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Other Functions, Other Genes: Alternative Activation of Antigen-Presenting Cells

Review

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Των εναντιων η φυσις γλιχεται και εκ τουτων αποτελει το συμφωνον.

Nature strives for the opposite and from it generates consonance.

—Herakleitos

In the course of inflammatory reactions, proinflammatory mechanisms are most important to guarantee elimination of the causative infectious, toxic, or allergenic agents. It is mandatory, however, that inflammatory processes, once induced, do not escalate but are again downregulated to allow healing. Therefore, proinflammatory and anti-inflammatory mechanisms must be activated spatially and temporally in a finely tuned manner. The inflammatory processes in sepsis are a good example for such a balanced interplay. Here, the causative agent is a microbial agent; however, massive secretion of cytokines such as interleukin (IL)-1 or tumor necrosis factor (TNF)-α actually mediates the detrimental developments. Via neuroinflammatory interactions, the septic organism tries to counteract the effects of these proinflammatory cytokines; finally, glucocorticoids are synthesized and secreted and may exert their pleiotropic anti-inflammatory effects (Wilckens and De Rijk, 1997). In addition, inflammatory diseases and allergies may not only be due to an aberrant overwhelming proinflammatory reaction, but they can also be caused by dysfunction or failure of anti-inflammatory control mechanisms. This notion was very recently confirmed by the finding that certain mutations in a novel anti-inflammatory molecule of bronchial epithelium (CC16) are associated with a tremendous increase in the risk of developing asthma (Laing et al., 1998). Interestingly, expression of CC16 strongly inhibits both production and biologic activity of interferon (IFN)-γ. Thus, proinflammatory reactions are closely interconnected with counter-regulatory anti-inflammatory pathways.

In the regulation of immune-mediated as well as nonspecific inflammation, antigen-presenting cells such as mononuclear phagocytes and dendritic cells play a major role. In the past, research in inflammation biology has focused on the proinflammatory actions of mononuclear phagocytes including phagocytosis, antigen processing, antigen presentation, T cell activation, and cytokine secretion. IFNγ and bacterial lipopolysaccharides were identified as the major mediators of this classical macrophage activation pathway. On the contrary, anti-inflammatory agents such as interleukin (IL)-4 and glucocorticoids were shown to inhibit expression of proinflammatory cytokines by macrophages, and this finding was interpreted as indicative of macrophage deactivation. More recently, however, IL-4 and glucocorticoids were found to induce increased expression of the macrophage mannose receptor and to enhance the capacity for endocytosis and antigen presentation of macrophages. Since this was proof against mere deactivation of macrophages by anti-inflammatory agents, Gordon and colleagues instead introduced the concept of alternative immunologic activation of macrophages (Stein et al., 1992). Evidence has now accumulated which indicates that alternatively activated macrophages express a special set of molecules enabling them to actively participate in anti-inflammatory processes, tolerance induction, and healing. Recently, dendritic cells known as specialized antigen-presenting cells (APC) supporting Th1 differentiation have also been shown to undergo alternative activation under certain conditions. Here we revisit Gordon's concept of alternative activation of APC and show that it fits well with what is known as "suppressive" functions of APC (Figure 1).

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Molecular Repertoire of Alternatively Activated Macrophages

Alternative activation of macrophages may be induced by IL-4 and glucocorticoids as well as by other cytokines such as IL-10, IL-13, and transforming growth factor (TGF)-β, with similar effects. Alternatively activated macrophages express phenotypic and molecular characteristics that differ considerably from those of classically activated macrophages. Regulation and expression of inflammation-associated molecules and genes in macrophages is regulated antagonistically by IL-4 and IFNγ, i.e., alternative macrophage molecules are induced by IL-4 and inhibited by IFNγ, while classical macrophage molecules are induced by IFNγ and inhibited by IL-4 (Table 1). Alternatively activated macrophages preferentially express the receptors of innate immunity with broad specificity for foreign antigens such as the macrophage mannose receptor (Stein et al., 1992), the β-glucan-receptor (Mosser and Handman, 1992), scavenger receptor type I (Geng and Hansson, 1992), and CD163, a member of the scavenger receptor cysteine-rich family (Högger et al., 1998). Despite this enhanced capacity for phagocytosis, alternatively activated macrophages do not exert enhanced killing functions towards microbes. NO production, for example, is counteracted in alternatively activated macrophages by enhanced expression of arginase, competing with NO synthases for L-arginine as its substrate (Munder et al., 1998). Similarly, O_2 production is suppressed in alternatively activated macrophages (Becker and Daniel, 1990). Thus, alternatively activated macrophages seem to be first-line defense cells that need not mount a strong Th1 immune response in order to function successfully.

