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**From IL-15 to IL-33: the never-ending list of new players in inflammation. Is it time to forget the humble Aspirin and move ahead?**

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4 **COMMENTARY**  
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8 **From IL-15 to IL-33: the never-ending list of new players in**  
9 **inflammation. Is it time to forget the humble Aspirin and move ahead?**  
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38 **Key words:** Interleukin-15, Interleukin-17, Interleukin-18, Interleukin-21, Interleukin-  
39 22, Interleukin-27, Interleukin-33; resolution of inflammation; autoimmune diseases,  
40 antinflammatory drugs.  
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**Abstract**

The study of the inflammatory response has seen a tremendous expansion over the last 30 years. Advancements in technology and better knowledge of the etiopathogenesis of several inflammatory conditions have facilitated this process allowing researchers to almost reach the core of problem. Thus, we now know that inflammation can be manifested in many different ways depending on the context that has elicited it. Viral and infectious, allergic and autoimmune, carcinogenic and resolutive are just a few examples of how inflammation can disguise itself.

However, and most intriguingly, it appears that the more we try to discover “an ideal target” and delineate borders for a specific class of inflammatory conditions the more we find similarities, overlaps or often links that we did not predict. These somehow disappointing findings have pushed researchers towards a frantic search for new and more “reliable” targets. As result, we have recently seen a surge of many novel mediators of inflammation. If we just limit our focus to inflammatory cytokines, the main topic of this commentary, the list seems never-ending: IL-15, IL-17, IL-18, IL-21, IL-22, IL-23, IL-27 and IL-33. Are these cytokines destined to supersede prostaglandins and other autacoids for their key role in inflammation? Are we going to see a cheap and effective alternative to Aspirin on the supermarket shelves in the next few years?

Here we summarize the most recent findings on the biological effects of these new inflammatory cytokines and discuss how these discoveries might influence our current view on therapeutic approaches to treat inflammation.

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4 Scientists working on inflammation would agree with us that this field of research has  
5 seen a tremendous expansion over the last 30 years. This could be explained in many  
6 different ways: surely, a better knowledge of the molecular mechanisms underlying the  
7 complex and different inflammatory diseases has provided us with a number of novel  
8 mediators and signalling pathways, all seeming to play pivotal roles in these processes.  
9 These findings are supported by a number of convincing and technically sophisticated  
10 evidences, including those generated with knockout and transgenic mice or produced  
11 after gene therapy protocols. However, we should not forget that “inflammation” is a  
12 generic term to describe a phenomenon that comes about in many different flavours  
13 depending on the context where it has developed, the time point we are investigating and  
14 the inflammatory stimuli we are using. More importantly, one aspect that we believe is  
15 fundamental for *biochemical pharmacologists* is to determine how these information can  
16 be translated into clinical practice and whether these new targets might be of “general  
17 use” or should be considered for “disease-tailored” therapies.  
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32 First, however, we should be more careful in defining inflammation in such a generic  
33 way and possibly go back in time to a more clear distinction between acute and chronic  
34 inflammation existed. Further attention should also be given to another important  
35 processes that have been recently described as para-inflammation. In this regard, in one  
36 of his excellent and enlightening reviews, Ruslan Medzhitov provided a clear distinction  
37 between classical instigators of inflammation such as infection and tissue injury and  
38 alternative inducers such as tissue stress and malfunction that similarly induce an  
39 adaptive immune response called para-inflammation [1]. Most interestingly, what we  
40 believe is now becoming clear is that lack of homeostatic control over the initial phase of  
41 the inflammatory response opens the doors to autoimmune diseases [2]. In fact, whenever  
42 an active resolute phase of the immune response fails to take place, then chronic  
43 inflammation follows and a completely new set of mediators enters in action [3].  
44 Consistent with this, there is a consensus among the scientific community that the  
45 persistent presence of chronic inflammation might be the initial thread that ultimately  
46 leads to autoimmunity [4].  
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4 In this context, i.e. during the establishment of chronic inflammation, plethoras of novel  
5 cytokines have been discovered. Here, we will be focusing in particular on these  
6 cytokines and on their contribution to the inflammatory process. We hope that this  
7 overview will help pharmacologists find their way when faced with the difficult decision  
8 (Figure 1) of identifying novel molecular targets to treat inflammatory diseases and  
9 highlight the possible “good and bad” of drugs targeting these molecules.  
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### 17 **Interleukin-15**

18 IL-15 was initially identified as a T cell proliferation stimulating cytokine produced by  
19 virally infected cells and has structural and biological similarities with IL-2. In fact, like  
20 IL-2, it stimulates CD4 and CD8 T cell proliferation [5] and binds a heterodimeric  
21 receptor composed by the same IL-2 receptor (IL-2R)  $\beta$  and  $\gamma$  chain but different  $\alpha$  chain  
22 [6]. Antigen presenting cells such as monocyte/macrophages and dendritic cells seem to  
23 be the main cellular sources of IL-15 although other cell types such as T cells and mast  
24 cells have been found to express it at lower levels or stored intracellularly, respectively  
25 [7, 8].  
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35 A large variety of stimuli induce IL-15 expression and/or release including  
36 lipopolysaccharide and other bacterial products, fungi, viruses and double-stranded RNA  
37 [8]. The mature 114 amino acid biologically active form of IL-15 derives from two  
38 different mRNA isoforms encoding for two IL-15 precursor proteins with either a long or  
39 short N-terminus [9, 10]. These N-terminal sequences, along with other posttranslational  
40 modifications, influence the limited secretion of IL-15 [11]. These control mechanisms  
41 are in fact responsible for the scarce release of this cytokine in the extracellular space,  
42 explaining the difficulties encountered for the detection of IL-15. In addition, some  
43 interesting studies have shown IL-15 to be highly expressed on the cell surface [12]  
44 providing further evidence about the different biological role compared to IL-2 and a  
45 possible explanation for the lack of detection in the culture supernatants.  
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57 *In vivo* studies using mice overexpressing IL-15, IL-15 knock-out or IL-15R $\alpha$  knock-out  
58 mice have shown that this cytokine plays an important role in the development of NK  
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4 cells, intestinal intraepithelial lymphocytes (i-IELs), and NK1<sup>+</sup> T cells (NK-T cells) [13,  
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6 14]. This suggests that IL-15 has an important role in the innate and mucosal immune  
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8 response and that drugs targeting this cytokine might be particularly useful for the  
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10 treatment of diseases characterized by mucosal inflammation such as colitis and  
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12 inflammatory bowel disease. However, the biological functions of IL-15 are not only  
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14 restricted to these pathologies since other studies have demonstrated that this cytokine is  
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16 a potent chemoattractant for T cells [15] and neutrophils [16], two cell types involved in a  
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18 wide variety of inflammatory response. Consistent with this, several studies have  
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20 associated IL-15 with a number of autoimmune diseases such as psoriasis, multiple  
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22 sclerosis and rheumatoid arthritis [17, 18].

