Arch Immunol Ther Exp, 2004, 52, 1–5
PL ISSN 0004–069X

WWW.AITE–ONLINE.ORG
Review

Received: 2003.07.02
Accepted: 2003.09.26
Published: 2004.02.25

Eicosanoids: an emerging role in dendritic cell biology

Hedi Harizi and Norbert Gualde

Laboratory of Immunology, Bordeaux University, Bordeaux, France

Source of support: la Ligue Régionale Contre le Cancer, Comité Départemental des Charentes et Comité Départemental de la Gironde.

Summary

The arachidonic acid (AA)-derived metabolites, termed eicosanoids, are potent lipid mediators with a key role in immune and inflammatory responses. In the immune system, eicosanoids such as prostaglandins (PGs) and leukotrienes (LTs) are produced predominately by antigen–presenting cells (APC), including macrophages and dendritic cells (DC). DC constitue a family of bone marrow-derived professional APC that play a critical role in the induction and modulation of both innate and adaptive immunity. For many years, macrophages were considered as major producers of eicosanoids that are thought to drastically affect their function. Studies concerning the modulation of DC biology by eicosanoids show that PGs and LTs have the potential to affect the maturation, cytokine-producing capacity, Th cell-polarizing ability, and migration of DC. In addition, the development of DC from bone marrow progenitors appears to be under the control of some eicosanoids. Understanding the actions of eicosanoids and their receptors on APC functions is crucial for the generation of efficient DC for therapeutic purposes in patients. In this review, we summarize the current understanding of how DC functions are modulated by eicosanoids.

Key words: **DC • eicosanoids • immunomodulation**

Abbreviations: **AA** – arachidonic acid, **APC** – antigen-presenting cells, **BM-DC** – bone marrow-derived dendritic cells, **COX-1 (2)** – cyclooxygenase type 1 (or 2), **DC** – dendritic cells, **EP** – E prostanoid, **LO** – lipoxygenase, **LT** – leukotrienes, **PG** – prostaglandins, **TILs** – tumor infiltrating lymphocytes.

Full-text PDF: http://www.aite-online.org/pub/aite/no_1/4454.pdf

Author's address: Hedi Harizi, Laboratoire d'Immunologie, CNRS UMR 5540, Université de Bordeaux 2, 146, rue Léo Saignat, 33076 Bordeaux, France, e-mail: harizihedi33@yahoo.fr

INTRODUCTION

Inflammatory processes are the physiological response of an organism to various stimuli such as trauma, infections or immunological reactions[24]. These processes are characterized by the stimulation of humoral and cellular mediator systems and the release of a variety of inflammatory mediators, such as interleukin 1α (IL-1α) and tumor necrosis factor α (TNF-α)[3, 45]. An increase in the levels of these mediators can result in the production of other mediators, such as eicosanoids.

Eicosanoids constitute a family of oxygenated arachidonic acid (AA) derivatives that potently mediate diverse physiological and pathophysiological processes[15]. AA, the precursor of pro-inflammatory eicosanoids, is released from membrane phospholipids by the action of phospholipase A2 (PLA_2) and is metabolized to prostaglandins (PGs) and leukotrienes (LTs) by the actions of cyclooxygenase (COX) and lipoxygenase (LO) enzymes, respectively. Disordered activation of PLA_2, LO, and COX enzymes have been implicated in many inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases. PLA_2 is activated by PLA_2-activating protein and LO by 5-lipoxygenase-activating protein. COX-2, the inducible isoform of COX, is usually not present under basal conditions and is induced by inflammatory stimuli, such as lipopolysaccharide (LPS)[1] or interferon γ (IFN-γ)[6]. For example, over-production of COX-2 and its major metabolite, PGE_2, has been found in many human cancers, and the major host-response mechanisms known to be affected by PGE_2 are tumor angiogenesis and immune responses[52].