In addition, alternatively activated macrophages exhibit enhanced expression levels of MHC class II molecules such as HLA-DR and HLA-DQ, indicating that they

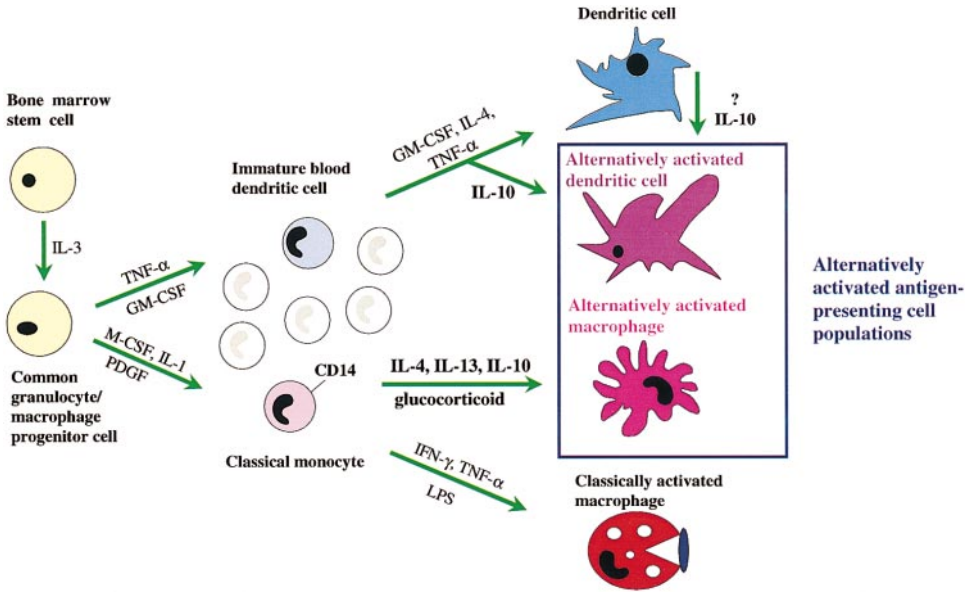

Figure 1. Differentiation of Alternatively Activated APC

are prepared for effective antigen presentation. With respect to immunoglobulin receptors, alternatively activated macrophages display cell surface expression of the low-affinity Fcε receptor (CD23); however, they do not express any of the three species of Fcγ receptors (Becker and Daniel, 1990). Thus, it seems that alternatively activated macrophages may be able both to induce differentiation of naive T cells into antigen-specific T helper cells, presumably of the Th2 type, and to exert Th2-associated effector functions (Cua and Stohlman, 1997).

In order to identify alternatively activated macrophages in vivo, monoclonal antibodies specific for alternatively activated macrophages have been used, including monoclonal antibody RM3/1 directed against a glucocortiocid-inducible splice variant of the scavenger receptor CD163 (Högger et al., 1998) and a monoclonal antibody against MS-1 high molecular weight protein (Goerdt et al., 1991; Walsh et al., 1991). In the healthy organism, alternatively activated macrophages are preferentially found in normal placenta and lung, where they function to protect the respective organ from unwanted inflammatory or immune reactions (Mues et al., 1989). Alternatively activated macrophages were also identified during the healing phase of acute inflammatory reactions, in chronic inflammatory diseases such as rheumatoid arthritis and psoriasis, and in wound healing tissue (Goerdt et al., 1993a; Szekanecz et al., 1994; Djemadji-Oudjiel et al., 1996). This distribution pattern suggests that alternatively activated macrophages may participate in the three phases of healing, i.e., downregulation of inflammation, angiogenesis, and elimination of tissue debris. With respect to downregulation of inflammation, alternatively activated macrophages are characterized by expression and synthesis of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (Fenton et al., 1992; Schebesch et al., 1997); they lack expression of proinflammatory cytokines such as IL-1, TNFα, IL-6, IL-12, and macrophage inflammatory protein (MIP)-1α (Cheung et al., 1990; Standiford et al., 1993; Bonder et al., 1998). Secondly, alternatively activated macrophages are associated with a high degree of vascularization in vivo and seem to be angiogenic in vitro (Goerdt et al., 1993b; Kodelja et al., 1997). Furthermore, phagocytosis of apoptotic cells leads to alternative activation and inhibition of proinflammatory cytokine secretion in macrophages in an autocrine/paracrine manner (Fadok et al., 1998). Thus, alternatively activated macrophages are strategically well located and well equipped to substantially contribute to healing in subsiding inflammatory reactions.