### 23 24 **Interleukin-17**

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26 If we had to label one of these novel cytokines a “superstar”, this would be, without any  
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28 doubt, IL-17. Indeed, it is fair to say that the discovery of this cytokine and its biological  
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30 function has revolutionized the field of immunology and has completely changed the way  
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32 we look at many immune-mediated inflammatory pathologies. The main reason for so  
33  
34 much popularity compared to the other cytokines is the identification of a particular  
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36 subset of T helper cells that specifically produce this cytokine and are for this reason  
37  
38 named Th17 cells.

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41 The discovery of this subset of T cells has changed a long known paradigm that classified  
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43 cell mediated immune response in Th1 or Th2 depending on the type of pathogen causing  
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45 the immune reaction, being intracellular for Th1 and extracellular for Th2. Th17 cells  
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47 have gained their unique position in this scenario as cells that defend against extracellular  
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49 bacteria and fungi. Most importantly, these cells have also been identified as key players  
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51 in the development of many autoimmune diseases as we will discuss later [19, 20].

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54 The most studied members of the IL-17 family (six members in total) are IL-17A and F.  
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56 Originally named cytotoxic T-lymphocyte-associated antigen 8 (CTL8), IL-17A is a 155  
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58 amino acid protein that functions as a homodimer that forms via two sulphidrylic  
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60 residues. Among the other 5 members, IL-17F is the one that shares the highest  
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4 homology with IL-17A (55%) [21]. The most well known receptors for IL-17 are IL-17R  
5 and IL-17RC [22]. Both receptors belong to the Type I transmembrane protein family and  
6 they can be found in a variety of tissues such as lungs, kidney, liver and spleen or  
7 myeloid cells, including CD4 and CD8 T cells,  $\gamma\delta$  T cells, NK cells, monocytes and  
8 PMN. Interestingly, human IL-17RA has been found to bind IL-17A with a very low  
9 affinity. However, when this receptor heterodimerizes with IL-17RC both binding and  
10 signalling activities are greatly increased [21]. Database searches have also identified an  
11 additional three receptors whose function or binding to IL-17 family members has yet to  
12 be established. A recent report has shown that IL-17RD (also known as SEF or IL-  
13 17RLM) associates with IL-17R and tumour necrosis factor receptor-associated factor 6  
14 (TRAF6), an IL-17R signalling molecule [23].  
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26 What are the inflammatory properties of IL-17? In this regard much information is  
27 available in the literature. However, it should be mentioned that some of the biological  
28 functions of IL-17 have been “indirectly” attributed to studying the modulation of Th17  
29 cell development or the expression of the IL-17R. Clearly, although these studies provide  
30 very important information regarding IL-17 biology, we should not forget that Th17 cells  
31 produce cytokines other than IL-17 (such as IL-21 or IL-22) and that the complex cross  
32 talk between different inflammatory mediators present in the inflamed tissues might have  
33 contributed to the effects that have been observed and reported.  
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43 The cloning and availability of recombinant IL-17A has allowed a number of studies on  
44 its inflammatory properties *in vitro* and *in vivo*. One of the main cellular targets of IL-  
45 17A is the neutrophil. Injection of IL-17 in different tissues or incubation of epithelial  
46 cells with this cytokine increases the local production of chemokines such as IL-8,  
47 monocyte chemoattractant protein-1 (MCP-1) and Gro- $\alpha$  [24]. Systemic injection or  
48 adenovirus-mediated gene transfer of IL-17 resulted in dramatic effects on *in vivo*  
49 granulopoiesis with a significant increase (five folds) in the peripheral white blood count  
50 and in particular a 10-fold rise in the absolute neutrophil count [25]. In our recent study  
51 we have shown that IL-17 *per se* sustains rather than induces inflammation amplifying  
52 the inflammatory response induced by a pre-existing tissue injury [26]. These effects  
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4 support the antimicrobial functions of Th17 cells and might also provide an explanation  
5 for the recruitment of neutrophils to certain inflammatory sites including the rheumatoid  
6 arthritis joint. Other effects of IL-17 include stimulation of the production of the  
7 hematopoietic cytokines granulocyte colony stimulating factor (G-CSF) and granulocyte  
8 macrophage (GM)-CSF, that promote the expansion of cells of myeloid lineages, or other  
9 inflammatory mediators such as IL-1, IL-6, TNF- $\alpha$  and PGE<sub>2</sub> [21, 22, 24].  
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17 As mentioned above, the majority of information of *in vivo* IL-17 biology derives from  
18 the study of Th17 cells and their role in the development of a wide range of autoimmune  
19 diseases. These include rheumatoid arthritis, multiple sclerosis, asthma, and  
20 inflammatory bowel disease to name just a few [27, 28]. However, more recent studies  
21 suggest that scientists have “rushed to judge” the role of Th17 cells in chronic  
22 autoimmune diseases [29] and that, as is often the case, these cells might not be solely  
23 responsible for autoimmunity.  
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### 32 **Interleukin-18**

33 Contrary to the other two cytokines described before, IL-18 belongs to the IL-1 family of  
34 cytokines and it was initially identified as a factor produced by IFN- $\gamma$  stimulated  
35 macrophages. The regulation of IL-18 production is similar to IL-15. The cytokine is  
36 constitutively expressed as a pro-form of 22 kDa and its 18 kDa active form released  
37 after the action of caspase-1 [30]. A unique feature of IL-18 is its regulation by a  
38 “carrier” or decoy receptor like molecule: the IL-18 binding protein (IL-18BP). This  
39 protein contributes significantly to the manifestation of the biological effects of IL-18  
40 since it acts as a naturally occurring antagonist, and most importantly, it is upregulated by  
41 IL-18 inducing stimuli as part of a negative feedback loop [31, 32]. Consistent with these  
42 findings, IL-18BP transgenic mice were able to completely neutralize IFN- $\gamma$  inducing  
43 activity of exogenously administered IL-18 and functionally protected against acute  
44 ischemic kidney injury or concanavalin A (ConA) induced hepatotoxicity [33].  
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57 IL-18 biological functions are both receptor dependent and independent. Binding of IL-  
58 18 to IL-18R $\alpha$  leads to the formation of a complex with IL-18R $\beta$  that in turn recruits a  
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4 number of signalling molecules such as myeloid differentiation primary response gene 88  
5 (MyD88), interleukin-1 receptor associated kinase (IRAK) and TRAF6 and results in the  
6 activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B), c-Jun N-terminal kinase (JNK) and p38 mitogen  
7 activated protein kinase (MAPK) [34, 35]. However, comparison of IL-18 and IL-  
8 18R $\alpha$  knock out mice showed a different phenotype when used in mouse models of  
9 autoimmune diseases. In fact, it has been shown that IL-18 deficient mice are susceptible  
10 to experimental autoimmune encephalomyelitis while IL-18R $\alpha$  knock out mice are  
11 resistant to this disease [36]. Similar opposite responses were observed in a mouse model  
12 of allograft rejection suggesting that IL-18 mediated antiinflammatory effects might be  
13 independent of IL-18R $\alpha$  [37]. Alternatively, ligands other than IL-18 could activate IL-  
14 18R $\alpha$ .

