatory cytokines. In myeloid DCs, non-TLR signals through DC-specific ICAM3-grabbing non-integrin (DC-SIGN) and RAF1 can augment TLR2-induced IL-10 production. Furthermore, activation of dectin 1 and the signalling molecules spleen tyrosine kinase (SYK) and ERK results in IL-10 production. In macrophages, a role for nucleotide-binding oligomerization domain 2 (NOD2) signalling in IL-10 induction, in crosstalk with TLR2, has been described. (b) Positive and negative feedback loops for IL-10 regulation in macrophages. The p38 and ERK pathways leading to IL-10 expression by macrophages are tightly controlled by interferon-γ (IFNγ) and IL-10 itself. IL-10 feeds back to induce the expression of dual-specificity protein phosphatase 1 (DUSP1), which negatively regulates p38 phosphorylation and thus limits IL-10 production. IL-10 can also positively feed back to upregulate tumour progression locus 2 (TLP2) expression, thus providing a positive amplification loop for its own production. In addition, IFNγ can also interfere with the phosphoinositide 3-kinase (PI3K)-AKT pathway, releasing glycogen synthase kinase 3 (GSK3). As GSK3 normally blocks IL-10 expression by acting on the transcription factors CAMP response element-binding protein (CREB) and activator protein 1 (AP1), IL-10 production is inhibited by IFNγ through its effects on PI3K, IL-10R, IL-10 receptor, MEK, MAPK/ERK1 kinase; MSK, mitogen- and stress-activated protein kinase; RIP2, receptor-interacting protein 2; STAT3, signal transducer and activator of transcription 3; TRAF3, TNFR-associated factor 3.

following TLR activation. IL-10 expression was only partially restored following rescue of ERK activation in these cells, indicating that NF-κB-mediated regulation of IL-10 production involves both ERK-dependent and ERK-independent mechanisms, as had been suggested by previous studies. Furthermore, pathogen triggering of DC-SIGN in human DCs resulted in the activation of RAF1, leading to acetylation of the NF-κB p65 subunit and to prolonged and increased IL-10 transcription. This effect was only observed after TLR-dependent NF-κB activation, suggesting that activation of DC-SIGN can modulate TLR-induced IL-10 production.

The regulation of IL-10 production in response to dectin 1 ligation depends on spleen tyrosine kinase (SYK) and initiates a signalling cascade that induces IL-2 and IL-10 production. IL-10 production downstream of dectin 1 also requires signalling through the ERK pathway, despite being independent of TLR activation. SYK is recruited to phosphorylated dectin 1 and initiates a signalling cascade that induces IL-2 and IL-10 production. IL-10 production by DCs requires both the ERK and p38 pathways, correlated with a loss of IL-10 expression following TLR stimulation. This could be reversed by chemically inhibiting p38 signalling.

Interestingly, abrogation of either ERK or p38 activation leads to a reduction, but not abrogation, of IL-10 expression, which suggests that two pathways might cooperate in TLR-induced IL-10 production. Supporting this hypothesis, inhibition of both the ERK and p38 pathways in LPS- or CpG-stimulated macrophages, primary DCs and human peripheral blood monocytes, primary cells lacking the p38 regulator dual-specificity protein phosphatase 1 (DUSP1) have prolonged p38 activation and increased levels of IL-10 expression following TLR stimulation. This could be reversed by chemically inhibiting p38 signalling.

The production of IL-10 by macrophages and DCs is also regulated by the activation of certain inhibitory pathways. ERK- and p38-dependent IL-10 production is inhibited by IFNγ. In addition to directly blocking TLR-induced MAPK activation, IFNγ induces the release of glycogen synthase kinase 3 (GSK3) by antagonizing phosphoinositide 3-kinase (PI3K)-AKT activation. This leads to inhibition of TLR-induced IL-10 production by suppressing the binding of activator protein 1 (AP1) to the Il10 promoter. Another negative feedback loop controlling IL-10 production by macrophages is mediated by IL-10 itself. IL-10 induces the expression of DUSP1, which negatively regulates p38 phosphorylation and thus limits IL-10 production. By contrast, IL-10 positively feeds back to upregulate Tlp2 expression, thus providing a positive amplification

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loop for its own production. IL-10 was also described to induce its own transcription in human monocytes in a STAT3-dependent manner\(^9\), which may result from its upregulation of TPL2 and thus ERK activation\(^6\). However, the mechanisms dictating the balance between IL-10-mediated negative and positive feedback loops are currently not clear. Furthermore, the inhibition of IL-10 production by NK cell- or T cell-derived IFN\(\gamma\) in vivo will also influence these loops.