The immune system of vertebrate animals has evolved to respond to different types of perturbations (invading pathogens, stress signals…), limiting self tissue damage. The decision to activate an immune response is made by antigen-presenting cells (APC)[17]. Among the APC that constitute the immune system, dendritic cells (DC) play a central role. They are professional APC able to initiate innate and adaptive immune responses against invading pathogens[5]. After their development in bone marrow, immature DC migrate to the periphery (i.e. a nonlymphoid organ, such as the skin and mucosae), where they actively internalize particles and proteins in the extracellular fluid and have a weak stimulatory capacity on naive T cells[7]. Internalized proteins are degraded into peptides, which are captured by major histocompatibility complex (MHC) molecules for presentation at the plasma membrane[49]. In response to inflammatory stimuli, DC cease their endocytic activity[39], increase their expression of MHC[9, 37] and co-stimulatory molecules[12] and produce large amounts of soluble mediators, including cytokines, nitric oxide and AA-derived products.

DC AS IMPORTANT SOURCE OF AA METABOLITES

DC differ from macrophages, which share a common precursor, because macrophages are believed to be more important for their production of cytokines than in priming naive T cell responses[31]. For many years, macrophages have been the focus of studies on the generation of AA-derived mediators, and these cells were considered as a major source of eicosanoids derived from COX and 5-LO pathways[25,36]. Considerable amounts of data have been accumulated implicating the ability of DC to produce AA metabolites, which modulate chemokines[44], and cytokine[48,51] production and immune responses. More recently, we have reported that *in vitro*-generated DC possess the whole enzymatic equipment necessary for the biosynthesis of eicosanoids starting with endogenous AA and produce a full range of AA products, in particular PGE_2[20]. Studies by other investigators[42, 43] have demonstrated that DC express the 5-LO pathway at marked levels *in vivo* and produce LTB_4. These findings suggest that by producing LO products, DC may participate in inflammatory/allergic reactions and the regulation of proximal steps of the immune responses[42].

EICOSANOIDS CONTRIBUTE TO THE GENERATION DC FROM BONE MARROW CELLS

Since it is not easy to isolate DC *in vivo* because of their low frequency[4], we optimized their production *in vitro* by seeding a myeloid precursor in the presence of granulocyte macrophage colony-stimulating factor and IL-4. The production, functional capabilities, and phenotypic markers of the cells generated *in vitro* are related to the growing factors and culture conditions used. We have investigated the effect of PGE_2 and LTB_4 on the generation of DC from bone marrow (BM–DC). We observed that the generation of BM-DC was diminished (-62%) when cultures were initiated with exogenous PGE_2, but increased (+38%) in the presence of LTB_4[18]. One may argue about the relevance of the data since it is not quite clear that PGE_2 is regularly produced as a lipid compound of the bone marrow. In fact, it is very well known that PGE_2 affects hematopoiesis[10, 13, 14, 41] and that the bone marrow contains monocytes and macrophages that generate a large variety of inflammatory lipids, including eicosanoids[34] as well as platelet-activating factor[11]. Hence it is quite possible that PGE_2 from the bone marrow modulates hematopoiesis, explaining why in the presence of indomethacin (a COX inhibitor) the production of BM-DC increased by 24%, suggesting that endogenous PGE_2 might play a role during the generation of DC from bone marrow progenitors. Addition of exogenous LTB_4 clearly enhanced the generation of BM-DC *in vitro*, while Nor-dihydroguarinic acid (a LO

inhibitor) appears to be a potent inhibitor of the generation of DC. Further studies with different culture conditions and different subsets of human DC are necessary to clarify the role of PGE_2 and other lipid mediators in the generation of DC for clinical and therapeutic purposes in patients.

LIPID MEDIATORS AS POTENT MODULATORS OF DC FUNCTIONS

The inflammatory response that initiates DC maturation and migration involves soluble mediators, including cytokines, nitric oxide and metabolites of COX and LO pathways, such as PG and LT[23]. Although the role of cytokines in DC biology and function has been studied extensively, the effect of lipid mediators on DC has only recently become the focus of investigations. Many new and important data have emerged concerning the effects of COX metabolites, in particular PGE_2 and PGD_2 and 5-LO products, such as LTC_4[8], on DC functions.