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27 Indeed, IL-18 has multiple roles potentially impacting both innate and adaptive immune  
28 responses since IL-18R $\alpha$  is expressed in neutrophils, macrophages, basophils, mast cells,  
29 naïve T cells, Th1 cells and B cells. In addition, this receptor is also expressed in a  
30 variety of non-immune cells including endothelial cells, smooth muscle cells, epithelial  
31 cells, synovial fibroblasts and chondrocytes [38, 39]. It is foreseeable that several new  
32 biological properties will be described for this cytokine in the years to come.

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40 Activated monocytes and macrophages are the main cellular source of IL-18. However, a  
41 robust IL-18 production can be obtained following stimulation with microbial products  
42 that cause the activation of caspase-1. This large release of IL-18 has been reported to be  
43 important for the clearance of intracellular pathogens via activation of Th1 cells [40] and  
44 viruses via stimulation of CD8 cytotoxic T cells [41]. Interestingly, IL-18 has also a role  
45 in the Th2 immune response since it enhances IL-13 production by T and NK cells when  
46 combined with IL-2 [42] and induces the secretion of IL-4, IL-5 and IL-10 *in vivo* in  
47 mouse models of disease [43-45]. Consistent with these observations IL-18 transgenic  
48 mice have been shown to produce high levels of both Th1 and Th2 cytokines [46].

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58 Several clinical and experimental studies have shown the clinical relevance of IL-18 in  
59 regulating the inflammatory response *in vivo*. In fact, this cytokine has been detected in  
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4 inflammatory fluids/tissues of several autoimmune diseases such as the cerebrospinal  
5 fluids of multiple sclerosis, the synovium of rheumatoid arthritis patients, the inflamed  
6 mucosa of Crohn's disease, psoriatic plaques and the atheroma of atherosclerotic patients  
7 [47]. This large body of evidences for the pathogenic potential of IL-18 in autoimmune  
8 diseases have prompted the development of different therapeutic strategies targeting this  
9 cytokine. These include the use of neutralizing antibodies, soluble receptors or inhibitors  
10 of IL-18 processing by caspase-1. Many of these have been proved effective in mouse  
11 models of chronic inflammatory diseases such as collagen-induced arthritis and are now  
12 undergoing clinical trials [48, 49].  
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### 22 **Interleukin-21**

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24 IL-21 is the most recent addition to the common  $\gamma$  chain family of cytokines that  
25 comprises IL-2, IL-4, IL-7, IL-9 and IL-15. It was "indirectly" discovered after screening  
26 the supernatants of more than 100 primary and immortalized cell lines for a factor that  
27 would induce the proliferation of BaF3 cells stably expressing full-length IL-21 receptor  
28 (IL-21R) [50-52]. The IL-21R $\alpha$  chain (IL-21R, also termed NILR for novel Interleukin  
29 receptor) forms a complex with the common cytokine receptor  $\gamma$  chain and this is  
30 required for full IL-21 signalling. In fact, although IL-21 is capable of binding IL-21R $\alpha$   
31 chain alone, it has been shown that cells lacking the common cytokine receptor  $\gamma$  chain  
32 are deficient in IL-21-induced signalling. Depending on the cell type, IL-21R can activate  
33 Jak1/Jak3 and in turn STAT1, STAT3, STAT4 and STAT5 signalling pathways. IL-21R  
34 is expressed in spleen, thymus, natural killer (NK), T and B cells, dendritic cells  
35 macrophages and keratinocytes and the effects of IL-21 seems to be dependent on the cell  
36 type and the differentiation or activation status of each cell type [53].  
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50 The sequence of the human IL-21 cDNA contains an open reading frame that encodes a  
51 polypeptide precursor of 162 amino acids while the mature form has a molecular weight  
52 of 15 kDa and consists of a 131 amino acid four-helix-bundle cytokine domain with  
53 highest sequence and structural homology to IL-2, IL-4, and IL-15 proteins [50]. In  
54 contrast to the wide expression of IL-21R in immune cells, IL-21 is very abundant in  
55 activated CD4 T cells but not in CD8 T cells, B cells, myeloid DCs and monocytes.  
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4 Further analyses have initially shown that IL-21 is selectively expressed in Th2 cells and  
5 is strongly induced in the secondary Th2 response. Consistent with this, infection of IL-  
6 21R deficient mice with *Schistosoma mansoni* parasites resulted in reduced Th2 response  
7 *in vivo* [54]. Interestingly, however, IL-21 knock out CD4 T cells differentiated *in vitro*  
8 showed no differences in Th1 or Th2 but a reduced ability to differentiate in Th17 cells  
9 [55]. In addition, the latter have also been shown to produce more IL-21 than Th1 or Th2  
10 cells [56].  
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19 IL-21 has pleiotropic effects on a variety of immune cells. This cytokine is well known  
20 for its role in the proliferation and survival of B cells as well as their differentiation in  
21 plasma cells. Overexpression of this cytokine *in vivo* or by hydrodynamic transfection in  
22 mice caused an increase in the number of immature transitional and memory B cells  
23 accompanied by increased serum levels of IgG and IgM [57]. Different results were  
24 obtained *in vitro* where IL-21 seems to play either an inhibitory or a promoting effect on  
25 B cell proliferation depending on the type of stimuli used to activate the cells [58, 59].  
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33 Being part of the same family as IL-4 and IL-15, IL-21 was expected to influence DC cell  
34 function and differentiation. Indeed, IL-4 and IL-15 are well known for their ability to  
35 promote DC development *in vitro* in presence of granulocyte-macrophage colony  
36 stimulating factor (GM-CSF). Unlike its siblings, IL-21 inhibits the functional maturation  
37 of DC inducing a reduced expression of MHC II and increased antigen uptake, common  
38 features of immature DC. This inhibitory effect was observed not only during the  
39 differentiation of DC, but also when IL-21 was added to DC stimulated with LPS [60].  
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48 The combination of IL-21 together with TGF- $\beta$  induces the differentiation of CD4 cells  
49 towards Th17 cells, while suppressing the generation of FoxP3+ regulatory T cells (Treg)  
50 revealing a negative modulatory role of this cytokine on Treg development [61]. In CD8  
51 T cells, IL-21 acts synergistically with IL-15 or IL-7 to induce proliferation of naïve and  
52 memory CD8 T cells [62]. Other studies have also shown that IL-21 can increase CD8 T  
53 cell antitumor functions and perforin expression in CD8 cells from HIV infected patients  
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6 Other cells influenced by IL-21 are NK cells. In this context, IL-21 promotes a more  
7 mature state and full effector function when this cytokine was added together with IL-15  
8 in vitro during the expansion and differentiation from CD34+ NK progenitor cells [64].  
9 Interestingly, IL-21 has also been shown to reduce the viability of NK cells while  
10 boosting their effector functions suggesting that this cytokine induces a transient and  
11 potent activation of these cells that in turn leads to their apoptosis [65].  
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19 Several recent studies have addressed the suitability of IL-21 targeting for the treatment  
20 of autoimmune chronic diseases. Not surprisingly, IL-21 blocking agents such as IL-21R-  
21 Fc fusion proteins have been shown a partial success in a model of SLE, the MRL-lpr  
22 mice [66], with a significant benefit in the mouse models of RA: the collagen-induced  
23 arthritis and the adjuvant induced arthritis [67, 68]. This complex nature of IL-21  
24 emerges also in EAE where administration of the recombinant cytokine at the onset of  
25 disease exacerbates pathology symptoms with similar effects being observed after  
26 administration of IL-21 blocking agents too [69].  
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### 35 **Interleukin-22**

