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Review

PRO- *versus* ANTI-INFLAMMATORY CYTOKINES: MYTH OR REALITY

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Abstract - Inflammation is characterized by an interplay between pro- and anti-inflammatory cytokines. Cytokines are commonly classified in one or the other category: interleukin-1 (IL-1), tumor necrosis factor (TNF), gamma-interferon (IFN-γ), IL-12, IL-18 and granulocyte-macrophage colony stimulating factor are well characterized as pro-inflammatory cytokines whereas IL-4, IL-10, IL-13, IFN-α and transforming growth factor-β are recognized as anti-inflammatory cytokines. In this review, we point out that this classification is far too simplistic and we provide numerous examples illustrating that a given cytokine may behave as a pro- as well as an anti-inflammatory cytokine. Indeed, the cytokine amount, the nature of the target cell, the nature of the activating signal, the nature of produced cytokines, the timing, the sequence of cytokine action and even the experimental model are parameters which greatly influence cytokine properties.

Key words: Inflammation, interleukin, chemokine, macrophages, neutrophils, endothelial cells

INTRODUCTION

Cytokines play an important role during the inflammatory process. Two cytokines, namely interleukin-1 (IL-1) and tumor necrosis factor (TNF) orchestrate the inflammatory response and initiate a cascade of mediators which are directly responsible for the various events associated with inflammation (e.g. increased vascular permeability, chemoattraction of circulating leukocytes, proteolysis…). Other cytokines such as IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF) amplify the release of IL-1 and TNF, thus favoring the inflammatory process. This is also the case for gamma-interferon (IFN-γ) the production of which is induced by IL-12 and IL-18. While the cytokines mentioned above are classified as "pro-inflammatory cytokines", IL-4, IL-10, IL-13, interferon-alpha (IFN-α) and transforming growth factor-β (TGF-β) are recognized as anti-inflammatory cytokines because of their ability to inhibit the release of pro-inflammatory cytokines, to induce the production of IL-1 receptor antagonist (IL-1ra) and the release of soluble TNF receptor (sTNFR) and to limit some of the pro-inflammatory activities of IL-1 and TNF. However, the events occurring during inflammation are not as simplistic as an interplay between pro- and anti-inflammatory actors. Indeed, they are far more complex ! In this short review we will provide some examples which illustrate the fact that each of these cytokines offers a "half angel - half devil" aspect and none can be simply labelled either "pro" or "anti".

A TOO SIMPLISTIC DICHOTOMY

René Magritte, the surrealistic Belgium artist, painted a pipe on a picture and wrote "Ceci n'est pas une pipe" (*This is not a pipe*). It is becoming more and more frequent to find reports reminiscent of this concept: e.g. "TNF is not a pro-inflammatory cytokine". For example, in their report entitled "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination" Liu *et al.* (42) showed that in response to injection of myelin oligodendrocyte glycoprotein, TNF-deficient mice of different genetic backgrounds displayed a multiple sclerosis-like disease with a higher incidence, a higher mortality, a longer duration and a more severe auto-immune disease than their wild type counterparts. Similarly, in an experimental model of collagen-induced arthritis, it was found that blocking the activity of IFN-γ (either by anti-IFN-γ antiserum or by using IFN-γ receptor