Various pathogen-derived products induce IL-10 expression by macrophages and DCs through the activation of signalling cascades that, although common to various stimuli and different cells, have distinct thresholds of activation depending on the cell type, which reflect the distinct amounts of IL-10 produced by these cells.

**IL-10 production by T\(_h\) cells.** IL-10 production was first described in T\(_h\)2 cells\(^{12,26}\), where its expression accompanies that of the T\(_h\)2-type cytokines IL-4, IL-5 and IL-13. T\(_h\)1 cells can also be induced to produce IL-10, but, in contrast to T\(_h\)2 cells, only under certain conditions\(^{10,11,16,69-71}\) (FIG. 1). Furthermore, T\(_h\)17 cells have recently been shown to produce IL-10 (REFS 72, 77–79). The fact that T\(_h\)1, T\(_h\)2 and T\(_h\)17 cells are dependent on DC- and macrophage-derived factors that are downregulated by IL-10, but these subsets can all be induced to produce IL-10, is indicative of a negative feedback loop that ensures that effector T cell responses do not result in immunopathology. It is of interest to note that IL-9-producing T\(_h\) cells, which have recently been suggested to be a unique T\(_h\) cell subset (T\(_h\)9 cells), also express IL-10 (REF. 80).

**Molecular signals for IL-10 induction in T\(_h\) cells.** IL-10-inducing signalling cascades have been studied less thoroughly in T\(_h\) cells than in macrophages and DCs. IL-10-producing T\(_h\)1 cells have been described in infectious diseases, human CD4\(^+\) T cell clones and mouse CD4\(^+\) T cells. T\(_h\)1 cells that produce both IFN\(\gamma\) and IL-10 can be generated by inducing T cells to proliferate with high levels of antigen-specific or polyclonal stimulation in the presence of IL-12 (REFS 10, 11, 69, 70) (FIG. 1). However, until recently the signals that determine whether T\(_h\)1 cells produce IL-10 were not known. Strong T cell receptor (TCR) triggering (high antigen dose)\(^7\) and endogenous IL-12 have now been shown to be essential for the differentiation of IL-10-producing T\(_h\)1 cells, as well as for maximal expression of IL-10 following re-stimulation of these cells\(^6\). IL-10 induction in T\(_h\)1 cells is STAT4 and ERK dependent\(^{22}\) (FIG. 1). Notch signalling can also induce IL-10 expression by T\(_h\)1 cells, a process that requires STAT4 (REF. 81). In T\(_h\)2 cells, IL-10 production seems to be regulated by the main T\(_h\)2-type associated signalling pathways and transcription factors: IL-4, STAT6 and GATA binding protein 3 (GATA3)\(^{82-84}\). IL-10 expression by T\(_h\)17 cells seems to occur in a STAT3- and, in some cases, STAT1-dependent manner\(^{79,85}\) (FIG. 1). Thus, to induce IL-10 expression, T\(_h\)1, T\(_h\)2 and T\(_h\)17 cells require the same signals needed for each T\(_h\) cell differentiation programme. However, IL-10 production by all these subsets requires ERK activation\(^{72}\), indicating that a common molecular mechanism exists for IL-10 production by T\(_h\) cells. Chemical inhibition of the p38 signalling pathway did not compromise the production of IL-10 by T\(_h\)1, T\(_h\)2 or T\(_h\)17 cells\(^2\), suggesting that in T\(_h\) cells the role of ERK is dominant over that of p38. This observation is in contrast to a joint role for ERK and p38 in IL-10 induction in macrophages and DCs.

IL-21 can enhance IL-10 expression by CD4\(^+\) T cells in the context of different stimuli\(^{10}\), and IL-27 enhances IL-10 expression by T\(_h\)1, T\(_h\)2 and T\(_h\)17 cells\(^{8,79,85,87,88}\). By contrast, IL-27 attenuates TLR-induced IL-10 expression by human monocytes\(^8\). Of interest, it has recently been shown that both IL-21 and IL-27 induce ERK activation\(^{89,91}\), but it is currently not clear whether this explains the ability of these cytokines to upregulate IL-10 production. Also, both IL-21 and IL-27, in addition to ERK, activate STAT3, which seems to be involved in IL-27-mediated IL-10 upregulation by T cells\(^{92}\).

Undoubtedly, all T cell subsets can produce IL-10, as well as their hallmark cytokines, following TCR triggering, but this depends on the environmental context and strength of stimulus\(^{10,11,69-71,82-94}\).