36 This cytokine belongs to the IL-10 family members with which it shares a homology of  
37 22%. First identified as “IL-10-related T cell derived inducible factor”, it was discovered  
38 first in mice and thereafter in human where it is located on chromosome 12q15 in close  
39 proximity to other IL-10 family members such as IL-19, IL-20 and IL-24. At variance  
40 from IL-10, IL-22 can function as monomer by binding to IL-22 receptor 1 (IL-22R1) or  
41 to a dimer composed of IL-22R1 and IL-10R2 receptor chains. Like in the case of IL-18,  
42 this signalling pathway is antagonized and regulated by IL-22 binding protein (IL-22BP)  
43 which function is to block IL-22 binding to IL-22R, thanks to shared sequence similarity  
44 with an extracellular region of IL-22R1 (sIL-22R1) [70-72].  
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55 IL-22R and IL-10R share a common  $\beta$  chain (IL-10R $\beta$ ) that in the latter case  
56 heterodimerizes with IL-10R $\alpha$  to form the IL-10R. Interestingly, the expression of these  
57 two receptors seems to be mutually exclusive with IL-22R being primarily expressed on  
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4 the epithelial cells of the gastrointestinal tract, pancreas, liver, kidney and skin while IL-  
5 10R is primarily found on cells of the immune system. Activation of IL-22R leads to the  
6 activation of many signalling pathways including STAT1, STAT3, MAP kinases and Akt  
7 [73].  
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13 Cells of both adaptive (CD4 and CD8 T cells, NKT cells and  $\gamma\delta$ T cells) and innate (mast  
14 cells, NK and CD11c+ cells) immune systems express and release IL-22 upon activation.  
15 Stimulation of T cells with a variety of agents including IL-9, IL-12, anti-CD3/CD28 or  
16 anti-CD3+ ICAM causes a strong upregulation of this cytokine. However, IL-22 was  
17 initially described as Th1, but not Th2 cell, produced cytokine and is now best known as  
18 a key Th17-derived effector molecule together with IL-17 [72, 74]. Consistent with these  
19 observations, IL-22 expression has been found to be markedly upregulated in several  
20 autoimmune diseases. More recent studies in this context have also provided novel  
21 information regarding the modulation of IL-22 expression. In particular, it has been  
22 suggested that while IL-17A expression requires the presence of both TGF- $\beta$  and IL-1  
23 and IL-6, IL-22 can be induced solely by IL-6 and preferentially by the activation of the  
24 transcription factor aryl hydrocarbon receptor (AHR) [75, 76].  
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37 As mentioned before, the pathological role of IL-22 has been demonstrated in several  
38 chronic inflammatory pathologies and mouse models of autoimmune diseases. In both  
39 cases the main focus has been the liver [77], the skin [78] and the gut [74]. Injection of  
40 IL-22 in mice causes the release of acute phase proteins including PAP1/Reg2 from the  
41 pancreas [79] and serum amyloid A from the liver [80]. In another study it was shown  
42 that hydrodynamic gene delivery of IL-22 cDNA in the liver significantly protected  
43 against injury, necrosis, and apoptosis induced by administration of ConA, carbon  
44 tetrachloride (CCl<sub>4</sub>), or Fas agonist via the induction of several anti-apoptotic proteins,  
45 including Bcl-xL, Bcl-2, and Mcl-1 [81]. Consistent with this, IL-22 deficient mice have  
46 been shown to be highly sensitive to hepatitis [82].  
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57 A great deal of attention has been given to the role of IL-22 in the skin. Subcutaneous  
58 injection with recombinant IL-22 as well as IL-17A or TNF- $\alpha$  led to the upregulation of  
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4 both CCL20 and CCR6 expression in skin as well as cutaneous T-cell infiltration [83].  
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6 IL-22 application in mice enhanced cutaneous S100A9 and MMP1 expression, two key  
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8 proteins that are abundant in psoriatic skin [84, 85]. Consistent with these observations, it  
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10 has been reported that psoriatic patients showed strongly elevated plasma levels of IL-22  
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12 and that this correlates directly with the disease severity and indirectly with anti-psoriatic  
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14 therapy [85].  
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17 Interesting results have also been obtained from the studies of the role of IL-22 in gut  
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19 pathophysiology. Similar to the study on the liver, microinjection-based local gene-  
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21 delivery of IL-22 gene within colonic epithelial cells led to rapid amelioration of local  
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23 intestinal inflammation in a mouse model of Th2-mediated colitis: the dextran sulfate  
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25 sodium–induced colitis [86].  
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28 Many approaches have been used to further support these findings including the use of  
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30 IL-22BP or neutralizing antibodies against IL-22. Overexpression of IL-22–binding  
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32 protein suppressed goblet cell restitution during the recovery phase of a dextran sulfate  
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34 sodium–induced model of acute colitis while administration of IL-22BP-Fc during septic  
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36 peritonitis led to enhanced accumulation of neutrophils and mononuclear phagocytes and  
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38 a reduced bacterial load at the site of infection [86]. Conversely, mice treated with IL-22–  
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40 neutralizing antibodies reduced acanthosis (thickening of the skin) and inflammatory  
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42 infiltrates [78].  
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### 44 **Interleukin-23**