PGE_2 is one of the best known and most well studied of COX products. In the immune system, PGE_2 is mainly produced by APC and exerts its actions, in part, through G protein-coupled PGE receptors, designated EP_1, EP_2, EP_3, and EP_4, with different second messenger signaling pathways[38]. Differential expression and regulation of these E prostanoid (EP) receptors mediate the diverse, and often antagonistic, effects of PGE_2 and its analogues on a variety of cell types[35, 46]. We have recently reported that *in vitro*-generated BM-DC express all EP receptors[19] and EP_2/EP_4 receptors play a central role in modulating DC functions by PGE_2. Our study confirms the fact that EP_2 and EP_4 have generally been associated with immunological modulation, as reported by other investigators[33].

When considering the question of DC differentiation and maturation, many new and interesting data have emerged concerning the role of PGE_2, which affects the activity of DC in a variety of ways depending on the maturational stage of these APC. In fact, PGE_2 may act as an enhancer of DC differentiation and affect the Th cell driving ability of DC. Previous studies have reported that addition of PGE_2 to a cocktail of pro-inflammatory cytokines, such as IL-1β, TNF-α and IL-6, promotes DC maturation and alloantigen-naive $CD4^+$ T cell stimulation by human monocyte-derived DC[27, 29] . However, used alone, PGE_2 was ineffective, suggesting that this lipid mediator is only a cofactor of pro-inflammatory cytokine-induced DC differentiation[29]. It also has been reported that COX-2-derived PGE_2 secreted by immature human DC is able to auto-regulate DC differentiation in a DC autocrine loop[50].

Another established function of PGE_2 is the regulation of cytokine production by APC, including macrophages and DC. Because IL-12 production by APC is central to the orchestration of both innate and acquired cell-mediated immune responses to many pathogens[47], the IL-12 producing capacity of DC has been investigated in response to inflammatory stimuli. The general consensus is that PGE_2 suppresses the secretion of DC-derived IL-12p70, which occurs through different and independent mechanisms. In a recent study[22] we have demonstrated that PGE_2-primed DC produce high levels of IL-10, which inhibits the production of IL-12p70. Other investigators[30] reported an inhibition of IL-12p70 by increasing the levels of IL-12p40. These results suggest that the inhibition of IL-12 production by PGE_2 implies a feed-back mechanism at the levels of APC[48], and molecules released during inflammation may have influence on IL-12 production by APC, which are highly susceptible to the induction of tolerance induced by PGE_2[22].

Among the DC-polarizing mediators produced at sites of inflammation/infection or during DC-T cell contact, recent studies suggest that PGD_2 and its metabolite PGJ_2 may play a key role in immune responses by affecting DC functions. In fact, PGD_2 inhibits the production of IL-12p70 by CD40 ligand- or LPS-activated DC through multiple signaling pathways[2,16].

In addition to their potential to modulate the maturation, IL-12-producing capacity and Th cell-polarizing ability of DC, there is new direct evidence that PG regulate chemokine receptor expression and migration of DC. Recently, two studies have addressed the effect of PGE_2 on DC migration. It has been reported that in the presence of IL-1α and TNF-α, PGE_2 up-regulates CCR7 expression and enhances DC migration in response to CCL19 or CCL21 (the so-called migratory type of human DC)[22]. In these conditions, DC secrete low levels of IL-12p70 and stimulate proliferation of $CD4^+$ T cells with Th1 and Th2 phenotypes. By contrast, human DC matured with CD40 in the absence of PGE_2 respond weakly to CCR7 ligands, secrete high levels of IL-12p70 and pro-inflammatory cytokines (the so-called pro-inflammatory type of human DC) and promote proliferation of a Th1 response[40]. Interestingly, this second type of APC becomes the migratory type of DC when cultured in the presence of CD40 ligand with PGE_2, suggesting that DC function depends on the culture conditions used *in vitro*, and PGE_2 permits the generation of different subsets of DC with the ability to induce Th cells to secrete an ample cytokine repertoire, and not only Th2 cytokines, as demonstrated previously by Kalinski et al.[28]. Depending on the site of encounter, PGE_2 has both inhibitory and stimulatory effects on DC activation. In peripheral tissues, PGE_2 seems to enhance DC activity.