**IL-10 and regulatory T cells.** T\(_{reg}\) cells, which are characterized by their specific expression of the transcription factor forkhead box P3 (FOXP3), do not express IL-10 following stimulation directly after ex vivo isolation\(^{95,96}\), unless isolated from the gut\(^97\) (BOX 1). Although FOXP3\(^+\) T\(_{reg}\) cells inhibit naive T cell proliferation in vitro independently of IL-10, in some cases, T\(_{reg}\) cells mediate their regulatory function in vivo through IL-10 (reviewed in REFs 1.14, 16, 98–100). Therefore, T\(_{reg}\) cells must receive signals in vivo to induce the expression of this suppressive cytokine. Both IL-2 and IL-4 have been shown to induce IL-10 production after culture of T\(_{reg}\) cells in vitro\(^{101,102}\). However, in these studies, the T\(_{reg}\) cell population analysed might have contained some effector T cells and therefore the source of IL-10 cannot be confirmed. So far the signals that induce IL-10 expression by FOXP3\(^+\) T\(_{reg}\) cells remain elusive, although transforming growth factor \(\beta\) (TGF\(\beta\)) has been shown to be required in vivo\(^{97}\) (FIG. 1).

Several populations of antigen-driven FOXP3\(^+\) IL-10-producing T cells with regulatory activity that are distinct from naturally occurring T\(_{reg}\) cells have been described (reviewed in REFs 1.2, 13, 14). These cells produce IL-10, but not IL-2, IL-4 or IFN\(\gamma\), and can be generated in vitro using various stimuli, such as cytokine cocktails (TGF\(\beta\), IL-10 and IFN\(\alpha\)) or immunosuppressive drugs (vitamin D3 and dexamethasone)\(^{12,13,14,21}\), or in vivo by repeated stimulation with soluble antigen\(^{71,103}\). Additional signals for IL-10 expression by these FOXP3\(^+\) regulatory T cells include co-stimulation through CD2 or CD46 and stimulation with type I IFNs or with immature DCs (reviewed in REFs 1.14, 104). Signals delivered through inducible T cell co-stimulator (ICOS) have also been suggested to induce IL-10 expression by FOXP3\(^+\) regulatory T cells\(^{105,106}\); a similar effect has been observed in T\(_2\) cells\(^{107,108}\), suggesting that, although it is involved in the induction of IL-10, ICOS is not a cell type-specific inducer of IL-10.
It will be of interest to determine whether IL-10-producing FOXP3− regulatory T cells differentiate directly from naive T cells or are derived from Tγ, Tβ, Tδ, T9 or Tγ,17 cells that have lost expression of their effector T cell cytokines but have maintained IL-10 expression. It is possible that FOXP3+ regulatory T cells that only make IL-10 have originally differentiated along a Tγ,1 cell pathway through repeated high-level antigenic stimulation, which results in IL-10 production and ultimately in the downregulation of Tγ,1 cell production of IFNγ by feedback inhibition of IL-12 production by DCs and macrophages41.

Additional cell types that produce IL-10. In addition to macrophages, DCs and CD4+ T cells, other cells of the immune system are also known to express IL-10. CD8+ T cells express IL-10 following TCR activation or interaction with CD40 ligand expressed by activated pDCs40,41, and this IL-10 production can be enhanced by IL-21 (REF 86). Stimulation of B cells with auto-antigens, TLR4 and TLR9 ligands or vitamin D3 also leads to IL-10 production124,125. Finally, mast cells can express IL-10 following TLR4 activation or during skin allergic or damage responses126,127. Recently, neutrophils were reported to produce IL-10 in response to TLR and C-type lectin co-activation through MYD88 and SYK, respectively128. These IL-10-producing neutrophils were shown to be recruited to the lung during mycobacterial infections and to regulate local immune inflammatory responses129. It is currently not clear whether the molecular mechanisms required for the induction of IL-10 by these cells are regulated by the common factors that regulate IL-10 production by Tγ,1 cells, macrophages and DCs.

Understanding the molecular pathways leading to IL-10 production by different immune cells might provide valuable information on possible targets for IL-10 manipulation. This will be useful in the design of intervention strategies to modulate IL-10 production and ultimately the immune response.

Transcription factors that regulate IL-10

Activating the IL10 promoter. The structure of the human and mouse IL10 promoters is similar and both contain a TATA box and a CCAAT box (CCAGT in mice). The human and mouse IL10 promoters have a high level of homology, particularly around certain putative binding sites for transcription factors. However, the presence of a conserved putative binding site in a gene promoter does not guarantee transcription factor binding.

