Invited Review

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Cytokine gene regulation by PGE_2, LTB_4 and PAF

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THE initial response of the host to noxious stimuli produces a nonspecific inflammatory response. A more specific immune response is believed to be modulated by two classes of molecules: lipid mediators (PG, LT and PAF) and cytokines, synthesized by phagocytes and parenchymal cells. In this review we discuss the increasing evidence of the interrelationship between eicosanoids, PAF and cytokines: IL-1 and TNF induce PG synthesis in various cells and PG, in turn, modulate cytokine production. We focused on the regulatory effects of LTB_4, PGE_2 and PAF on cytokine gene expression.

Key words: Alveolar macrophages, Cyclic nucleotides, Endothelial cells, IL-1, IL-6, Monocytes, mRNA, Neutrophils, TNF, Transcription

When confronted with a variety of noxious stimuli, the host responds by producing an array of soluble factors and by mobilizing various cell populations. In most instances, the initial response is relatively nonspecific and consists of various degrees of inflammation. Among the soluble mediators which participate in this inflammatory response and which may also modulate the subsequent more specific immune response, two classes of molecules have emerged as the principal protagonists: lipid mediators, derived from cell membrane phospholipids, and cytokines, synthesized by phagocytes and parenchymal cells.

Within minutes of stimulation, eicosanoids such as prostaglandins (PG) and leukotrienes (LT), as well as platelet activating factor (PAF) are produced by the action of phospholipase A_2 (PLA_2) on the membrane phospholipid 1-0-alkyl-2-arachidonoyl-sn-glycero-3-phosphocholine and subsequent oxidative metabolism of the freed arachidonic acid or acetylation of the remaining 1-alkyl-2-lyso-glycerophosphocholine (lyso-PAF) molecule, respectively. These lipid mediators in turn can act on a variety of cell populations, often, including the cells which produced them.[1] Their bioactions are thought to be mediated by specific cell membrane receptors. Recently, a PAF receptor from guinea-pig lung has been cloned[2] and its proposed structure suggests that it is associated with a G protein. Functional studies had previously suggested that this may also be the case with LTB_4 receptors.[3] Postreceptor events and signal transduction pathways in cellular responses triggered by LT, PG and PAF are objects of intense research using metabolic inhibitors and receptor antagonists. In the present review, we will focus on the regulatory effects of LTB_4, PGE_2 and PAF on cytokine gene expression (Table 1).

Table 1. Summary of actions of eicosanoids and PAF on cytokine gene regulations.

Cytokine	Mediator	Transcription	mRNA	Protein
TNFα	LTB_4		↑	↑
	PGE_2 (low dose)		↑	↑
	PGE_2 (high dose)		↓	↓
	PAF		↑	↑
IL-1	LTB_4	↑	↑	±
	PGE_2		–	–
	PAF		↑	↑
IL-6	LTB_4	↑	↑	↑

Tumour Necrosis Factor (TNFα)

TNFα is a cytokine produced preferentially by activated macrophages, but also by NK cells and neutrophils. TNFα may play a role in immune modulation[4] and anti-tumour defences,[5] in addition to being a potent mediator for numerous inflammatory responses, such as endotoxic shock, adult respiratory distress syndrome and bowel necrosis.[6–8] In these conditions, however, synergy with other mediators, including PAF, may be needed for expression of disease.

When human monocytes are exposed to graded concentration of LTB_4, their cell-free supernatants contain increased amounts of TNFα which peaks at 8–16 h.[9] The maximal effect of LTB_4 is observed at concentrations of 10^{-10} M. Endogenous lipoxygenase metabolites may also be involved in enhanced TNFα production following some stimuli, such as silica, asbestos,[10] PAF[11] or lipopolysaccharide (LPS).[12] Evidence for such an involvement is derived from use of 5-lipoxygenase (5-LO) inhibitors which can partially or totally block TNFα production. Addition of exogenous LTB_4 can restore TNFα production under certain

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circumstances.[11] In contrast, inhibition of 5-LO activation using MK-886, which binds the 5-lipoxygenase-activating protein (FLAP), does not affect TNFα production[13] in response to phorbol ester, Concanavalin A, LPS or zymosan. TNFα gene expression can be stimulated by phorbol esters, LPS or TNFα itself. Under these conditions, inhibition of PLA_2 by bromophenacyl bromide or quinacrine, or of lipoxygenases by ketoconazole or nordihydroguaiaretic acid (NDGA) results in inhibition of TNFα mRNA accumulation and TNFα gene transcription.[14–16] On the other hand, exogenous LTB_4 increases TNFα mRNA.[14] Interestingly, the dual cyclooxygenose (CO)/5-LO inhibitor, tebufelone, at 20–25 μM, inhibits TNFα mRNA accumulation while enhancing TNFα production.[17]

In comparison to 5-LO metabolites, CO metabolites such as PGE_2 have been shown to inhibit TNFα production at high concentrations,[18,19] presumably by augmenting cAMP levels in the cells. Low concentrations of PGE_2, however, appear to stimulate guanylate cyclase and result in augmented TNFα production.[20,21] TNFα mRNA accumulation is also inhibited by PGE_2,[22] an effect associated with decreased TNFα transcription[14] (Fig. 1).