In lymphoid organs, this lipid mediator plays an inhibitory role by decreasing MHC class II expression and altering the APC function of DC, as demonstrated by our study[20]. In contrast to PGE_2, PGD_2 produced locally in the peripheral tissues inhibits the migration of DC to the lymph nodes[2].

Among the panel of AA metabolites produced by BM–DC, we noticed that LTB4 is released but in lower quantity compared with PGE_2[21]. It was reported before that LTB_4 up-regulates IL-1, IL-2 and IFN-γ production, and enhances natural killer cell activity[26] – effects which are quite opposite to what is usually known concerning the immunomodulation induced by PGE_2. When we investigated the effects of LTB_4 on BM-DC phenotype and functions, we found that neither exogenously added nor endogenously produced LTB_4 had any effect[22]. However, we demonstrated that treatment of BM-DC with LTB_4 dose-dependently enhanced the release of endogenous IL-6, without any effect on IL-10[21]. These results suggest that eicosanoids, such as PGE_2 and LTB_4, differentially modulate the ability of DC to secrete bioactive cytokines.

CONCLUSIONS

The production, functional capabilities, and phenotypic markers of DC generated *in vitro* are related to the growing factors used. In our study, we report that the generation of DC issued from bone marrow progenitors, as well as their immunotolerant functions, depends upon the presence of eicosanoids.

The question of the use of eicosanoid for producing therapeutic DC involves a quite puzzling problem. Broadly speaking, it is obvious that DC, which are considered as professional APC, which therefore might essentially stimulate T cells, produce a lipid mediator, such as PGE_2, which is well known to be involved in immune suppression. Numerous reports have reported the involvement of PGE_2 produced by tumor cells in the suppression often associated with cancer. Hence it is a typical two-edged sword problem, and even if PGE_2 is used as a cytokine cocktail co-factor for producing therapeutic DC, one should keep in mind that, for instance, the AIMV medium which was used for the production of tumor infiltrating lymphocytes (TILs) was supplemented with indomethacin to improve the *in vitro* generation of TILs. Considering our data, one cannot say if it is good or not that PGE_2 is a stabilizing factor of the DC maturation. However, one should worry about the yield during the generation on DC *in vitro* in the presence of PGE_2, since each time we added prostaglandin to our cultures of DC we observed a clear decrease in the number of cells produced, as we have recently reported[18]. Further studies with EP receptor knock-out mice, EP agonists/antagonists, and different subsets of human DC are necessary to clarify the role of PGE_2 and other lipid mediators in the generation and functions of DC and their therapeutic potential.