In addition to epigenetic control (BOX 2), the expression of IL10 depends on transcription factor binding. The transcription factors specific protein 1 (SP1)129,130, SP3 (REF 121), CCAAT/enhancer binding protein-β (C/EBPβ)122,123, IFN-regulatory factor 1 (IRF1) and STAT3 (REF 124) have been proposed to bind to and transactivate IL10 in macrophage and T cell lines of mouse or human origin (FIGS 3, 4). Also, binding of the NF-κB p50 subunit to the IL10 promoter in a human T cell lymphoma cell line has been described135. Moreover, some of these findings depend on the cell type and on the stimulus used. For example, whereas one study indicates that IL10 promoter activity relies on an SP1 site located between positions −636 and −631 relative to the initiation site129, another report shows that IL10 promoter activity relies on the C/EBPβ motif positioned between the TATA box and the translation start point132. Although both studies were carried out using the human monocyctoc cell line THP1, the type of stimulation was different (LPS versus cyclic AMP (cAMP), respectively), which might account for the differences observed.

Studies using mouse primary cells have shown that homodimers of NF-κB p50 bind to the proximal IL10 promoter, activating IL10 transcription in primary macrophages136, and p50-deficient macrophages have an impaired expression of IL-10 following LPS stimulation compared with wild-type macrophages137. Furthermore, IL-10 induction in response to double-stranded RNA stimulation and viral infection of mouse macrophages was described to be protein kinase R (PKR) dependent and to be regulated by binding of NF-κB to a distinct site in the IL10 promoter137. In addition to NF-κB, a role for C/EBPβ in C/EBPβ-mediated IL10 production was confirmed in mouse primary macrophages; nuclear accumulation and DNA binding of C/EBPβ was involved in IL10 production in response to adenosine and Escherichia coli infection, and C/EBPβ-deficient macrophages failed to produce IL-10 (REF 128).

Recently, two cofactors of the homeobox (HOX) family, pre-B-cell leukaemia transcription factor 1 (PBX1) and PBX-regulating protein 1 (PREP1), were implicated in inducing IL-10 expression by mouse macrophages129. In this study, the expression of IL-10 was triggered by the interaction of macrophages with apoptotic cells and depended on p38; in human cells, transcription of IL10 cells was mediated by the binding of PBX1 and

Box 2 | Epigenetic control of IL10 expression

Several studies suggest that the expression of interleukin-10 (IL-10) is regulated by changes in the structure of the chromatin at the IL10 locus91,130−132 (FIG. 5). Various DNase hypersensitive sites (HSSs) were found in the mouse Il10 locus, most of which are common to IL-10-producing T cells, macrophages and dendritic cells (DCs). However, a macrophage-specific regulatory element (HSS−4.5), which is absent in T cells, was also found133. Although chromatin remodelling seems to be one of the initial events leading to IL-10 expression, additional signals are required to allow high rates of IL-10 transcription. Epigenetic imprinting of the IL10 locus in mice, as measured by histone acetylation, was observed in high-IL-10-producing T helper 2 (T2,2) cells44 and macrophages41 but not in low-IL-10-producing Tγ,1 cells44, despite the open conformation of the IL10 locus observed for all these cell types. In macrophages, the histones at the Il10 locus were also reported to be hyperphosphorylated135,136. Furthermore, by interacting with the distal segment of the IL10 promoter, histone deacetylase 11 negatively regulated the expression of this cytokine in human and mouse antigen-presenting cells137.

Several studies have identified GATA binding protein 3 (GATA3) as a possible initiator of chromatin remodelling and histone acetylation of the IL10 locus in mice91,131. However, as GATA3 is only expressed by Tγ,2 cells and not in other IL-10-producing Tγ,1 cells, macrophages or DCs, other mechanisms must operate in these cells to induce chromatin remodelling at the IL10 locus. A clue may come from the finding that, in macrophages, remodelling of the Il10 locus occurs following TLR stimulation138 or Fc receptor binding in an extracellular signal-regulated kinase (ERK)-dependent manner139.