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46 Interleukin-23, together with IL-27, is recently discovered cytokine structurally related to  
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48 IL-12. In fact, while IL-12 is a heterodimeric cytokine composed of two disulfide-linked  
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50 subunits, p35 and p40, IL-23 was identified after the isolation of p19 which is a novel  
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52 partner of IL-12p40. Similarly to p35 subunit of IL-12, p19 requires coexpression of p40  
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54 for secretion. IL-23 is produced by activated monocytes and activated antigen-presenting  
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56 cells (APC), including DCs and macrophages, T cells, B cells, and endothelial cells [87,  
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58 88].  
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4 IL-23 binds a receptor composed of IL-12R $\beta$ 1 and a second subunit designated IL-23R  
5 while IL-12R is composed of two subunits termed  $\beta$ 1 and  $\beta$ 2 that interact with p40 or  
6 p35, respectively. Both the IL-12R1 and IL-23R chain lack intrinsic signalling activity  
7 and are associated with intracellular proteins to induce downstream signalling. IL-23R  
8 associates with Jak2 and activates a wide range of STATs: STAT1, STAT3, STAT4, and  
9 STAT5 although STAT3 seems to play the most relevant role [89, 90].  
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17 APCs such as macrophages and dendritic cells, appear to be the main cellular sources of  
18 IL-23 although other studies have shown the expression of this cytokine in a variety of  
19 cell types such as microglia [91] and Paneth cells [92]. Initial studies on the biological  
20 functions of this cytokine proposed an overlapping action with IL-12 as inducer of IFN- $\gamma$   
21 producing Th1 cells. However, IL-23 is now most known as a Th17 development  
22 promoting cytokine; it is important to note that IL-23 is not necessary for Th17  
23 differentiation, but rather for expansion and maintenance of these effector cells [90, 93].  
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32 The link between IL-23 and Th17 cells has promoted a number of studies on the role of  
33 this cytokine in autoimmune inflammatory diseases. Here the initial attention focused on  
34 EAE and CIA, showing that IL-23-deficient mice are completely resistant to the  
35 development of this disease [94]. However, most of the recent studies on IL-23 evolve  
36 around its role in the development of intestinal inflammation where this cytokine seems  
37 to play a unique and critical role even when compared to other members of its family  
38 such as IL-12. Colonic DC seem to be the main cellular source of IL-23, and its  
39 production in the gut seems essential to overcome the suppressive effects of Treg cells,  
40 favouring the establishment of an immune response to intestinal pathogens [95].  
41 Consistent with this hypothesis, IL-23 deficient mice have a marked increase in the  
42 number of FoxP3+ cells in the intestine [96].  
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54 More recent studies in humans have expanded the role of IL-23 as an intestinal-specific  
55 cytokine to sentinel of mucosal immunity. Infection of the gastric mucosa by the gram-  
56 negative bacterium *Helicobacter pylori* is considered one of the main causes of gastritis  
57 and ulcer; these conditions are mediated by the induction of IL-23 and the release of IL-  
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4 17 [97]. The recruitment and activation of innate immune cells such as neutrophils by the  
5 latter is thus important for the clearance of intestinal pathogens and re-establishment of  
6 homeostatic mucosal immunity. However, as with many other cytokines described here,  
7 IL-23 is a double-edged sword that, if produced in large non-physiological quantities,  
8 might also cause chronic inflammation. In fact, it has been shown that a population of  
9 CD14<sup>+</sup> macrophages present in Crohn's disease patients produce high levels of IL-23 and  
10 that this in turn lead to the development of pathogenic IFN- $\gamma$  and IL-17 producing T cells  
11 [98]. Similar findings have been reported in spondylitis ankylosante where the increased  
12 production of IL-23 by Paneth cells appears to be the main cause of the intestinal  
13 inflammation characteristic of this disease [92]. Finally, and most importantly, a genome-  
14 wide association study has shown that coding single-nucleotide polymorphism within the  
15 IL-23R, but not IL-12R $\beta$ 2, predisposes and significantly correlates with susceptibility to  
16 inflammatory bowel disease [99, 100]. As a consequence of the structural and functional  
17 similarities between IL-12 and IL-23, it seems probable that IL-23, like IL-12, would also  
18 have a function in the regulation of Th1-cell responses. These findings, together with the  
19 results of several clinical trials now under development, will further substantiate the  
20 suitability of IL-23 as promising target for the development of novel therapeutics for  
21 autoimmune chronic intestinal inflammation.  
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### 39 **Interleukin-27**

40 IL-27 belongs to the greater family of IL-6/IL-12 cytokine family and like its siblings IL-  
41 12, IL-23 and IL-35, is a heterodimeric cytokine composed of Epstein–Barr virus-  
42 induced gene 3 (EBI-3), a p40-related molecule, and p28, a p35-related molecule.  
43 However, IL-27 differs from IL-12 and IL-23 in that its subunits are not tight together by  
44 a disulfide bond and this has led to the suggestions that p28 alone might be able to exert  
45 IL-27 biological effects [101]. In line with this hypothesis, the kinetic of p28 expression  
46 is significantly faster than that of EBI3 in activated DC. On the other hand, the scarce  
47 recovery of p28 in the extracellular medium of mouse and human cells does not provide  
48 support to this hypothesis [102].  
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4 The IL-27 receptor (IL-27R) has two components: the same gp130 signal transducing  
5 chain of IL-6 receptor and the IL-27ra (WSX-1, TCCR). Although IL-27ra alone can  
6 bind IL-27 and IL-27ra-FC fusion protein has been shown to neutralize IL-27, the  
7 presence of gp130 is essential for signal transduction. Leukocytes of both adaptive and  
8 innate immune arms such as neutrophils, monocytes, mast cells, T, B and NK cells  
9 express IL-27R while IL-27 has been shown to be mainly produced by APC during  
10 inflammatory conditions. The signalling pathway initiated by IL-27 activates JAK1 and  
11 JAK2, resulting in phosphorylation of STAT1, STAT2, STAT3, and STAT5 in naive  
12 CD4+ T cells. However, only STAT1 and STAT3 are critical to IL-27 bioactivity, as  
13 demonstrated by the loss of IL-27 activity in STAT1- and STAT3-deficient mice [102-  
14 104].