REFERENCES

1. Aderem A. A., Cohen D. S., Rwight S. D. and Cohen Z. A. (1986): Bacterial lipopolysaccharides prime macrophages for enhanced release of arachidonic acid metabolites. J. Exp. Med., 164, 165–179.
2. Angeli V., Faveeuw C., Roye O., Fontaine J., Teissier E., Capron A., Wołowczuk I., Capron M. and Trottein F. (2001): Role of the parasite–derived prostaglandin D2 in the inhibition of epidermal Langerhans cell migration during schistosomiasis infection. J. Exp. Med., 193, 1135–1147.
3. Bachwich P. R., Chensue S. W., Larrick J.W. and Kunkel S. L. (1986): Tumor necrosis factor stimulates interleukin-1 and prostaglandin E2 production in resting macrophages. Biochem. Biophys. Res. Commun., 14, 94–101.
4. Banchereau J. (1997): Dendritic cells: therapeutic potentials. Transfus. Sci., 18, 313–326.
5. Banchereau J., Briere F., Caux C., Lebeque S., Liu Y. J., Pulendran B. and Palucka K. (2000): Immunobiology of dendritic cells. Annu. Rev. Immunol., 18, 767–811.
6. Barrios-Rodiles M. and Chadee K. (1998): Novel regulation of cyclooxygenase-2 expression and prostaglandin E2 production by IFN-γ in human macrophages. J. Immunol., 161, 2441–2448.
7. Bell D., Young J. W. and Banchereau J. (1999): Dendritic cells. Adv. Immunol., 72, 255–324.
8. Breyer R. M., Bagdassarian C. K., Myers S. A. and Breyer M. D. (2001): Prostanoid receptors: subtypes and signaling. Annu. Rev. Pharmacol. Toxicol., 41, 661–690.
9. Cella M., Engering A., Pinet V. and Lanzavecchia A. (1997): Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature, 388, 782–787.
10. Denizot Y., Dulery C., Trimoreau F., Desplat V. and Praloran V. (1998): Arachidonic acid and human bone marrow stromal cells. Biochim. Biophys. Acta, 27, 209–215.
11. Denizot Y., Trimoreau F., Dupuis F., Verger C. and Praloran V. (1995): PAF and haematopoiesis. III. Presence and metabolism of platelet-activating factor in human bone marrow. Biochim. Biophys. Acta, 1265, 55–60.
12. De Smedt T., Pajak B., Muraille E., Lespagnard L., Heinen E., De Baetselier P., Urbain, J., Leo O. and Moser M. (1996): Regulation of dendritic cell numbers and maturation by lipopolysaccharide *in vivo*. J. Exp. Med., 184, 1413–1424.
13. Gentille P. S. and Pelus L. M. (1987): Modulation of myelopoiesis by PGE2. Inhibition of granulocyte-monocyte progenitors (CFU-GM) cell cycle rate. Exp. Haematol., 15, 119–126.
14. Gentile P. S. and Pelus L. M. (1988): *In vivo* modulation of myelopoiesis by prostaglandin E2. IV. Prostaglandin E2 induction of myelopoietic inhibitory activity. J. Immunol., 141, 2714–2720.
15. Goetzl E. J., An S. and Smith W. (1995): Specificity of expression and effects of eicosanoid mediators in normal physiology and human diseases. FASEB J., 9, 1051–1058.
16. Gosset P., Bureau F., Angeli V., Pichavant M., Faveeuw C., Tonnel A. B. and Trottein F. (2003): Prostaglandin D2 affects the maturation of human monocyte-derived dendritic cells: consequence on the polarization of naive Th cells. J. Immunol., 170, 4943–4952.
17. Granucci F., Zanoni I., Feau S. and Ricciardi-Castagnoli P. (2003): Dendritic cell regulation of immune response: a new role of interleukin-2 at the intersection of the innate and adaptive immunity. EMBO J., 22, 2548–2551.

18. Harizi H. and Gualde N. (2002): Dendritic cells produce eicosanoids, which modulate generation and functions of antigen-presenting cells. Prostaglandins Leukot. Essent. Fatty Acids, 66, 459–466.

19. Harizi H., Grosset C. and Gualde N. (2003): Prostaglandin E2 modulates dendritic cell functions via EP2 and EP4 receptor subtypes. J. Leukoc. Biol., 73, 756–763.

20. Harizi H., Juzan M., Grosset C., Rashedi M. and Gualde N. (2001): Dendritic cells issued in vitro from bone marrow produce PGE2 that contributes to the immunomodulation induced by antigen-presenting cells. Cell. Immunol., 209, 19–28.