Overall, analysis of the chromatin conformation at the IL10 locus may help to explain the different levels of IL10 expression and the different factors involved in this expression by different cell types, although many questions still remain unanswered.
Molecular regulation of interleukin-10 expression: the interleukin-10 locus and promoter. The mouse interleukin-10 (Il10) locus (top panel) and Il10 promoter (bottom panel) are represented here. Several DNAse hypersensitive sites (HSSs), and their relative position to the Il10 starting site (+1), are indicated. Most of these HSSs are common to all cells, although some cellular specificity is also observed. Two of these sites (HSS–4.5 and HSS+6.45) have been studied in more detail, and their role in Il10 regulation has been described. HSS–4.5 contains hyperacetylated histones and binds nuclear factor-kB (NF-kB) in macrophages, whereas HSS+6.45 binds JUN proteins in T helper 2 (T\(_{h2}\)) cells. Both HSS–4.5 and HSS+6.45 were shown to enhance the Il10 promoter activity in reporter assays. The biological role for the other HSSs needs to be further clarified. The proximal elements that regulate the expression of IL-10, including the Il10 promoter, have been well studied. Several transcription factors have been shown to bind to the Il10 promoter and to enhance Il10 transcription in various cell types. In T\(_{h2}\) cells, GATA binding protein 3 (GATA3) functions as a master regulator for Il10 expression by binding to sites in the Il10 locus (including to the promoter) and inducing locus remodelling. Also represented are putative signal transducer and activator of transcription (STAT) binding sites in the mouse Il10 promoter. ATF1, activating transcription factor 1; C/EBPβ, CCAAT/enhancer binding protein-β; CREB, cAMP-responsive-element-binding protein; DC, dendritic cell; Enh, enhancer; GATA3, GATA binding protein 3; SMAD4, mothers against decapentaplegic homologue 4; SP, specific protein.

PREP1 to the apoptotic cell-response element (ACRE) in the IL10 promoter\(^{129}\). The transcription factors CAMP-responsive-element-binding protein (CREB) and activating transcription factor 1 (ATF1) have been shown to be activated by MSks in LPS-stimulated mouse macrophages and to bind to the Il10 promoter, thus suggesting a direct effect of the kinases MSK1 and MSK2 in the regulation of IL-10 induction\(^{44}\) (FIG. 2b). There is also evidence for TGFβ1-induced SMAD4 binding to and activating the Il10 promoter in mouse T\(_{h1}\) cells\(^{130}\); however, it is worth noting that TGFβ1 inhibits the development of T\(_{h1}\) and T\(_{h2}\) cells in vitro and thus their production of IL-10 (REF. 72).

The transcription factor GATA3 was shown to be a master regulator of IL-10 expression in mouse T\(_{h2}\) cells by binding to and initiating changes in the chromatin structure at the Il10 locus\(^{42,64}\). Although one of the binding sites for GATA3 is located in the Il10 promoter, GATA3 alone does not transactivate the Il10 promoter\(^{81}\). GATA3 may thus be responsible for remodelling the Il10 locus in T\(_{h2}\) cells, with other factors being necessary to induce high levels of IL-10 expression in other cell types such as T\(_{h1}\) cells that do not express GATA3 (REFS 69,72).

Originally described as a T\(_{h2}\) cell-specific factor\(^{131}\), the transcription factor MA\(\text{F}\) has been shown to bind to the Il10 promoter and have a role in the transcriptional regulation of IL-10 in mouse macrophages stimulated with LPS and IL-4, although MAF alone is not sufficient to induce Il10 expression in these cells\(^{132}\). Other recent reports have also implicated MAF in the expression of IL-10 by T\(_{h1}\), cells, showing binding of this transcription factor to MAF recognition elements in the Il10 promoter\(^{85}\), and in the differentiation of IL-10-producing FOXP3 regulatory T cells\(^{68}\). Finally, MAF expression is also detectable in T\(_{h1}\), T\(_{h2}\) and T\(_{h17}\) cells, correlating with IL-10 production, and MAF expression depends on ERK activation in T\(_{h1}\) and T\(_{h17}\) cells, similar to IL-10 expression\(^{72}\). Taken together, these reports suggest that MAF may be a universal transcription factor for the regulation of IL-10 production, important in all IL-10-producing cells of both the innate and the adaptive immune systems.

As discussed, various transcription factors have been described to bind to and activate the IL10 promoter (FIGS 3, 4). The activity of one transcription factor or another to regulate IL10 expression seems to depend on the cell type and type of stimuli. Furthermore, multiple studies suggest that IL-10 is not regulated in a simple and linear manner, which is in accord with its function to keep diverse immune responses in check.