knock-out mice) resulted in an accelerated onset of the disease (70). These results suggested that IFN-γ, instead of being a pro-inflammatory cytokine, was rather involved in counteracting the development of the disease in this experimental model. As well, one can assert that "IL-10 is not an anti-inflammatory cytokine". Evidence comes from *in vivo* works in which pro-inflammatory or immunostimulating activities have been reported for IL-10. This is the case for autoimmune diabetes whose onset and development are accelerated in transgenic mice overexpressing IL-10 in pancreatic islets (52,74). Also, IL-10 treatment accelerates allograft rejection of islet cells (77) and heart (56). In a model of endotoxin-induced uveitis, intra-peritoneal injection of IL-10 potentiated the ocular inflammation (59). Finally, in a tumor model, IL-10 was reported to favor tumor rejection (6) and using transfected mouse mammary adenocarcinoma cells expressing IL-10, Di Carlo *et al.* (20) showed that the tumor growth area was associated with an enhanced level of the chemokine "monocyte-chemoattractant protein-1" (MCP-1) and of inducible nitric oxide synthase (iNOS), an enhanced expression of VCAM-1 and ELAM-1 adhesion molecules and an enhanced recruitment of leukocytes as compared to mice receiving the parent adenocarcinoma. This parallels the fact that IL-10 induces E-selectin expression on small and large blood-vessel endothelial cells (71).

We will now review few parameters which influence the behavior of the different cytokines and may explain why, depending upon the situation, both pro- and anti-inflammatory properties can be described for the same mediators.

THE AMOUNT OF CYTOKINE

The intensity of the inflammatory response is associated with different physiological events which correlate with the levels of the produced cytokine. The pro-inflammatory cytokines are the most necessary mediators to set-up an anti-infectious response; however, an exacerbated production of these cytokines may be deleterious and even lead to death when used in animal models and be associated with poor outcome in human pathologies such as sepsis. On the other hand, while anti-inflammatory cytokines are a prerequisite to control the cascade of pro-inflammatory mediators, their excessive production is associated with a severe immune depression as observed in patients following trauma or major surgery. Consequently, an increased sensitivity to nosocomial infections is observed in these patients.

The amount of a given cytokine clearly influences its properties. The best example is given with TGF-β (9): in addition to its role in controlling inflammation, TGF-β restrains cell proliferation and controls turnover of the extracellular matrix. At high concentration, TGF-β suppresses cell proliferation and stimulates the production of pathological amounts of extracellular matrix (fibrosis) whereas at low levels, TGF-β predisposes to excessive cell proliferation, atherogenesis or reduced production of extracellular matrix and impaired wound healing. Similarly, it has been reported that some effects of TNF were influenced by the amount of this cytokine used in the experimental model. Low doses were found to induced angiogenesis whereas high concentrations were associated with an inhibition of angiogenesis (23). Moreover, in an elegant experimental model of arthritis induced by the injection of acidified type II collagen, it was demonstrated that low amounts of IL-12 were pro-inflammatory whereas 100 fold higher amounts were associated with an anti-inflammatory process (37). Injection of 5 ng of IL-12 a day increased the severity of the disease, a property which was essentially TNF-dependent whereas treatment with 500 ng a day significantly decreased the mean arthritis index of the pathology, a phenomenon which was essentially IL-10-dependent. Interestingly, only large amounts of IL-12 induced circulating corticosterone.

THE NATURE OF THE TARGET CELL

The anti-inflammatory properties of our quintet of anti-inflammatory cytokines have essentially been coined with monocytes/macrophages used as target cells. There are numerous examples which illustrate that the story might be completely different with other target cells. Thus, IL-10 was first identified and defined as a cytokine capable to repress the production of IFN-γ by Th1 clones (25), but more recently it was demonstrated that IL-10 enhanced the production of IFN-γ by NK cells (63), increased the intracellular expression of IFN-γ and IL-2 in $CD8^+$ T-cells in combination with IL-2 after antigen stimulation (60) and increased the number of IL-2 secreting $CD4^+$ T-cell clones (40). Furthermore, IL-4 and IL-10 which inhibit the LPS-induced production of IL-8 by macrophages, amplify that of endothelial cells (18). The different efficiency to inhibit IL-8 production depending on the nature of the target cells has also been reported for INF-α which limits this production by LPS-activated peripheral blood mononuclear cells and by TNF-α-stimulated bone marrow stroma cells but which is inefficient when acting on LPS-activated neutrophils (2). While IL-13 diminishes chemokine production by

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