Suppressive Functions of Alternatively Activated Macrophages

Immunosuppressive functions of macrophages have been first described by Herberman and colleagues in the

Table 1. Molecular Repertoire of Alternatively versus Classically Activated Macrophages

	Alternative Activation[a]	Classical Activation
Cytokines	IL-1R antagonist IL-10	IL-1 IL-6 IL-12 TNFα
Chemokines	DC-CK1/AMAC-1	MIP-1α
Immune receptors	FcεRII (CD23s) Mph mannose R Scavenger RI β-glucan R CD163 (RM3/1)	FcγRI (CD64) FcγRII (CD32) FcγRIII (CD16)
Killer molecules	Arginase	NO, iNOS O_2

[a] Regulation and expression of inflammation-associated macrophage molecules and genes are regulated antagonistically by IL-4 and IFNγ, i.e., alternative macrophage molecules are induced by IL-4 and inhibited by IFNγ, while classical macrophage molecules are induced by IFNγ and inhibited by IL-4.

mid-1970s (Oehler et al., 1977). Several lines of evidence indicate today that alternatively activated macrophage and suppressor macrophage populations may at least partially overlap. Placental macrophages, protecting the immunologically privileged embryo, and alveolar macrophages, protecting the lung from unwanted environmentally induced inflammation, are the prototype naturally occurring suppressor macrophages (Chang et al., 1993). The suppressive effectivity of alveolar macrophages is so strong that dendritic cell antigen presenting functions in the lung may be totally suppressed (Holt et al., 1988). Both placental and alveolar macrophages have been shown to be typical alternatively activated macrophage populations (Mues et al., 1989; Kodelja et al., 1998). With respect to experimentally derived suppressor macrophages, circumstantial evidence also indicates a close relationship to alternatively activated macrophages. Experimentally derived suppressor macrophages have been preferentially investigated using antigen-independent processes in tumor-bearing animals or during certain infections (Chang et al., 1988; Saha et al., 1994). Antigen-specific suppressive actions of macrophages have also been reported (Kirschmann et al., 1994). In these model systems, IFNγ, the classical macrophage activating cytokine, has been shown to directly inhibit suppressor macrophage activity (Schmidt Pak et al., 1995). Vice versa, alternatively activated macrophages in vitro actively inhibit mitogen-induced proliferation of peripheral blood lymphocytes and $CD4^+$ T cells (Schebesch et al., 1997). These findings convincingly confirm that alternative activation generates immunosuppressive macrophage populations.