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26 Among all the cytokines described here, IL-27 is the most well known for its “dual  
27 personality”. Indeed, several lines of evidence initially proposed that IL-27 is a  
28 proinflammatory cytokine that promotes Th1 differentiation thanks to its ability to induce  
29 the release of IFN- $\gamma$  by unpolarized T cells and because of the reduced production of  
30 IFN- $\gamma$  by antigen-stimulated IL-27ra-deficient cells. Most interestingly, when compared  
31 to its mother cytokine IL-12, IL-27 is released by APC soon after their activation and IL-  
32 27R is expressed by naïve T cells while IL-12R $\beta$ 2 is absent in these cells [105, 106].  
33 Together these findings point to IL-27 as key cytokine governing the initial phase of  
34 naïve T cells differentiation in Th1 effector cells.

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45 However, this scenario changed significantly after the generation of IL-27ra knock out  
46 mice since it was found that these animals had only a transient defect in Th1 polarization  
47 following infection with *Leishmania major* and normal IFN- $\gamma$  production at the later  
48 stage of the disease when the parasite starts to proliferate [107]. Most strikingly, using  
49 other mouse models of infections *Trypanosoma cruzi* [108] or *Trypanosoma gondii* [109]  
50 it was noted that IL-27ra-deficient mice developed severe organ damages as a result of  
51 exacerbated activation of T cells. Similar findings have been described for a number of  
52 other cell types where while the cytokine *per se* induced the activation of these cells in  
53 vitro, the analysis of the IL-27ra-deficient mice gave opposite results. For instance,  
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4 stimulation of mast cells with IL-27 upregulates the expression of inflammatory  
5 mediators such as IL-1 $\beta$ , TNF- $\alpha$ , OX40 and RANKL [110] while IL-27ra deficient mice  
6 exhibited enhanced mast cell response upon antigen challenge [111].  
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11 Other studies further consolidated the antiinflammatory property of IL-27. The  
12 mechanisms underlying this effect are not clear as yet but include the suppression of  
13 several key inflammatory cytokines such as IL-2, IL-6 and IL-17. In CD4 T cells, IL-27  
14 inhibits the differentiation of Th17 cells while in CD8 T cell it enhances cytotoxic  
15 activity against tumours. IL-27 also influences B-cell differentiation and immunoglobulin  
16 production inducing proliferation of activated naive but not memory B cells [103].  
17 Recombinant IL-27 suppresses reactive oxygen intermediates production by activated  
18 macrophages and neutrophils [112] and DCs from IL-27ra deficient mice showed an  
19 increased response to LPS stimulation by expression of CD80 and CD86 costimulatory  
20 molecules and Th1-related cytokine genes [103].  
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### 32 **Interleukin-33**

33 Of all the cytokines that are described in this review, IL-33 is the most recently  
34 discovered. IL-33 was first described in 2005 and belongs to the IL-1 cytokine family  
35 [113]. Like IL-1 and IL-18, IL-33 is expressed as prodomains and only become  
36 functionally mature proteins following proteolytic processing by caspase-1. In fact, *in*  
37 *vitro* incubation of IL-33 with caspase-1 yielded an 18 kDa mature protein from a 30 kDa  
38 precursor [114, 115]. Interestingly, the pro-form of IL-33 has been found to localize in  
39 the nucleus thanks to a nuclear localization sequence present in the propeptide and  
40 proposed to function as transcriptional repressor [116]. However, the exact role of  
41 nuclear pro-IL-33 is still not known.  
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52 The receptor for IL-33 is a heterodimer composed of ST2, the orphan IL-1 family  
53 receptor, and IL-1RAcP, and it is present in a transmembrane and secreted form. The  
54 transmembrane form is expressed primarily on mast cells and Th2 cells and thus thought  
55 to play a key role in the development of a Th2 response [117]. Consistent with this,  
56 administration of recombinant IL-33 both *in vitro* and *in vivo* causes the release of Th2  
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4 cytokines IL-5 and IL-13 while suppressing the production of Th1 cytokine IFN- $\gamma$  [118].  
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6 The soluble isoform originates from differential mRNA processing and because of this  
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8 lack of nine amino acids present at the C-terminus of the molecule. This spliced isoform  
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10 is produced by antigen presenting cells such as monocytes and macrophages and acts as  
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12 decoy receptor and thus antagonizes the effects of IL-33 [119, 120]. In fact, patients  
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14 suffering chronic inflammatory diseases have high levels of soluble ST2 [121, 122].  
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17 IL-33 is widely expressed in several tissues and cell types including smooth muscle cells,  
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19 epithelial cells, fibroblasts, keratynocytes, dendritic cells and activated macrophages.  
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21 Binding of IL-33 to ST2 homodimers activates a cascade of signalling events leading to  
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23 the activation of NF- $\kappa$ B and several MAPKs. Other studies have also shown that IL-33  
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25 can activate a heterodimeric receptor complex composed by ST2 and IL-1RAcP and thus  
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27 initiate the classical IL-1 signalling cascade involving Erk, p38 and JNK activation [115].  
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31 Administration of IL-33 in the peritoneal cavity of mice induced a selective increase of  
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33 mononuclear cells, eosinophils and plasma cells in the spleen while in the lung led to the  
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35 accumulation of eosinophils and mononuclear cells [123]. These effects are consistent  
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37 with its ability to induce a Th2 response and to act as chemoattractant for Th2 cells [118].  
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39 In addition, IL-33 has been shown to promote the differentiation of CD34+ precursor  
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41 cells in mast cells [124] and to induce the release of several inflammatory cytokines such  
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43 as TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and MCP-1 from bone marrow derived mast cells [125]. These  
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45 findings are particularly interesting since recent views on the pathogenesis of RA suggest  
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47 that activation of mast cells might play an important role in the pathogenesis of this  
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49 disease. In this context, there seems it is possible to envisage a link between IL-33, mast  
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51 cells and RA [126]. Administration of soluble ST2 has been proved to decrease the  
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53 development of this disease possibly *via* direct inhibition of macrophage activation [127].  
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55 Further studies using similar pharmacological tools have been carried out in mouse  
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57 models of septic shock where administration of soluble ST2 was found to reduce  
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59 systemic inflammation and mortality [128].  
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## 61 **Conclusions**

