Effects of interleukin 4 on monocyte functions: comparison to interleukin 13

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Introduction

Human monocytes belong to the mononuclear phagocytes and play an important role in antigen non-specific and antigen-specific immune responses against bacteria, viruses, parasites and tumour cells. Peripheral blood monocytes originate in the bone marrow from pluripotent stem cells which give rise to committed colony forming unit-granulocyte/macrophage precursors (CFU-GM) that differentiate into promonocytes, monoblasts and monocytes. These monocytes leave the bone marrow and enter the circulation, where they remain for approximately three days (Johnston, 1988). Peripheral blood monocytes form a heterogeneous population with regard to cell size, density, morphology, phenotype and function (Figdor *et al.*, 1986). Subsequently, they enter the tissues and differentiate into tissue-specific macrophages such as Küppfer cells, histiocytes, alveolar macrophages, microglial cells and osteoclasts, under the influence of factors produced in the local environment.

Monocytes express receptors for IL4 and respond to this Th2 cytokine with dramatic changes in morphology, phenotype and function. Recently, we described a novel cytokine, interleukin-13, and characterized its biological activities (McKenzie *et al.*, 1993). IL13 is a protein consisting of 132 aa and has a MW of ≈ 10 kDa. It turns out that IL13 affects human monocytes in a similar way as does IL4 (de Waal Malefyt *et al.*, 1993), and there is evidence that IL4R and IL13R may share a common component which is involved in signal transduction (Zurawski *et al.*, 1993). In this paper, we will review the activities of IL4 toward monocytes and compare them with those of IL13.

Effects of IL4 and IL13 on the differentiation of monocytes

Although the effects of IL4 on haematopoiesis are beyond the scope of this communication, some comments could be made on the effects of IL4 on the differentiation of myeloid cells. IL4 alone has no growth factor activity, but it significantly enhances the growth of granulocyte progenitors from $CD34^+$ cells or bone marrow from 5-FU-treated mice when IL3, GM-CSF or G-CSF is present (Rennick *et al.*, 1987; Broxmeyer *et al.*, 1988). However, IL4 has also been shown to inhibit the growth of macrophage progenitors in human and mouse bone marrow cultured with M-CSF or GM-CSF and inhibited myelopoiesis in the long-term Dexter type of *in vitro* cultures (Jansen *et al.*, 1989; Rennick *et al.*, 1992). This could be explained by the fact that IL4 induces the differentiation of the progenitors into macrophages which are end stage cells that generally do not proliferate. IFNγ has been shown to stimulate CFU-M from $CD34^+$ $HLA\text{-}DR^+$ bone marrow progenitors when IL3, GM-CSF or G-CSF was present, and to inhibit CFU-G in the presence of G-CSF (Snoeck *et al.*, 1993). IL4 antagonized this activity of IFNγ and reversed both the suppression of CFU-G and the enhancement of CFU-M. Antagonistic activities of IL4 and IFNγ are also observed on cytokine production and on expression of FcγR by mature monocytes (see below).

IL4 and IL13 induce dramatic changes in the morphology of peripheral blood monocytes. Monocytes cultured in the presence of IL4 or IL13 form long cytoplasmic protrusions, have a dendritic appearance and adhere strongly to the substrate. Clumping of cells through homotypic interactions can also be ob-

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served (te Velde *et al.*, 1988; McKenzie *et al.*, 1993). IL4 or IL13 downregulates the expression of CD14 and FcγR and upregulates the expression of class II MHC antigens on monocytes. Based on their morphology and phenotype, these cells resemble dendritic cells which also express high levels of class II MHC antigens but don't express FcγR and CD14. However, dendritic cells express CD1 antigens which are not induced by IL4 or IL13 on monocytes and appear to be better antigen-presenting cells (Steinman, 1991).