Besides the well known suppressive macrophage mediators, i.e., PGE_2 and lipocortin I, macrophage-derived IL-10 and TGFβ have been shown to exert downmodulating and anti-inflammatory effects. Other cytokines with suppressive activity such as IL-16 and monoclonal nonspecific suppressor factor (MNSF)-β have not been shown to be expressed by macrophages (Nakamura et al., 1995), while ubiquitin cross-reactive protein (UCRP), which, like MNSFβ, belongs to the ubiquitin gene superfamily, is expressed upon classical activation. Since the proinflammatory cytokine macrophage migration inhibitory factor (MIF) may also be expressed by alternatively activated macrophages (Calandra et al., 1995), it seems that proinflammatory and anti-inflammatory actions are finely balanced in either activation pathway. This may hold true as well for a novel β-chemokine, dendritic cell-derived CC-chemokine (DC-CK)1 (Adema et al., 1997), which is also named alternative macrophage activation associated CC-chemokine (AMAC)-1 (Kodelja et al., 1998), that has recently been cloned from IL-4-treated antigen-presenting cells. This new chemokine is highly homologous to MIP-1α. In contrast to MIP-1α, which is inducible by classical macrophage mediators and is inhibited by IL-4 and glucocorticoids, its expression is specifically induced by alternative macrophage mediators such as IL-4, IL-13, and IL-10 and is inhibited by IFNγ. In vivo, alveolar macrophages, the prototype suppressor macrophages, and some lymphoid dendritic cells express DC-CK1, while the prototype dendritic cells, i.e., epidermal Langerhans cells, do not. Functionally, it has been shown that DC-CK1 preferentially attracts naive $CD4^+$ T cells. Thus, DC-CK1 is a chemokine that may be involved in bringing together an alternatively activated APC and a specific T cell as a prerequisite to T cell activation, expansion, and differentiation. However, expression of DC-CK1 in alternatively activated macrophages as well as in dendritic cells indicates that DC-CK1 itself may not determine whether specific immunity or tolerance is induced; other molecular and phenotypic traits of the particular APC may also be involved.

Modulation of Granuloma Immunity by Alternatively Activated Suppressor Macrophages

A good example of the balancing functions of alternatively activated suppressor macrophages in inflammatory reactions is provided by various models of granuloma formation. During the initiation phase of a granuloma, first-line defense tissue macrophages and other injured cellular tissue components secrete proinflammatory cytokines (IL-1, TNFα) and chemokines (MIP-1α), activating endothelial cells and attracting blood-derived macrophages to the lesion. These early lesional macrophages then start to synthesize granuloma initiation factors, among them homologs of the immunophilin gene family. In the phase of immune modulation, T cells secreting cytokines along the lines defined by the Th1 and Th2 dichotomy induce disease susceptibility or resistance. In schistosomiasis (Stadecker and Villanueva, 1994), for example, rejection of eggs is primarily induced by large granulomas and is accompanied by a dominant Th1 immune response. During the course of the disease, the newly developing granulomas are smaller and lack a prominent T cell component. These late granuloma macrophages strongly express IL-10 and induce clonal anergy in schistosoma egg antigen-specific Th1 cells while supporting schistosoma egg antigen-specific Th2 cells. The Th1-suppressive activity of these granuloma macrophages is so intense that they are even effective as efferent suppressor macrophages in preinfected syngeneic recipients (Villanueva et al., 1994). Thus, alternatively activated macrophages might also act in alleviating disease activity or inducing tolerance in autoimmune and allergic diseases despite established sensitization.

Induction of Tolerance by Alternatively Activated Suppressor Macrophages

UVB-induced contact tolerance is another excellent model for functional integration of all facets of suppressive actions of alternatively activated macrophages. Contact tolerance is a state of unresponsiveness to epicutaneously applied facultative contact allergens that is thought to represent the physiological reaction to the environmental allergen thread. Contact tolerance is maintained by continuous contact with low-dose antigen or by UVB irradiation. While the APC mediating low-dose contact tolerance are still elusive, UVB-induced contact tolerance has been shown to be mediated by alternatively activated macrophages (Stevens et al., 1995). UVB irradiation induces Langerhans cells to emigrate from the epidermis into the dermis and further on to the regional lymph nodes. Subsequently, the epidermis is repopulated by $CD36^+CD11b^+CD1a^-$ macrophages that express excessive amounts of IL-10, as well as TGFβ, but lack IFNα and -β (Knop et al., 1987). By secreting DC-CK1/AMAC-1, these UVB-induced alternatively activated macrophages may attract $CD8^+$ naive