Enhancing IL10 transcription. Following the description of several distal regulatory elements in Il10\(^{61,133-135}\) (FIG. 3), the search for transcription factors with a role in regulating IL10 expression has been expanded to those that bind regions of the locus outside of the promoter region.
The NF-kB p65 subunit binds to a newly described kB site located 4.5 kb upstream of the Il10 start site and has a role in enhancing IL-10 expression by LPS-stimulated mouse macrophages (Fig. 3). This is in keeping with a report that mice deficient for inhibitor of NF-kB kinase 2 (IKK2) show a defect in IL-10 production in LPS-stimulated macrophages. This kB site is exposed in IL-10-producing LPS-, CpG- or zymosan A-stimulated mouse macrophages and DCs but is absent in T cells. This suggests that different molecular mechanisms might regulate the expression of Il10 in the innate versus adaptive immune systems and that the production of IL-10 by innate immune cells might be subject to additional regulation, as it is the first checkpoint for the initiation of immune responses and determines the class of the resulting adaptive immune response. Of interest, however, is that ERK signalling is required for optimal IL-10 induction in macrophages, DCs and T\textsubscript{H} cell subsets, which questions whether transcription factors that are required for IL-10 induction in DCs and macrophages may also have a role in inducing IL-10 in T cells. One of the transcription factors implicated in TLR-induced IL-10 expression in mouse macrophages and DCs, by the activation of ERK, is FOS, the expression of which is strongly induced by high levels of ERK activation.

Studies have suggested there is a role for JUN proteins in regulating II10 in mouse T\textsubscript{H} cells, but not T\textsubscript{H} cells, through binding to a regulatory element located ~6.45 kb downstream of the II10 start site. This finding supports our suggestion that alternative mechanisms probably operate to regulate II10 induction in T\textsubscript{H} and T\textsubscript{H} cells and possibly in other T\textsubscript{H} cell subsets, although common factors, such as ERK and MAF, are required for II10 induction in various cell types.

Although there are no data so far to show direct binding of the various STAT\textsubscript{s} to the IL10 locus, an increasing amount of evidence suggests a role for the STAT\textsubscript{s} in regulating the induction of IL-10 expression in both primary macrophages and T cells. In mouse T cells, the induction of IL-10 by IL-27 seems to depend on both STAT1 (REFS 79,87) and STAT3 (REFS 79,85), and STAT3 is also involved in IL-6-induced IL-10 expression. By contrast, a recent study on human monocytes describes an inhibitory role for IL-27 on IL-10 production through STAT1 (REF 89). In addition, as STAT3 is required for T\textsubscript{H}17 cell differentiation, this transcription factor may have an indirect role in IL-27-mediated induction of IL-10 by T\textsubscript{H}17 cells by modulating T\textsubscript{H}17 cell differentiation. Another study suggests that IL-10 induces its own expression by human monocyte-derived macrophages in an autocrine manner through the activation of STAT3 (REF 67). In this study, activation of the IL10 promoter depended on the integrity of the STAT3-binding site. Considering the data from human cell lines that show binding of STAT3 to the IL10 promoter, it is possible that the STAT3-dependent effects on IL10 activation in primary cells might be related to promoter transactivation. Finally, STAT4, which is important for the differentiation of IFN\textgamma- and IL-10-producing mouse T\textsubscript{H} cells, was also reported to have a role in inducing IL-10 expression by mouse NK cells. The molecular mechanisms underlying the participation of other STAT\textsubscript{s} in the control of IL-10 expression require further clarification, particularly as several STAT\textsubscript{s} are required for the differentiation of T\textsubscript{H} cell subsets and thus can modulate the induction of IL-10 in an indirect manner.

The list of transcription factors involved in the regulation of IL10 expression is expanding (Fig. 4), which reflects the degree of precision and complexity that the expression of this cytokine demands. The exact contribution of many of the transcription factors discussed above remains elusive and may in some cases be cell specific, but may also depend on the type of stimulus that triggers IL10 expression or may affect IL10 expression indirectly. With the identification and characterization of distal regulatory regions in the IL10 locus, a role for other transcription factors might also be revealed.
Silencing IL10 expression. Recent studies have provided evidence for the role of certain transcription factors in silencing IL10 expression. For example, it has been suggested that the transcription factor ETS1 has a role in repressing the production of IL-10 by mouse T<sub>H</sub>1 cells, as ETS1-deficient T<sub>H</sub>1 cells show a marked increase in the production of this cytokine. However, it is possible that the effect of ETS1 on IL-10 expression results from diminished T<sub>H</sub>1 cell differentiation, as no interaction of ETS1 with the IL10 locus has been shown. Similarly, an increase in IL-10 expression was observed in mice deficient for the T<sub>H</sub>1 cell-specific transcription factor T-bet (also known as TBX21) that were infected with *M. tuberculosis*, suggesting that T-bet might have a role in the negative regulation of IL-10 expression by T<sub>H</sub>1 cells. However, as IFNγ expression is also lost in the absence of T-bet, this effect on IL-10 could reflect a blockade of T<sub>H</sub>1 cell differentiation, with the increase in IL-10 expression resulting from other cells. This notion is strongly supported by the observation that IL-10 production by T<sub>H</sub>1 cells is accompanied by the expression of high levels of IFNγ and T-bet.