Cytokine production by monocytes is inhibited by IL4 and IL13

Human monocytes and mouse macrophages produce large amounts of a number of cytokines, including IL10, following activation by LPS (de Waal Malefyt *et al.*, 1991; Fiorentino *et al.*, 1991). Endogenously produced IL10 has autoregulatory effects on the production of cytokines by monocytes and inhibits the secretion of IL1, IL6, IL8, TNFα, GM-CSF, G-CSF and IL10 itself. Neutralization of this endogenously produced IL10 by a specific mAb results in enhanced production of cytokines by LPS-activated monocytes (de Waal Malefyt *et al.*, 1991). Under these conditions, IL4 and IL13 strongly inhibit the production of IL1α, IL1β, IL6, IL8, IL10, TNFα, GM-CSF, G-CSF and MIP1α (te Velde *et al.*, 1990b; Hart *et al.*, 1989; de Waal Malefyt *et al.*, 1993; Minty *et al.*, 1993). Downregulation of these cytokines has been shown to occur at the mRNA level. IL4, IL13 and IL10 also inhibit the production of IL12 p35, IL12 p40 and IFNα (de Waal Malefyt *et al.*, 1993; Doherty *et al.*, 1993). In addition, IL4 has been shown to downregulate the production of MIP-1β (Ziegler *et al.*, 1991) and platelet-derived growth factor (PDGF) (S. Breitt, pers. comm.) by monocytes. The inhibitory effect of IL4 on the production of IL1 and TNFα has been demonstrated on human peripheral blood monocytes, human alveolar macrophages, human peritoneal macrophages and murine macrophages (Sone *et al.*, 1992; Hart *et al.*, 1991). Furthermore, IL4 inhibited cytokine production by monocytes activated by IL1, TNFα or IFNγ (Lee *et al.*, 1990; Vellenga *et al.*, 1991). However, IL4 and IL13 do not inhibit the production of all cytokines. Both IL4 and IL13 enhance the production of IL1 receptor antagonist by LPS-activated monocytes (Fenton *et al.*, 1992; Orino *et al.*, 1992; Wong *et al.*, 1993; de Waal Malefyt, 1993). Taken together, these data indicate that IL4 has antiinflammatory activities through the inhibition of proinflammatory cytokine production and enhancement of IL1ra production, a cytokine which itself possesses antiinflammatory activities.

IL4 and IL13 modulate expression of Fc receptors

The expression of Fc receptors by monocytes is strongly influenced by cytokines. IL4 and IL13 induce the expression of the low affinity Fc receptor for IgE (FceRII, CD23) on the cell surface and IL4 has been shown to induce the release of soluble CD23 (te Velde *et al.*, 1990c; Vercelli *et al.*, 1988; McKenzie *et al.*, 1993). This enhanced expression of CD23 may be important in allergy, since atopic patients have enhanced FcεR-mediated cytotoxic activity (Melewiicz *et al.*, 1981). Multiple cytokines are involved in regulation of FcγR expression. IFNγ and IL10 enhance the expression of FcγRI (CD64), whereas TGFβ upregulates the expression of FcγRI (CD16) (te Velde *et al.*, 1990a, 1992; Wong *et al.*, 1991). IL4 and IL13 downregulate the constitutive expression of all three FcγR: CD64, CD32 and CD16 (de Waal Malefyt *et al.*, 1993). Addition of combinations of these cytokines showed that IL10 could prevent the IL4- or IL13-induced downregulation of CD16, CD32 and CD64, whereas IFNγ could partially rescue the IL4- or IL13-induced downregulation of CD64, but not that of CD32 and CD16 (de Waal Malefyt *et al.*, 1993). In addition, IL4 inhibited the TGFβ-induced expression of CD16 (Wong *et al.*, 1991). FcγRI expression has been correlated with ADCC activity of monocytes (Tripathi *et al.*, 1991). The spontaneous ADCC activity of monocytes is enhanced by IFNγ or IL10 and inhibited by IL4 or IL13 (te Velde *et al.*, 1990a; te Velde *et al.*, 1992). However, IL4 and IL13 strongly inhibited the IFNγ or IL10-induced ADCC activity despite the fact that CD64 expression was not downregulated, indicating that besides CD64 expression, other mechanisms must play a role in the IL4- and IL13-induced inhibition of monocyte cytotoxicity (de Waal Malefyt *et al.*, 1993).

IL4 inhibits production of NO and killing of intracellular parasites

Monocytes and macrophages are hosts for a number of intracellular parasites, including schistosoma, toxoplasma and leishmania species. Activation of macrophages by IFNγ leads to killing of these intracellular parasites via production of toxic nitrogen oxide metabolites (James *et al.*, 1989). IL4 is able to inhibit the killing of these intracellular parasites by blocking NO production. IL10 and TGFβ share this activity with IL4 and combinations of these factors are synergistic (Oswald *et al.*, 1992a). The IL10-induced inhibition of NO production and parasite killing is mediated through the downregulation of TNFα production by the monocyte, which acts as a cofactor for the IFNγ-induced macrophage activation (Oswald *et al.*, 1992b). Additional mechanisms

seem to play a role in the IL4-mediated suppression of NO production and parasite killing. However, IL4 and IL10 inhibit not only intracellular parasites by this mechanism, but also other organisms, like *Candida albicans* and *Salmonella typhimurium* (Cenci *et al.*, 1993; al-Ramadi *et al.*, 1992). IL13 and IL4 also inhibited the production of NO by macrophages established from bone marrow by cultures with GM-CSF but not from macrophages grown in M-CSF (Doherty *et al.*, 1993). This corresponded to an enhanced survival of *Leishmania major* in the IL13- or IL4-treated GM-CSF cultured macrophages, but not in the IL13 or IL4-treated M-CSF cultured macrophages. IL4 has also been shown to inhibit the IFNγ-induced production of reactive oxygen radicals (O^-, H_2O_2) (Abramson *et al.*, 1990; Bhaskaran *et al.*, 1992). These mechanisms, together with the inhibited production of TNFα, IL1 and IL6, may also explain the IL4-mediated inhibition of IFNγ-activated monocytes to kill tumour cells (te Velde *et al.*, 1988).