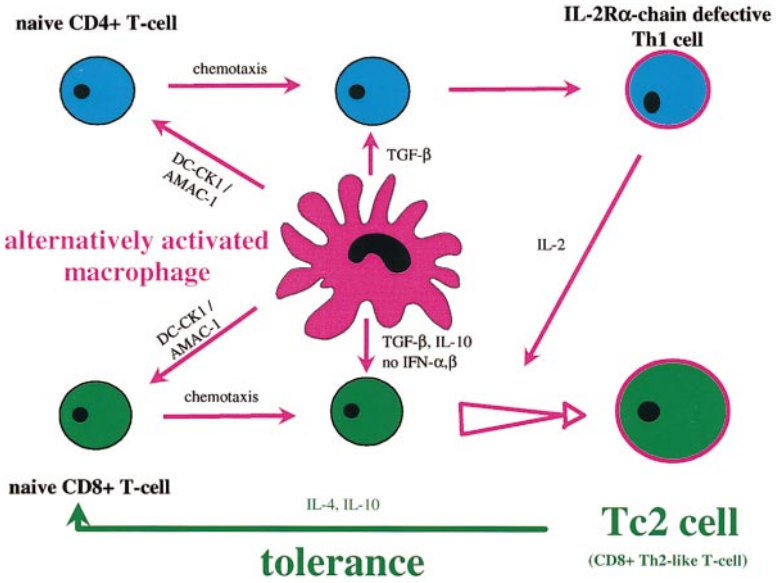

Figure 2. Induction of Contact Tolerance by Alternatively Activated APC

T cells that are induced to differentiate into tolerogenic $CD8^+$ T cells secreting Th2-associated cytokines such as IL-4 and IL-10 (Tc2 cells) (Baadsgaard et al., 1988; Steinbrink et al., 1996). Differentiation of Tc2 cells is dependent on $CD4^+$ T cells and is mediated by their IL-2 production (Baadsgaard et al., 1988; Desvignes et al., 1996). IL-2-producing T helper cells are induced by alternatively activated macrophage-derived TGFβ; however, these T helper cells are defective in IL-2 receptor α chain expression and thus cannot develop into fully mature effector Th1 cells (Stevens et al., 1995) (Figure 2).

Alternative Activation of Dendritic Cells

Dendritic cells may also be alternatively activated and may be induced to exert suppressive effects. Transfer of pancreatic lymph node dendritic cells prevents autoimmune diabetes in nonobese diabetic mice (Clare-Salzler et al., 1992). Alternative activation by IL-10 inhibits tumor antigen presentation by Langerhans cells (Beissert et al., 1995). Alternative activation by IL-10 can furthermore induce cultured Langerhans cells to clonally anergize antigen-specific Th1 cell lines, while their accessory cell functions towards Th2 cell lines are preserved (Enk et al., 1993). IL-10-treated immature dendritic cells induce tolerance in naive T cells, and IL-10 induces tolerance in vivo (Steinbrink et al., 1997). In addition, untreated Langerhans cells stimulate Th1 cells, while UVB-irradiated epidermal dendritic cells, similar to UVB-induced alternatively activated macrophages, induce Th2 cells and may mediate tolerance (Simon et al., 1990; Dai and Streilein, 1997).

Concluding Remarks

The concept of alternative immunologic activation of antigen-presenting cells has facilitated the understanding of the often confusing results regarding the versatile functions of APC in diverse experimental settings. Both the major APC populations, i.e., macrophages and dendritic cells, may be alternatively activated. Preferential mediators of alternative activation are IL-4 and glucocorticoids as well as IL-10. Functionally, alternatively activated APC are important players in downmodulating inflammation and immunity. Alveolar and placental macrophages are typical examples of naturally occuring, alternatively activated macrophages; they represent first-line defense cells that, if they function successfully, need not mount a strong Th1 immune response. Instead, alternatively activated macrophages exert Th2-associated effector functions characterized by a high capacity for endocytotic clearance and antigen presentation accompanied by reduced proinflammatory cytokine secretion. By secreting anti-inflammatory mediators such as IL-10, PGE_2, and other molecules yet to be identified, alternatively activated macrophages exert immunosuppressive effects towards Th1-mediated immune reactions. In concert with special chemokines such as DC-CK1/AMAC-1, both alternatively activated macrophages and dendritic cells may induce peripheral tolerance towards self-components or environmental allergens. Thus, further clarification of alternative activation pathways of APC and their effector molecules may help develop novel immunotherapeutic strategies for chronic inflammatory conditions including established autoimmune and allergic diseases. To this end, it seems necessary to direct a major effort toward dissecting the functional and molecular repertoire of alternatively activated APC and to test their integrated functions in elaborate animal models of human disease.

