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Role of cytokines in the modulation of nitric oxide production by cyclic AMP.

Abstract

Enhanced levels of cyclic AMP (cAMP), resulting from stimulation of adenylyl cyclase through activation of distinct pharmacological receptor systems, have a remarkable impact on the activity of the immune system. Among other responses, production of nitric oxide (NO) is also affected. The effects of cAMP range from stimulation to inhibition (or no effect) of immune-stimulated biosynthesis of NO, with a preponderance of stimulatory interference. cAMP has been shown to be a potent, dual modulator of cytokine expression. It dose-dependently suppresses secretion of major NO up-regulatory cytokines tumor necrosis factor-a (TNF-a) and interferon-g (IFN-g). On the other hand,

production of IL-10, which is known to regulate the inducible NO synthase (iNOS) activation in both a positive and negative direction, is inversely enhanced. It is suggested that the dual effects of cAMP on NO formation are likely to result from the differences in the concentration ratio of these cytokines. The value of this parameter depends on the type and concentration of cAMP-stable derivatives and cAMP-enhancing agents, such as prostaglandins, b-adrenoceptor agonists, phosphodiesterase inhibitors, forskolin and cholera toxin. The cytokine ratio may be influenced by dynamically developing multiple down- and up-regulatory feedback circuits among cytokines, NO, and cAMP.

Full text

INTRODUCTION

Adenosine and its natural derivative cyclic 3',5'-adenosine monophosphate (cAMP) are important factors of intracellular signaling. The adenosine/cAMP pathways thus influence a variety of biochemical processes which have been implicated in the control of inflammation [1], as well as in the pathogenesis of many diseases, for example myocardial ischaemia, acute renal failure, pancreatic disorders, schizophrenia, epilepsy, Alzheimer's and Parkinson's disease [2]. Nitric oxide (NO) is thought to play an important role in etiopathogenesis of these and other diseases [3]. Increasing attention is being paid to the clinical potential of cAMP, adenosine [4-6], and NO [7] in various fields of medicine.

Through distinctive modulation of secretion of pro-inflammatory and anti-inflammatory cytokines, adenosine and cAMP exert a considerable impact upon the activity of immune system. Not surprisingly, they have been found to be potent modulators of nitric oxide (NO) expression, the well recognised effector molecule of non-specific defence mechanisms. How-ever, the experimental data show an embarrassing variation encompassing both up- and down-regulatory effects. Herein, the situation is exemplified by demonstrating the NO-modulatory potential of cAMP-stable derivatives and one of the groups of potent cAMP-elevating agents, prostaglandins (PGs). The aim of this work is to look for plausible explanations for controversial data, with special emphasis on the role of cytokines.

cAMP AND NITRIC OXIDE PRODUCTION

Effects of cAMP stable derivatives

Of a plethora of membrane-permeable stable derivatives of cAMP, dibutyryl-cAMP (db-cAMP), 8-bromo-cAMP, and *(S)-p*-cAMP have been most frequently used in studies investigating the role of cAMP in NO biosynthesis (Table 1). When applied alone, the agents did not stimulate formation of NO by rat aortic muscle cells [8-10], RAW 264.7 [11] or ANA-1 [12] murine macrophage cell lines, or murine spleen fibroblasts [13], although they stimulated iNOS mRNA [14] and NO synthesis in vascular smooth muscle cells of rats [15, 16], rat glomerular mesangial cells [17, 18], peritoneal macrophages [19, 20], murine fibroblasts [21], L929 fibrosarcoma cell line [13], and human neuroblastoma cells [22]. As a rule, the combination of cAMP stable derivatives with primary immune stimuli provided by lipopolysaccharide (LPS), or cytokines such as IL-1beta, IFN-gamma, TNF-alpha, and their cocktails, has been found to augment all iNOS mRNA, iNOS protein and NO levels in various cells such as human intestinal epithelial cells [23], rat vascular smooth muscle cells [8, 24, 25], brain [26, 27] and umbilical endothelial cells [28], cardiac [9] and aortic myocytes [10, 29], rat Kupffer cells stimulated with LPS but not with TNF-alpha [30], and rodent macrophages or cell lines [11, 31, 32]. Nevertheless, only low concentrations have been found to be stimulatory while high concentrations were inhibitory in a mouse macrophage line ANA-1, cultured in the presence of IFN-gamma [12]. Although seldom in the direction of the action in this class of compounds, cAMP stable derivatives inhibited NO production in murine spleen fibroblasts [13], LPS-activated rat astroglial cells, thioglycolate-elicited murine macrophages [32, 33], but not in murine RAW 264.7 macrophages [34].