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4 Looking back at pharmacology textbooks for “ant inflammatory drugs” students will find  
5 few short sentences on the role of cytokines in inflammatory diseases while a great deal  
6 of attention was given to small molecules and short lived mediators such as histamine,  
7 bradykinin, serotonin and prostaglandins. These key mediators of inflammation would be  
8 responsible for the appearance of the first signs of inflammation such as *calor*, *dolor*  
9 *rubor* and *tumor* (heat, pain, redness, and swelling) and the recruitment and/or activation  
10 of the “first line of defence” of the immune system i.e. neutrophils, macrophages. This  
11 early phase (lasting from few hours to a day or so) would then continue and become  
12 “chronic inflammation”: a different immune response characterized by the influx of  
13 lymphocytes and the formation of granulomatous tissues. According to a common  
14 consensus at that time, therapeutic interventions during the early phase of inflammation  
15 would block this self-propagating response and thus provide an effective treatment for  
16 both acute and chronic inflammatory diseases. As a result of this, very little attention was  
17 given to the later stage of the inflammatory response and to all the pathways governing  
18 this phase.  
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33 The discovery of cytokines as potent inducers of inflammation has significantly  
34 revolutionized the field and changed the way we look now at both the early and late stage  
35 of inflammation. In fact we now know that there are a number of “early inflammatory  
36 cytokines” such as IL-1, IL-8 and TNF- $\alpha$ , just to name a few, that play a key role to the  
37 initiation of the inflammatory response like prostaglandins and kinines. In addition to  
38 this, the scientific community has also filled in the “empty box” of the signalling  
39 pathways governing chronic inflammation and provided us with a long list of cytokines  
40 that appear to be promising targets for the treatment of a variety of chronic autoimmune  
41 diseases. We have provided here a brief description of few selected recent ones that are  
42 emerging as the next “holy grail” to treat inflammation and summarized their main  
43 structural and biological features (**Table I and II**).  
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55 However, we cannot help notice that there is still a great deal of “segregation” within the  
56 scientific community that leads them to sectorialize themselves in specific niches and  
57 loose track of the “bigger picture”. Indeed, it is now becoming clear that there is not a  
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4 clear mark that divides innate and adaptive immune response and that, for instance,  
5 lymphocytes, the latecomers in inflammation, can also influence the initial phase of the  
6 inflammatory response. Similarly, “early-birds” of inflammation such as neutrophils are  
7 actively recruited by Th17 cells that currently sit on the podium of chronic inflammatory  
8 diseases.  
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15 In this respect, we think that more fruitful discoveries will be available when scientists  
16 will loosen up their boundaries and approach the study of novel mediators of  
17 inflammation with a more open mind i.e. without putting their bets on a given molecule  
18 in a specific cell in the context of a specific inflammatory disease. Similar efforts might  
19 revealed useful when, in a opposite way, we do not recognize individuality to different  
20 inflammatory pathologies and thus we think that a novel treatment for rheumatoid  
21 arthritis will be also effective in multiple sclerosis, psoriasis or systemic lupus  
22 erythematosus.  
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32 Thus, the discovery of a novel mediator of inflammation should prompt scientist, and  
33 especially biochemical pharmacologists, to first explore the effects of this novel  
34 mediators in “far-distant” cellular and physio/pathological contexts and second to  
35 investigate how tissue and disease specific these effects are. In a similar fashion,  
36 researchers interested in the discovery of new antiinflammatory drugs or natural bioactive  
37 compounds should not limit their investigations only to the well-known mediators of  
38 inflammation but also to these fashionable and recently discovered molecules. This open-  
39 arm approach might significantly accelerate the discovery of novel effective therapeutic  
40 strategies and avoid a “rush to judgement” [29] we have seen so far applied to  
41 inflammation and immune biology research.  
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52 We think that the history and curriculum vitae of Aspirin provide us with a very good  
53 example of expanding initial findings and incorporating novel information that can  
54 significantly change the way we use a drug in the clinic. Indeed, after the initial discovery  
55 of Aspirin as cyclooxygenase inhibitor, we now know that aspirin and salicylic acid act  
56 also as inhibitors of NF- $\kappa$ B activation when given at high doses [129] or that can trigger  
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4 the transcellular biosynthesis of a series of 15-epimer (aspirin-triggered 15-epi-LXA<sub>4</sub>)  
5 [130], which share many anti-inflammatory activities with the native LXA<sub>4</sub>.  
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10 We think that this continuously evolving story on the molecular mechanisms responsible  
11 for the anti-inflammatory effects of Aspirin is the main reason behind the long lasting  
12 success of this drug. In light of this consideration, we hope that in the future researchers  
13 will consider the discovery of mediators of inflammation not only as novel “piece of  
14 biology” but also the starting point to ask themselves one simple and important question:  
15 are we going to change the box with Aspirin in our cupboard at home with something  
16 safer?  
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#### 24 **Acknowledgments**

25  
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**Figure legend.**

**Figure 1.** Scientific “dilemma” faced by biochemical pharmacologists wishing to find “the right switch” to shut down inflammation.