21. Harizi H., Juzan M., Moreau J.-F. and Gualde N. (2003): Prostaglandins inhibit 5-lipoxygenase-activating protein expression and leukotriene B4 production from dendritic cells via an IL-10-dependent mechanism. J. Immunol., 170, 139–146.

22. Harizi H., Juzan M., Pitard V., Moreau J.-F. and Gualde N. (2002): Cyclooxygenase-2-issued PGE2 enhances the production of endogenous IL-10, which down-regulates dendritic cell functions. J. Immunol., 168, 2255–2263.

23. Harris S. G., Padilla J., Koumas L., Ray D. and Phipps R. P. (2002): Prostaglandins as mediators of immunity. Trends Immunol., 23, 144–150.

24. Homaidan F. R., Chakroun I., Haidar H. A. and EL-Sabban M. (2002): Protein regulators of eicosanoid synthesis: role in inflammation. Curr. Protein Pept. Sci., 3, 467–484.

25. Humes J. L., Bonney R. J., Pelus L., Dahlgren M. E., Sadowski S. J. and Kuehl F. A. jr. (1997): Macrophage synthesis and release of prostaglandins in response to inflammatory stimuli. Nature, 269, 149–151.

26. Hwang O. (1989): Essential fatty acid and immune response. FASEB J., 3, 2052–2064.

27. Jonuleit H., Kuhn U., Muller G., Steinbrink K., Paragnik L., Schmitt E., Knop J. and Enk A.H. (1997): Pro-inflammatory cytokines and prostaglandins induce maturation of potent immunostimulatory dendritic cells under fetal calf serum-free conditions. Eur. J. Immunol., 27, 3135–3142.

28. Kalinski P., Hilkens C. M., Snijdewint F. G. and Kapsenberg M. L. (1997): IL-12-deficient dendritic cells, generated in the presence of prostaglandin E2, promote type 2 cytokine production in maturing human naive T helper cells. J. Immunol., 159, 28–36.

29. Kalinski P., Schuitemaker J. H., Hilkens C. M. and Kapsenberg M. L. (1998): Prostaglandin E2 induces the final maturation of IL-12-deficient $CD1a^{+}CD83^{+}$ dendritic cells: the levels of IL-12 are determined during the final dendritic cell maturation and are resistant to further modulation. J. Immunol., 161, 2804–2809.

30. Kalinski P., Vieira P. L., Schuitemaker J. H., de Jong E. C. and Kapsenberg M. L. (2001): Prostaglandin E2 is a selective inducer of interleukin-12p40 production and an inhibitor of IL-12p70 heterodimer. Blood, 97, 3466–3469.

31. Kambayashi T., Wallin R. P. and Ljunggren H. G. (2001): cAMP-elevating agents suppress dendritic cell function. J. Leukoc. Biol., 70, 903–910.

32. Luft T., Jefford M., Luetjens P., Toy T., Hochrein H., Masterman K. A., Maliszewski C., Shortman K., Cebon J. and Maraskovsky E. (2002): Functionally distinct dendritic cell (DC) populations induced by physiologic stimuli: prostaglandin E2 regulates the migratory capacity of specific DC subsets. Blood, 100, 1362–1372.

33. Meja K. K., Barnes P. J. and Giembycz M. A. (1997): Characterization of the prostanoid receptor(s) on human blood monocytes at which prostaglandin E2 inhibits lipopolysaccharide-induced tumour necrosis factor-α generation. Br. J. Pharmacol., 122, 149–157.

34. Nakayama Y., Shindo T., Akihama T. and Miura A. B. (1984): Prostaglandin E2 production by human bone marrow cells: a comparison with peripheral blood mononuclear cells. J. Exp. Med., 144, 417–423.

35. Narumiya S., Sugimoto Y. and Ushikubi F. (1999): Prostanoid receptors: structures, properties and functions. Physiol. Rev., 79, 1193–1226.