Silencers of IL-10 expression have also been identified in cells of the innate immune response. MHC class II transactivator (CIITA) has been shown to negatively regulate the expression of IL-10 by mouse DCs and the activity of the IL10 promoter in a mouse macrophage cell line. As mentioned above, it is also possible that STAT1 negatively regulates IL-10 expression in human monocytes. However, it is still unclear whether STAT1 directly or indirectly affects the IL10 locus. In addition, isolated peritoneal macrophages from B cell lymphoma 3 (BCL-3)-deficient mice produce increased amounts of IL-10, suggesting that BCL-3 is an inhibitor of IL-10 expression in macrophages; although, again, it is questionable whether this effect is direct or indirect. BCL-6 has been reported to have a role in inhibiting the production of T<sub>H</sub>2 cell-specific cytokines including IL-10 (REF 142), and in its absence T cells activated with strong co-stimulation show a large upregulation of IFN, IL10 and IL13 mRNA, whereas over-expression of BCL-6 in wild-type T cells strongly inhibits the production of IL-10 following activation. However, it is unknown whether BCL-6 directly regulates the IL10 locus. In recent reports, BCL-6 was required for T follicular helper cell differentiation, but it inhibited the differentiation of other T<sub>H</sub>2 cell subsets, by direct interaction with T-bet, GATA3 and retinoic acid receptor-related orphan receptor-γt (RORγt). It is therefore possible that the previously reported BCL-6-mediated IL-10 suppression in T<sub>H</sub>2 cells is a consequence of the inhibition of the T<sub>H</sub>2 cell differentiation pathways and therefore not due to a direct effect of BCL-6 on IL10 transcription. In support of this, no BCL-6 consensus binding sites have as yet been found in the IL10 promoter.

The complexity of IL10 regulation by different cells of the immune system, having both positive and negative feedback loops, shows the tight control that is essential to achieve a balance between an effective immune response and immunopathology. This complex regulation ranges from common to distinct pathways of IL-10 induction in different cell types.

**Mechanisms of post-transcriptional regulation**

Modulation of mRNA stability is an important component in the regulation of expression of several cytokines (reviewed in REF 146) and most cytokine genes have a long 3′ untranslated region (UTR), containing class II adenosine–uridine-rich elements (ARE) that target mRNAs for rapid degradation. Multiple copies of potential mRNA destabilizing motifs are found in the 3′ UTR of IL10 mRNA. Various factors can alter the stability of IL10 mRNA, including IL-10 itself, which triggers IL10 mRNA degradation and adenosine receptor activation, which acts by relieving the translational repressive effect of the IL10 3′ UTR thereby increasing the mRNA half-life and the amount of IL-10 produced.

More recently, IL10 mRNA has been identified as a tristetraprolin (TTP) target in a wide genome screen. TTP is a RNA-binding molecule that can induce rapid degradation of mRNA following binding to AREs in 3′ UTRs. Supporting this finding, macrophages from TTP-deficient mice showed a decrease in the rate of IL10 mRNA decay and an increase in IL-10 secretion. Moreover, activation of p38 has been reported to stabilize the IL10 mRNA by inhibiting the action of TTP. Interestingly, IL-10 induces TTP expression in a STAT3-dependent manner, contributing to the establishment of an anti-inflammatory programme.

Finally, a role for microRNAs in the regulation of IL-10 expression has been described. A recent report shows that the human microRNA miR-106a, expressed in cells of both lymphoid and myeloid origin, binds the 3′ UTR of the IL10 mRNA and induces its degradation.

This level of post-transcriptional regulation of IL-10 expression might explain why, despite the existence of common pathways for IL-10 induction, different cells ultimately secrete different amounts of IL-10. Thus, in addition to genetic regulation, post-transcriptional regulation contributes to the fine tuning of IL-10 expression.

**Conclusion and outstanding questions**

Owing to the key role of IL-10 in the immune response and the link between defective IL-10 production and certain autoimmune and inflammatory diseases, an understanding of the molecular mechanisms that regulate the expression of this cytokine is crucial.

The fact that various cell types can express IL-10 makes the subject of IL10 regulation challenging. It also highlights the complexity of this regulation. Several early studies on the molecular regulation of IL-10 reported apparent differences. The fact that cell lines and different conditions were used in most of these studies has certainly been a contributing factor to these discrepancies. Indeed, recent studies using primary T cells, macrophages and DCs show more consistent results between laboratories with respect to the regulation of IL10 expression.