Concluding remarks

IL4 and IL13 have dramatic effects on monocyte morphology, phenotype and function. Both cytokines change the morphology of monocytes, inhibit production of pro-inflammatory cytokines, inhibit the expression of FcγR and inhibit the production of NO and O^- which diminishes killing of intra- and extracellular pathogens (de Waal Malefyt *et al.*, 1993; Doherty *et al.*, 1993). In addition, IL4 and IL13 inhibit the expression of CD14, the receptor for the LPS/LPS binding protein complex and of CD13 (aminopeptidase N), a cell surface marker with enzymatic activity (Van Hal *et al.*, 1992). However, IL4 and IL13 also have stimulatory activities toward monocytes. IL4 and IL13 enhance class II MHC expression on monocytes, which may be related to an enhanced capacity to present antigen. This has been demonstrated for protein antigens in the mouse and alloresponses in humans (te Velde *et al.*, 1988; Zlotnik *et al.*, 1987). In addition, IL4 and IL13 induce expression of CD23 and enhance the expression of CD11b, CD11c, CD18, CD29 and CD49e (FNR) (de Waal Malefyt *et al.*, 1993). These β1 and β2 integrins play an important role in cell-cell interactions and interactions with the extracellular matrix (Hogg, 1989). The enhanced expression of these antigens may play a role in the IL4- and IL13-induced changes in adhesion and morphology. Finally, IL4 has been shown to activate 15-lipoxygenase, an enzyme involved in the oxidation of low density lipoprotein (LDL) to its atherogenic form in monocytes (Conrad *et al.*, 1992). This activation could be inhibited by IFNγ. Therefore, IL4 could play a role in the pathogenesis of atherosclerosis and the formation of foam cells.

IL13 shares many of the known activities of IL4 on monocytes (de Waal Malefyt *et al.*, 1993; Doherty *et al.*, 1993). Both cytokines inhibited monocyte functions which are related to cellular (Th1) immune responses. In addition, it has been shown that IL13, like IL4, induced human B-cell proliferation, B-cell differentiation and IgG4 and IgE production (Punnonen *et al.*, 1993). IL13, like IL4, also induced the transcription of the germline ε locus and acts as a switch factor (Cocks *et al.*, 1993). These results may partially be explained by the finding that IL4R and IL13R share a common subunit which is involved in signal transduction (Zurawski *et al.*, 1993). IL4 and IL13 are predominantly products of Th2 cells, although human Th1 cells are able to produce IL13 (de Waal Malefyt and H. Yssel, in prep.). IL13 production is more abundantly and longer produced by T-cell clones than IL4. However, in contrast to IL4, IL13 is not active as T-cell growth factor (de Waal Malefyt and H. Yssel, in prep.). These data indicate that IL4 and IL13 may have similar and unique roles in regulation of immune responses despite the fact that both IL4 and IL13 have similar effects on monocyte physiology and function.

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The anti-tumour and proinflammatory actions of IL4

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Introduction

As a highly pleiotropic cytokine, IL4 has been shown to stimulate proliferative or differentiative responses in numerous cell types, not only in the lymphoid and non-lymphoid haematopoietic lineage, but also in cells of non-haematopoietic origin, such as endothelial cells. In terms of anti-tumour activity, IL4 has been shown to induce a potent cytotoxic response against tumours which is likely mediated by several host effector cell types. Both lymphoid-independent inflammatory cell mechanisms and CTL-mediated anti-tumour responses have been reported as a result of IL4 expression. This report attempts to summarize the biologic basis for the anti-tumour mechanisms initiated by IL4, defining existing controversies with regard to these mechanisms and offering approaches for future research investigations and clinical applications of this important action of IL4.

The localized anti-tumour action of IL4 *in vivo*

The action of IL4 (or other cytokines) locally at the inoculation site of transplantable tumours has been readily assessed by a "tumour-cytokine transplantation assay" (Tepper, 1992), in which a constitutively acting gene for IL4 is transfected directly into the tumour cells, or alternatively, by mixing tumour cells with an IL4-producing cell type prior to injection. Using such an assay, we have demonstrated that the expression of an activated murine IL4 gene locally results in a potent anti-tumour effect, with com-