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Commentary

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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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 ethiopathogenesis 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.

Scientists working on inflammation would agree with us that this field of research has seen a tremendous expansion over the last 30 years. This could be explained in many different ways: surely, a better knowledge of the molecular mechanisms underlying the complex and different inflammatory diseases has provided us with a number of novel mediators and signalling pathways, all seeming to play pivotal roles in these processes. These findings are supported by a number of convincing and technically sophisticated evidences, including those generated with knock out and transgenic mice or produced after gene therapy protocols. However, we should not forget that "inflammation" is a generic term to describe a phenomenon that comes about in many different flavours depending on the context where it has developed, the time point we are investigating and the inflammatory stimuli we are using. More importantly, one aspect that we believe is fundamental for *biochemical pharmacologists* is to determine how these information can be translated into clinical practice and whether these new targets might be of "general use" or should be considered for "disease-tailored" therapies.

First, however, we should be more careful in defining inflammation in such a generic way and possibly go back in time to a more clear distinction between acute and chronic inflammation existed. Further attention should also be given to another important processes that have been recently described as para-inflammation. In this regard, in one of his excellent and enlightening reviews, Medzhitov provided a clear distinction between classical instigators of inflammation such as infection and tissue injury and alternative inducers such as tissue stress and malfunction that similarly induce an adaptive immune response called para-inflammation [1]. Most interestingly, what we believe is now becoming clear is that lack of homeostatic control over the initial phase of the inflammatory response opens the doors to autoimmune diseases [2]. In fact, whenever an active resolutive phase of the immune response fails to take place, then chronic inflammation follows and a completely new set of mediators enters in action [3]. Consistent with this, there is a consensus among the scientific community that the persistent presence of

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Fig. 1. Scientific "dilemma" faced by biochemical pharmacologists whishing to find "the right switch" to shut down inflammation.

chronic inflammation might be the initial thread that ultimately leads to autoimmunity [4].

In this context, i.e. during the establishment of chronic inflammation, plethoras of novel cytokines have been discovered. Here, we will be focusing in particular on these cytokines and on their contribution to the inflammatory process. We hope that this overview will help pharmacologists find their way when faced with the difficult decision (Fig. 1) of identifying novel molecular targets to treat inflammatory diseases and highlight the possible "good and bad" of drugs targeting these molecules.

1. Interleukin-15

IL-15 was initially identified as a T cell proliferation stimulating cytokine produced by virally infected cells and has structural and biological similarities with IL-2. In fact, like IL-2, it stimulates CD4 and CD8 T cell proliferation [5] and binds a heterodimeric receptor composed by the same IL-2 receptor (IL-2R) β and γ chain but different α chain [6]. Antigen presenting cells such as monocyte/macrophages and dendritic cells seem to be the main cellular sources of IL-15 although other cell types such as T cells and mast cells have been found to express it at lower levels or stored intracellularly, respectively [7,8].

A large variety of stimuli induce IL-15 expression and/or release including lipopolysaccharide and other bacterial products, fungi, viruses and double-stranded RNA [8]. The mature 114 amino acid biologically active form of IL-15 derives from two different mRNA isoforms encoding for two IL-15 precursor proteins with either a long or short N-terminus [9,10]. These N-terminal sequences, along with other posttranslational modifications, influence the limited secretion of IL-15 [11]. These control mechanisms are in fact responsible for the scarce release of this cytokine in the extracellular space, explaining the difficulties encountered for the detection of IL-15. In addition, some interesting studies have shown IL-15 to be highly expressed on the cell surface [12] providing further evidence about the different biological role compared to IL-2 and a possible explanation for the lack of detection in the culture supernatants.

In vivo studies using mice overexpressing IL-15, IL-15 knock out or IL-15Rα knock out mice have shown that this cytokine plays an important role in the development of NK cells, intestinal intraepithelial lymphocytes (i-IELs), and $NK1^+$ T cells (NK-T cells) [13,14]. This suggests that IL-15 has an important role in the innate and mucosal immune response and that drugs targeting this cytokine might be particularly useful for the treatment of diseases characterized by mucosal inflammation such as colitis and inflammatory bowel disease. However, the biological functions of IL-15 are not only restricted to these pathologies since other studies have demonstrated that this cytokine is a potent chemoattractant for T cells [15] and neutrophils [16], two cell types involved in a wide variety of inflammatory response. Consistent with this, several studies have associated IL-15 with a number of autoimmune diseases such as psoriasis, multiple sclerosis and rheumatoid arthritis [17,18].

2. Interleukin-17

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

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

The most studied members of the IL-17 family (six members in total) are IL-17A and F. Originally named cytotoxic T-lymphocyte-associated antigen 8 (CTL8), IL-17A is a 155 amino acid protein that functions as a homodimer that forms via two sulphidrylic residues. Among the other 5 members, IL-17F is the one that shares the