Several general conclusions from these studies can be made: first, many cells of the innate and adaptive immune response produce IL-10 regardless of the stimulus. Second, different stimuli, or the strength of the stimulus, give rise to different levels of IL-10 in the same cell type. Third, some of the molecular mechanisms for the regulation of IL-10 differ according to the cell type.
type, although common mechanisms also exist. And fourth, IL-10 is induced in many situations together with pro-inflammatory cytokines, although the pathways that induce IL-10 expression may actually negatively regulate the expression of these pro-inflammatory cytokines.

Several outstanding questions and future challenges remain. Which cells are induced to produce IL-10 during an immune response to specific pathogens and gut flora, and which IL-10-producing cells are required to prevent host damage or to conversely inhibit immune responses, thereby contributing to chronic infection? What signalling pathways and transcription factors can specifically induce IL-10 in different immune cells independently of the induction of pro-inflammatory cytokines? What signalling pathways are required in different cells, and what is the hierarchy of transcription factor binding to IL10 regulatory elements? Is IL-10 production in vivo dictated by the environment and inflammatory stimuli, and what maintains the remodelling of the IL10 locus? For example, can T regulatory cells detect signals and inflammatory molecules induced by microorganisms and their products in the microenvironment and turn on IL-10 production and thus reduce tissue damage? Many of these questions will be answered by comparing the kinetics and quantity of IL-10 expression and production in different immune cells stimulated with different stimuli and by elucidating the molecular signalling pathways leading to IL-10, by traditional biochemical methods, bioinformatics or high-throughput approaches, such as chromatin immunoprecipitation sequencing.

Outstanding questions might be answered by dissecting the mechanisms that regulate the expression of IL-10 in different cells, during different immune responses to microorganisms and in different anatomical locations (for example, comparing IL-10 expression in the lungs to the blood during M. tuberculosis infection). An understanding of how IL-10 expression is regulated during such immune responses undoubtedly will be of use in developing therapeutic strategies to target IL-10 production in disease.


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Acknowledgements

We thank L. Gabrysova for critical reading of and commenting on this review and A. Howes for careful proof reading.

Competing interests statement

The authors declare no competing financial interests.
About the authors
Margarida Saraiva received her Ph.D. from the University of Cambridge, UK, in 2002. She subsequently carried out her postdoctoral research at the Medical Research Council National Institute for Medical Research (NIMR) on the molecular mechanisms of interleukin-10 (IL-10) gene regulation. In 2007 she joined the Life and Health Sciences Research Institute (ICVS) in Portugal. Her research programme focuses on the molecular regulation of macrophage and dendritic cell (DC) responses to Mycobacterium tuberculosis.

Anne O’Garra trained at the NIMR. She was then recruited to the DNAX Research Institute, California, USA. Her findings identified the roles of several key cytokines in the activation or downregulation of immune responses, and with this knowledge she is now pursuing therapeutic strategies for intervention in infectious diseases. Her most important contributions relate to the discovery of the immunosuppressive functions of IL-10, the production of IL-12 by essential antigen-presenting cells (APCs), DCs and macrophages, and the roles of IL-18 and IL-12 in inducing CD4+ T helper 1 (T(H)1) cell responses. Despite several offers of distinguished posts in the USA, she returned to the UK in 2001 to a permanent position as the Head of a new Division of Immunoregulation at the NIMR, to be an interface between the Divisions of Immunology and Infectious Diseases.

Online summary
• Interleukin-10 (IL-10) is not a cell type-specific cytokine, but instead it is broadly expressed by many immune cells.
• Several layers of regulation regulate IL-10 production, including changes in the chromatin structure, enhancement or silencing of IL10 transcription and post-transcriptional regulatory mechanisms.
• Many of the molecular events leading to IL10 expression are similar and common to various IL-10-producing immune cells, but cell type-specific signals also exist.
• Induction of IL-10 often occurs together with pro-inflammatory cytokines, although pathways that induce IL-10 may actually negatively regulate these pro-inflammatory cytokines.
• Understanding the specific molecular events that regulate the expression of IL-10 will be important for the design of new strategies of immune intervention.

TOC
The regulation of IL-10 production by immune cells
Margarida Saraiva and Anne O’Garra
The anti-inflammatory cytokine interleukin-10 (IL-10) has a central role in limiting inflammatory responses to protect against excessive tissue damage. Recent evidence suggests that many types of immune cell can produce IL-10, but how is its transcription regulated in these different cell types?