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References

Adema, G.J., Hartgers, F., Verstraten, R., de Vries, E., Marland, G., Menon, S., Foster, J., Xu, Y., Nooyen, P., McClanahan, T., et al. (1997). A dendritic-cell-derived C-C chemokine that preferentially attracts naive T cells. Nature *387*, 713–717.

Baadsgaard, O., Fox, D.A., and Cooper, K.D. (1988). Human epidermal cells from ultraviolet light-exposed skin preferentially activate autoreactive CD4+2H4+ suppressor-inducer lymphocytes and CD8+ suppressor/cytotoxic lymphocytes. J. Immunol. *140*, 1738–1744.

Becker, S., and Daniel, E.G. (1990). Antagonistic and additive effects of IL-4 and interferon-gamma on human monocytes and macrophages: effects on Fc receptors HLA-D antigens, and superoxide production. Cell. Immunol. *129*, 351–362.

Beissert, S., Hosoi, J., Grabbe, S., Asahina, A., and Granstein, R.D. (1995). IL-10 inhibits tumor antigen presentation by epidermal antigen-presenting cells. J. Immunol. *154*, 1280–1286.

Bonder, C.S., Dickensheets, H.L., Finlay-Jones, J.J., Donnelly, R.P., and Hart, P.H. (1998). Involvement of the IL-2 receptor gamma-chain (gammac) in the control by IL-4 of human monocyte and macrophage proinflammatory mediator production. J. Immunol. *160*, 4048–4056.

Calandra, T., Bernhagen, J., Metz, C.N., Spiegel, L.A., Bacher, M., Donnelly, T., Cerami, A., and Bucala, R. (1995). MIF as a glucocorticoid-induced modulator of cytokine production. Nature *377*, 68–71.

Chang, Z.-L., Bonvini, E., Varesio, L., Holden, H.T., and Herberman, R.B. (1988). Differential in vitro modulation of suppressor and antitumor functions of mouse macrophages by lymphokines and/or endotoxin. Cell. Immunol. *114*, 282–292.

Chang, M.-D.Y., Pollard, J.W., Khalili, H., Goyert, S.M., and Diamond, B. (1993). Mouse placental macrophages have a decreased ability to present antigen. Proc. Natl. Acad. Sci. USA *90*, 462–466.

Cheung, D.L., Hart, P.H., Vitti, G.F., Whitty, G.A., and Hamilton, J.A. (1990). Contrasting effects of interferon-gamma and interleukin-4 on the interleukin-6 activity of stimulated human monocytes. Immunol. *71*, 70–75.

Clare-Salzler, M.J., Brooks, J., Chai, A., Van Herle, K., and Anderson, C. (1992). Prevention of diabetes in nonobese diabetic mice by dendritic cell transfer. J. Clin. Invest. *90*, 741–748.

Cua, D.J., and Stohlman, S.A. (1997). In vivo effects of T helper cell type 2 cytokines on macrophage antigen-presenting cell induction of T helper subsets. J. Immunol. *159*, 5834–5840.

Dai, R., and Streilein, J.W. (1997). Ultraviolet B-exposed and soluble factor-pre-incubated epidermal Langerhans cells fail to induce contact hypersensitivity and promote DNP-specific tolerance. J. Invest. Dermatol. *108*, 721–726.

Desvignes, C., Bour, H., Nicolas, J.-F., and Kaiserlian, D. (1996). Lack of oral tolerance but oral priming for contact sensitivity to dinitrofluorobenzene in major histocompatibility complex class II-deficient mice and in CD4+ T cell-depleted mice. Eur. J. Immunol. *26*, 1756–1761.

Djemadji-Oudjiel, N., Goerdt, S., Kodelja, V., Schmuth, M., and Orfanos, C.E. (1996). Immunohistochemical identification of type II alternatively activated dendritic macrophages (RM 3/1+++, MS-1+/−, 25F9−) in psoriatic dermis. Arch. Dermatol. Res. *288*, 757–764.

Enk, A.H., Angeloni, V.L., Udey, M.C., and Katz, S.I. (1993). Inhibition of Langerhans cell antigen-presenting function by IL-10. A role for IL-10 in induction of tolerance. J. Immunol. *151*, 2390–2398.