PAF can enhance TNFα production by rat alveolar macrophages[11] and human monocytes[23–25] and myeloid cells.[26] In the macrophages, the activation pathway may involve 5-LO, since inhibitors such as NDGA or AA-861 can abrogate the effect of PAF.[11] In human monocytes and myeloid cell lines, the involvement of the 5-LO pathway in PAF-mediated TNFα production is still unclear. PAF induces, however, a bimodal dose-response pattern in these cells, with both a nanomolar and a femtomolar concentration peak of activation.[26] Enhanced accumulation of TNFα mRNA is maximally stimulated by 10^{-13} and 10^{-7} M PAF in monocytes and in HL-60 promyelocytic leukemia cells induced by 1,25 $(OH)_2$ vitamin D_3 to differentiate into macrophages.[26]

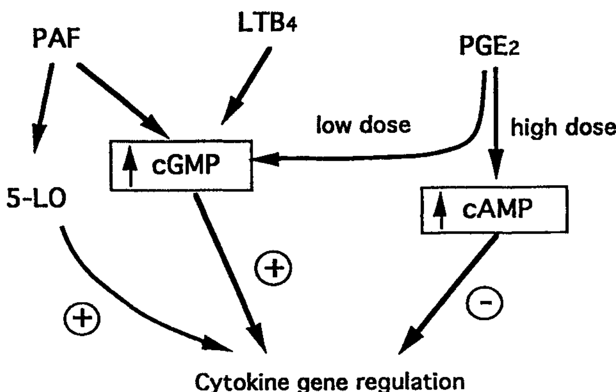

FIG. 1. Schematic representation of cytokine gene regulation by eicosanoids and PAF, involving cyclic nucleotides.

Interleukin-1 (IL-1)

IL-1 is a key protagonist of immune and inflammatory events, being involved, among other effects, in T-cell activation by accessory cells and in induction of fever and other features of inflammation.[27] It is produced principally by monocytes/macrophages,[28] but also by a variety of other cell types such as B-cells, endothelial cells, keratinocytes, polymorphonuclear (PMN) leukocytes, etc. There are two species of IL-1, designated IL-1α and IL-1β, which share cell receptors and have similar bioactions in spite of being derived from two separate genes.

Addition of exogenous LTB_4 to monocytes stimulates IL-1β transcription and mRNA accumulation (Rola-Pleszczynski and Stankova, *in preparation*), but little IL-1 protein release.[29] Earlier reports that IL-1 activity was enhanced in supernatants from LTB_4-treated monocytes[30] were consistent with measures of both IL-1 and IL-6 in bioassays of lymphocyte activating factor (LAF) activity in monocyte supernatants.[29,31]

Prostaglandins, on the other hand, have been known for some time to inhibit lymphokine secretion.[32] PGE_2 inhibits IL-1 production by monocytes via a post-transcriptional mechanism involving increased cAMP levels within the cell.[33] PGE_2 also inhibits secretion of IL-1 by large granular lymphocyte (LGL)[34] but has no direct effect on IL-1 secretion by phagocytic cells of the thymic reticulum[35] or by peritoneal macrophages.[36] While PGE_2 inhibits TNFα mRNA accumulation in monocytes, it has no effect on IL-1α or IL-1β mRNA levels.[22]

PAF stimulates IL-1α and IL-1β production in human monocytes in a concentration-dependent manner, in synergy with other stimuli such as LPS, MDP or IFNγ.[24,37–39] As with TNFα, IL-1 production in PAF-treated monocytes follows a bimodal pattern, with peak activities at 10^{-13} and 10^{-8} M PAF.[24,39] In rats treated with a continuous infusion of PAF via an osmotic mini-pump, IL-1 production by splenic macrophages was enhanced by lower doses of PAF, while higher doses had an inhibitory effect.[40] At the present time, it is unclear whether PAF regulates IL-1α and IL-1β production via transcriptional or post-transcriptional mechanisms. IL-1β mRNA expression in THP-1 cells, however, can be enhanced by 10^{-10} M PAF.[41]

Interleukin-6

IL-6 is a multifunctional cytokine produced by monocytes, macrophages, endothelial cells, fibroblasts, keratinocytes, T-cells and some tumour cells. Its numerous synonyms reflect its various biological activities, as B-cell stimulatory factor 2, interferon

β_2, hybridoma-plasmacytoma growth factor, hepatocyte-stimulating factor.[42-46] IL-6 is an important regulator of T- and B-cell functions, haematopoiesis and acute phase responses.[47,48] Infectious agents, endotoxin and the inflammatory cytokines TNFα and IL-1 can induce IL-6 production, while dysregulation of IL-6 expression is associated with certain chronic inflammatory, autoimmune and haematopoietic disorders. The findings that IL-6 production is associated with inflammatory states suggests that its production may also be modulated by inflammatory lipid mediators.