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Figure 1 greyscale

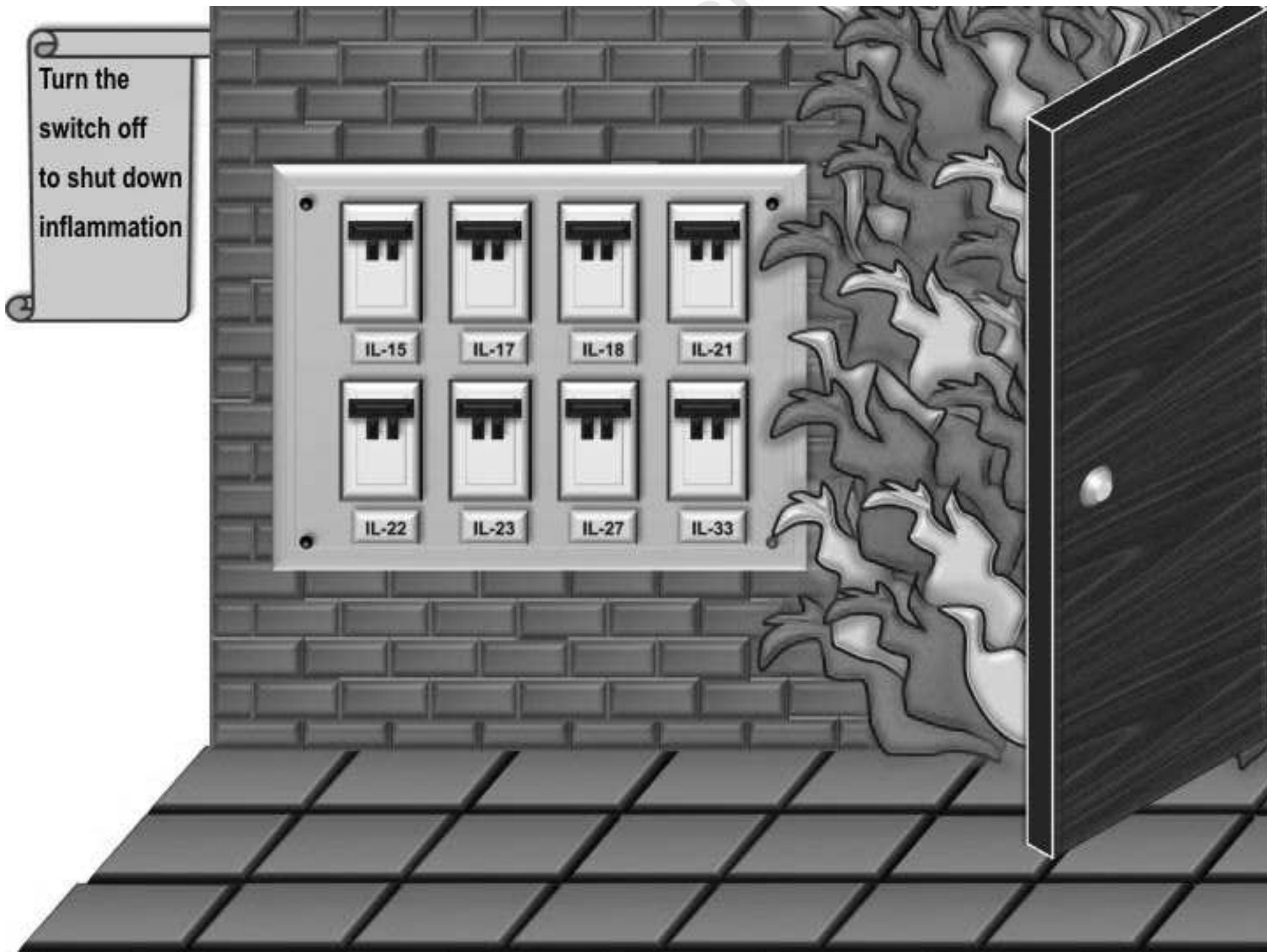


Figure 1



Designation	Cytokine family	Structural features	Cellular/tissue distribution	Biological functions
IL-15	IL-2	Four helical bundle cytokine	Monocytes, macrophages, dendritic cells, T cells and mast cells	-CD4 and CD8 T cell proliferation -Chemoattractant for T cell and neutrophils -Development of NK cells and intestinal intraepithelial lymphocytes
IL-17A to F	IL-17	Homo/Heterodimer; structural homolog of the cysteine knot family	Th17 cells, neutrophils, epithelial and endothelial cells	-Production of chemokines (IL-8, MCP-1, Gro- $\alpha$ ), cytokines (G-CSF, (GM)-CSF, IL-1, IL-6, TNF- $\alpha$ ) and PGE <sub>2</sub> -PMN recruitment -Granulopoiesis and development of autoimmune disease
IL-18	IL-1	Pro-form: 22kDa Mature form: 18 kDa	Activated monocytes and macrophages	-Clearance of intracellular pathogens and viruses -IL-13 production by T and NK cells
IL-21	IL-2	Pro-form: 162 amino acids, Mature form: 131 amino acids, 15 kDa	Activated CD4 T cells	-Proliferation and survival of B cells -Inhibition of DC differentiation -Inhibition of Treg development -CD8 T cell antitumor functions -Differentiation of CD4 cells in Th17 -NK cell maturation and apoptosis
IL-22	IL-10	Homo/Heterodimer helix bundle	Th1, Th17, NK T cells, $\gamma\delta$ T cells, mast cells and CD11c <sup>+</sup> cells.	-Release of acute phase proteins -Expression of CCL20, CCR6 and MMP1 in the skin
IL-23	IL-12	Heterodimer composed by two subunits (p19 and p40)	Monocytes, activated antigen presenting cells, T cells, B cells, endothelial cells, microglia and Paneth cells	-IFN- $\gamma$ producing Th1 cells -Differentiation of CD4 cells in Th17 -Suppressive effect on Treg cells
IL-27	IL-12	Heterodimer composed of two subunits (EBI-3 and p28)	Antigen Presenting Cells	-Pro-inflammatory: Differentiation of CD4 cells in Th1 -Anti-inflammatory: -Suppression of IL-2, IL-6 and IL-17 -Reduced differentiation of CD4 cells in Th17 -CD8 T cell antitumor functions -B cell differentiation and immunoglobulin production -Suppression of ROS production by macrophages and neutrophils -Inhibition of DC maturation
IL-33	IL-1	Pro-form: 30 kDa Mature form: 18 kDa	Smooth muscle cells, epithelial cells, fibroblasts, keratinocytes, dendritic cells and activated macrophages	-Release of Th2 cytokines (IL-5 and IL-13) -Suppression of IFN- $\gamma$ production -Induction of a Th2 response -Chemoattractant for Th2 cells -Differentiation of CD34 <sup>+</sup> precursor cells in mast cells -Release of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and MCP-1 from bone marrow derived mast cells

**Table I.** Summary of the cellular distribution and biological function of the indicated cytokines.

Designation	Receptor family	Components	Cellular/tissue distribution
IL-15	IL-2R	Heterodimer (same IL-2R $\beta$ and $\gamma$ chain, different $\alpha$ chain)	Monocytes, macrophages, dendritic cells, neutrophils and T cells
IL-17	IL-17R	Homodimer (single $\alpha$ chain: IL-17RA) or heterodimer (IL-17RA/IL-17RC)	CD4 and CD8 T cells, gd T cells, NK cells, monocytes and neutrophils Lung, kidney, liver and spleen
IL-18	IL-18R	Heterodimer ( $\alpha$ and $\beta$ chain)	Neutrophils, macrophages, basophils, mast cells, naïve T cells, Th1 cells, B cells, endothelial cells, smooth muscle cells, epithelial cells, synovial fibroblasts and chondrocytes
IL-21	IL-21R	Heterodimer ( $\alpha$ and $\gamma$ chain) IL-21R $\alpha$	NK cells, T and B cells, dendritic cells, macrophages and keratinocytes Spleen and thymus
IL-22	IL-22R	Homodimer (IL-22R1) or heterodimer (IL-22R1 and IL-10R2)	Epithelial cells of the gastrointestinal tract, pancreas, liver, kidney and skin CD4 and CD8 T cells, NK T cells, $\gamma\delta$ T cells, mast cells, NK and CD11c <sup>+</sup> cells
IL-23	IL-12R	Heterodimer IL-12R $\beta$ 1 and IL-23R	Monocytes, activated APC, T cells, B cells, endothelial cells, microglia and Paneth cells
IL-27	IL-27R	gp130 signal transducing chain of IL-6 receptor and IL-27ra (WSX-1, TCCR)	Neutrophils, monocytes, mast cells, T, B and NK cells
IL-33	IL-1R	Homodimer (ST2) or heterodimer (ST2 and IL-1RAcP)	Mast cells and Th2 cells

**Table II.** Summary of the indicated cytokine receptors and their cellular distribution