Fadok, V.A., Bratton, D.L., Konowal, A., Freed, P.W., Westcott, J.Y., and Henson, P.M. (1998). Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. J. Clin. Invest. *101*, 890–898.

Fenton, M.J., Buras, J.A., and Donnelly, R.P. (1992). IL-4 reciprocally regulated IL-1 and IL-1 receptor antagonist expression in human monocytes. J. Immunol. *149*, 1283–1288.

Geng, Y.-j., and Hansson, G.K. (1992). Interferon-gamma inhibits scavenger receptor expression and foam cell formation in human monocyte-derived macrophages. J. Clin. Invest. *89*, 1322–1330.

Goerdt, S., Walsh, L.J., Murphy, G.F., and Pober, J.S. (1991). Identification of a novel high molecular weight protein preferentially expressed by sinusoidal endothelial cells in normal human tissues. J. Cell Biol. *113*, 1425–1437.

Goerdt, S., Bhardwaj, R., and Sorg, C. (1993a). Inducible expression of MS-1 high-molecular weight protein by endothelial cells of continuous origin and by dendritic cells/macrophages in vivo and in vitro. Am. J. Pathol. *142*, 1409–1422.

Goerdt, S., Kolde, G., Bonsmann, G., Hamann, K., Czarnetzki, B., Andreesen, R., Luger, T., and Sorg, C. (1993b). Immunohistochemical comparison of cutaneous histiocytoses and related skin disorders: diagnostic and histogenetic relevance of MS-1 high molecular weight protein expression. J. Pathol. *170*, 421–427.

Holt, P.G., Schon-Hegard, M.A., and Oliver, J. (1988). MHC class II antigen-bearing dendritic cells in pulmonary tissues of the rat. Regulation of antigen presentation activity by endogenous macrophage population. J. Exp. Med. *167*, 262–274.

Högger, P., Dreier, J., Droste, A., Buck, F., and Sorg, C. (1998). Identification of the integral membrane protein RM3/1 on human monocytes as a glucocorticoid-inducible member of the scavenger receptor cysteine-rich family (CD163). J. Immunol. *161*, 1883–1890.

Kirschmann, D.A., He, X., and Murasko, D.M. (1994). Inhibition of macrophage-induced antigen-specific T-cell proliferation by polyI:C role of suppressor macrophages. Immunology *82*, 238–243.

Knop, J., Taborski, B., and de Maeyer-Guignard, J. (1987). Selective inhibition of the generation of T suppressor cells of contact sensitivity in vitro by interferon. J. Immunol. *136*, 3684–3687.

Kodelja, V., Müller, C., Tenorio, S., Schebesch, C., Orfanos, C.E., and Goerdt, S. (1997). Differences in angiogenic potential of classically vs alternatively activated macrophages. Immunobiology *197*, 478–493.

Kodelja, V., Müller, C., Politz, O., Hakij, N., Orfanos, C.E., and Goerdt, S. (1998). Alternative macrophage activation-associated CC-chemokine-1, a novel structural homologue of macrophage inflammatory protein-1 alpha with a Th2-associated expression pattern. J. Immunol. *160*, 1411–1418.

Laing, I.A., Goldblatt, J., Eber, E., Hayden, C.M., Rye, P.J., Gibson, N.A., Palmer, L.J., Burton, P.R., and Le Souef, P.N. (1998). A polymorphism of the CC16 gene is associated with an increased risk of asthma. J. Med. Genet. *35*, 463–467.

Mosser, D.M., and Handman, E. (1992). Treatment of murine macrophages with interferon-gamma inhibits their ability to bind leishmania promastigotes. J. Leukocyte Biol. *52*, 369–376.

Mues, B., Langer, D., Zwadlo, G., and Sorg, C. (1989). Phenotypic characterization of macrophages in human term placenta. Immunology *67*, 303–307.

Munder, M., Eichmann, K., and Modolell, M. (1998). Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype. J. Immunol. *160*, 5347–5354.

Nakamura, M., Xavier, R.M., Tsunematsu, T., and Tanigawa, Y. (1995). Molecular cloning and characterization of a cDNA encoding monoclonal nonspecific suppressor factor. Proc. Natl. Acad. Sci. USA *92*, 9463–9467.