When human monocytes are cultured in the presence of graded concentrations of LTB_4, a significant stimulation of production of bioactive and immunoreactive IL-6 is observed.[29,31] Nanomolar concentrations of LTB_4 are optimal, while the ω-oxidation products 20-OH-LTB_4 and 20-COOH-LTB_4 are only 22% and 2% effective, respectively. LTB_4 induces an accumulation of IL-6 mRNA in treated monocytes with a superposable dose-response, and maximal accumulation at 1 h. While IL-6 mRNA half-life in untreated cells is approximately 1 h, it is extended to 3 h in LTB_4-treated monocytes. Moreover, nuclear transcription of IL-6 mRNA is augmented at 30 min by a factor of five in LTB_4-treated cells. Furthermore, LTB_4-treated monocytes contain a nuclear protein factor (NF) which binds to a promoter region of the IL-6 gene, called NF-IL-6-binding domain, and which may be involved, among other factors, in LTB_4-mediated induction of IL-6 gene transcription.[31]

PAF can also stimulate IL-6 production by human monocytes in the picomolar range and this stimulation is enhanced by prior treatment with TNFα or IFNγ.[49] In contrast, rat alveolar macrophages require a second stimulus, such as LPS or MDP, to respond to PAF with augmented IL-6 production.[50] This augmented production is brought down to baseline by pretreatment of the cells with the FLAP inhibitor MK-886 or the 5-LO inhibitor AA-861, suggesting that under these conditions, the action of PAF is mediated by endogenous 5-LO metabolites. Human PMN and endothelial cells can also respond to PAF with enhanced IL-6 production and IL-6 mRNA accumulation (unpublished).

Conclusions

There is increasing evidence to suggest that the production of eicosanoids, PAF and cytokines may be interrelated: IL-1 and TNF induce PG synthesis in various cells[51-53] and PG, in turn, modulate cytokine production, as discussed in this review. In contrast, LT can augment IL-1, IL-6 and TNF production and endogenous LT production may play a role in TNF and IL-6 synthesis. IL-1, TNF and IFN can also induce the synthesis of PAF in several cell types, including endothelial cells, neutrophils and macrophages,[54-56] while PAF can, in turn, augment IL-1, IL-6 and TNF production by rat and human cells. Such a positive feedback loop at this level, with potential for amplification of immune or inflammatory responses, may be counterbalanced by the negative feedback action of IL-6 on both IL-1 and TNF.[57,58] This negative feedback may account for the limited production of IL-1 by LTB_4-stimulated monocytes which readily produce large amounts of IL-6. It may also explain the augmented production of IL-1 and TNF observed after treatment of monocytes with a dual CO/5-LO inhibitor, a treatment which may preferentially inhibit IL-6 production (Fig. 2).

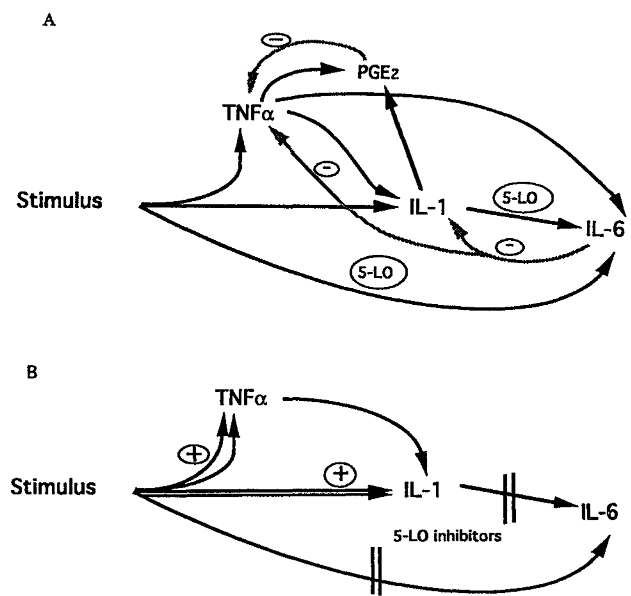

FIG. 2. Schematic representation of mutual regulatory pathways between TNF, IL-1 and IL-6. (A) Proposed preferential involvement of 5-LO in IL-6 production. (B) Proposed mechanism of action of 5-LO inhibitors in suppressing the negative feed-back of IL-6 on TNF and IL-1 production.

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