36. Nathan C. F. (1987): Secretory products of macrophages. J. Clin. Invest., 79, 319–327.

37. Pierre P., Turley S. J., Gatti E., Hul, M., Meltzer J., Mirza A., Inaba K., Steinman R. M. and Mellman I. (1997): Developmental regulation of MHC class II in mouse dendritic cells. Nature, 388, 787–792.

38. Robbiani D. F., Finch R. A., Jager D. Muller W. A., Sartorelli R. C. and Randolph G. J. (2000): The leukotriene C4 transporter regulates CCL19 (MIP-3β, ELC)-dependent mobilization of dendritic cells to lymph nodes. Cell, 103, 757–768.

39. Sallusto F., Cella M., Danielli C. and Lanzavecchia A. (1995): Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products. J. Exp. Med., 182, 389–400.

40. Scandella E., Men Y., Gillessen S., Forster R. and Groettrup M. (2002): Prostaglandin E2 is a key factor for CCR7 surface expression and migration of monocyte-derived dendritic cells. Blood, 100, 1354–1361.

41. Shibata Y., Burdick M. K., Bjorkman D. R. and Volkman A. A. (1997): Regulatory role of PGE2-activated adhesion molecules in myelopoiesis. Adv. Exp. Med. Biol., 400B, 741–749.

42. Spanbroek R., Hildner M., Steinhilber D., Fusenig N., Yoneda K., Radmark O., Samuelsson B. and Habenicht A. J. R. (2000): 5-Lipoxygenase expression in dendritic cells generated from $CD34^{+}$ hematopoietic progenitors and in lymphoid organs. Blood, 96, 3857–3865.

43. Spanbroek R., Stark H. J., Jassen-Timmen U., Kraft S., Hilder M., Andl T., Bosch F. X., Fusenig N. E., Bieber T., Radmark O., Samuelsson B. and Habenicht A. J. (1998): 5-Lipoxygenase expression in Langerhans cells of normal human epidermis. Proc. Natl. Acad. Sci. USA, 95, 663–668.

44. Takayama K., Garcia-Gardena G., Sulkhova G. K., Gomander J., Gimbrone M. A. jr. and Libby P. (2002): Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor. J. Biol. Chem., 277, 44147–44154.

45. Tanner W. G., Welbom M. B. and Shepherd V. L. (1992): Tumor necrosis factor-α and interleukin-1α synergistically enhance phorbol myristate acetate-induced superoxide production by rat bone marrow–derived macrophages. Am. J. Resp. Cell. Mol. Biol., 7, 379–384.

46. Tilley S. L., Coffman T. M. and Koller B. H. (2001): Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J. Clin. Invest., 108, 15–23.

47. Trinchieri G. (1995): Interleukin-12: a pro-inflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen–specific adaptive immunity. Annu. Rev. Immunol., 13, 251–273.

48. Van der Pouw Kraan T. C., Boeije L. C., Smeenk R. J., Wijdenes J. and Aarden L. A. (1995): Prostaglandin E2 is a potent inhibitor of human interleukin-12 production. J. Exp. Med., 181, 775–779.

49. Watts C. (1997): Capture and processing of exogenous antigens for presentation on MHC molecules. Annu. Rev. Immunol., 15, 821–850.

50. Whittaker D. S., Bahjat K. S., Moldawer L. L. and Clare-Salzler M. J. (2000): Autoregulation of human monocyte-derived dendritic cell maturation and IL-12 production by cyclooxygenase-2 mediated prostanoid production. J. Immunol., 165, 4298–4304.

51. Williams J. A. and Shacter E. (1997): Regulation of macrophage cytokine production by prostaglandin E2: distinct roles of cyclooxygenase-1 and -2. J. Biol. Chem., 272, 25693–25699.

52. Yang L., Yagamata N., Yadav R., Brandon S., Courtney R. L., Morrow D. J., Shyr Y., Bothby M., Joyce S., Carbone P. D. and Breyer R. M. (2003): Cancer-associated immunodeficiency and dendritic cell abnormalities mediated by the EP2 receptor. J. Clin. Invest., 111, 727–735.