Oehler, J.R., Herberman, R.B., Campbell, D.A., Jr., and Djeu, J.Y. (1977). Inhibition of rat mixed lymphocyte cultures by suppressor macrophages. Cell. Immunol. *29*, 238–250.

Saha, B., Das, G., Vohra, H., Ganguly, N.K., and Mishra, G.C. (1994). Macrophage-T cell interaction in experimental mycobacterial infection. Selective regulation of co-stimulatory molecules on Mycobacterium-infected macrophages and its implication in the suppression of cell-mediated immune response. Eur. J. Immunol. *24*, 2618–2624.

Schebesch, C., Kodelja, V., Müller, C., Hakij, N., Orfanos, C.E., and Goerdt, S. (1997). Alternatively activated macrophages actively inhibit proliferation of peripheral blood lymphocytes and CD4+ T cells in vitro. Immunology *92*, 478–486.

Schmidt Pak, A., Ip, G., Wright, M.A., and Young, M.R.I. (1995). Treating tumor-bearing mice with low-dose γ-interferon plus tumor necrosis factor-α to diminish immune suppressive granulocyte-macrophage progenitor cells increases responsiveness to interleukin 2 immunotherapy. Cancer Res. *55*, 885–890.

Simon, J.C., Cruz, P.D.J., Bergstresser, P.R., and Tigelaar, R.E. (1990). Low dose ultraviolet B-irradiated Langerhans cells preferentially activate CD4+ cells of the T helper 2 subset. J. Immunol. *145*, 2087–2091.

Stadecker, M.J., and Villanueva, P.O.F. (1994). Accessory cell signals regulate Th-cell responses: from basic immunology to a model of helminthic disease. Immunol. Today *15*, 571–574.

Standiford, T.J., Kunkel, S.L., Liebler, J.M., Burdick, M.D., Gilbert, A.R., and Strieter, R.M. (1993). Gene expression of macrophage inflammatory protein-1 alpha from human blood monocytes and alveolar macrophages is inhibited by interleukin-4. Am. J. Respir. Cell Mol. Biol. *9*, 192–198.

Stein, M., Keshav, S., Harris, N., and Gordon, S. (1992). Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J. Exp. Med. *176*, 287–292.

Steinbrink, K., Sorg, C., and Macher, E. (1996). Low zone tolerance to contact allergens in mice: a functional role for CD8+ T helper type 2 cells. J. Exp. Med. *183*, 759–768.

Steinbrink, K., Wölfl, M., Jonuleit, H., Knop, J., and Enk, A.H. (1997). Induction of tolerance by IL-10-treated dendritic cells. J. Immunol. *159*, 4772–4780.

Stevens, S.R., Shibaki, A., Meunier, L., and Cooper, K.D. (1995). Suppressor T cell-activating macrophages in ultraviolet-irradiated human skin induce a novel, TGG-beta dependent form of T cell activation characterized by deficient IL-2r alpha. J. Immunol. *155*, 5601–5607.

Szekanecz, Z., Haines, G.K., Lin, T.R., Harlow, L.A., Goerdt, S., Rayan, G., and Koch, A.E. (1994). Differential distribution of intercellular adhesion molecules (ICAM-1, ICAM-2, and ICAM-3) and the MS-1 antigen in normal and diseased human synovia. Their possible pathogenetic and clinical significance in rheumatoid arthritis. Arthritis Rheum. *37*, 221–231.

Villanueva, P.O.F., Harris, T.S., Ricklan, D.E., and Stadecker, M.J. (1994). Macrophages from schistomal egg granulomas induce unresponsiveness in specific cloned Th-1 lymphocytes in vitro and down-regulate schistosomal granulomatous disease in vivo. J. Immunol. *152*, 1847–1855.

Walsh, L.J., Goerdt, S., Pober, J.S., Sueki, H., and Murphy, G.F. (1991). MS-1 sinusoidal endothelial antigen is expressed by factor XIIIa+, HLA-DR+ dermal perivascular dendritic cells. Lab. Invest. *65*, 732–741.

Wilckens, T., and De Rijk, R. (1997). Glucocorticoids and immune function: unknown dimensions and new frontiers. Immunol. Today *18*, 418–424.