Effects of PGs

By themselves, neither PGE1 [15] nor PGE_2 [12, 35] have usually been found to activate NOS, but PGE_2 seems to be required for maintaining the endothelial NOS activity in cerebral vessels of newborn pigs [36], and mediates NO synthesis in mouse air pouch inflammation [37]. Also PGF2alpha can positively interact with physiological NO formation in rat ovarian tissue [38], and during rabbit pseudopregnancy [39]. PGs have been regularly found to interfere with production of NO by immune-stimulated cells (Table 1). Thus, PGE_1 enhanced the effects of all IFN-gamma, TNF-alpha, and IL-1beta in rat vascular smooth muscle cells [15], and the same effect was observed with PGE_2 in cells of various origin, such as rat Kupffer cells [40], murine macrophages [12, 31], and Jurkat

cells [41]. Conversely, production of NO was suppressed by PGE_2 in murine peritoneal macrophages elicited with thioglycolate [33], in IL-1-activated rat mesangial cells [42], and in the murine macrophage cell line J774 stimulated with LPS and IFN-gamma combined with phosphodiesterase inhibitor IBMX (3-isobutyl-1-methylxanthine) [35]. The NO-inhibitory activity of PGE_2 and the PGI_2 analogue iluprost was found in mouse monocyte/macrophage cells J774 when the compounds were added concomitantly with LPS, but not afterwards [43]. Occasionally, PGs were found to be without any influence upon the LPS-induced NO production by mouse [44] and rat [45] peritoneal macrophages. Interestingly, leukotriens have been reported to be without influence [46] or rather to possess NO up-regulatory function [45].

CYTOKINES AND HIGH-OUTPUT NITRIC OXIDE PRODUCTION

Synthesis of NO is genetically controlled by three isoforms of the enzyme NO synthase (NOS) [47]. The endothelial and neuronal enzymes govern formation of low amounts of NO, and function within the cardiovascular and neural systems. The high-output generation of NO is effected by the inducible isoform (iNOS) which is present in many cell types, typically in macrophages. As a rule, its activity is constitutively quiescent, but may be induced by LPS. Various cytokines have been found either to up-regulate or down-regulate the expression of iNOS mRNA, protein, and biosynthesis of NO.

A central NO-stimulatory role is played by IFN-gamma that may trigger NO production on its own in many cells types and under various experimental conditions [48, 49]. However, some types of cells, e.g. rat microglial cells [50] and hepatocytes [51], are refractory to the effects of IFN-gamma alone, and require the additional presence of other synergising cytokines such as TNF-alpha and IL-1beta [52]. TNF-alpha may occasionally stimulate NO on its own [53] but it mainly provides the major co-stimulatory signal for the activation of NO by other cytokines such as IFN-gamma [49, 54]. Similar to IFN-gamma, IL-1 is also endowed with the capacity to activate iNOS on its own in a variety of cell types and tissues, *e.g.* smooth muscle cells [55], chondrocytes [56], neurons [57], or islet beta-cells [58], and plays a key role in the regulation of hepatic iNOS activity [59]. IL-2 is known to be an important iNOS activator in NK cells [60].

IL-4 and IL-10 are generally regarded to be inhibitors of NO production. However, they frequently exhibit the opposite, *i.e.* NO-stimulatory potential. Thus, while a

number of studies document NO down-regulatory effect of IL-4 [61, 62], this cytokine, added after iNOS has already been activated by IFN-gamma, can potentiate NO formation in murine macrophages [62], and human monocytes activated with IL-4 plus IFN-gamma [63]. Similar ambiguous activity is expressed by IL-10. While it has been found to inhibit NO production under various experimental conditions [64, 65], it may increase NO biosynthesis in resident macrophages and macrophage cell lines stimulated with LPS, LPS + IFN-gamma, IFN-gamma, or IFN-gamma + TNF-alpha [66, 67]. The direction of the IFN-alpha/beta interference may depend on a priming NO stimulus. It has been found to augment the LPS- [49] or lipid A-induced NO [68], while inhibiting the IFN-gamma-induced NO in murine macrophages [69].

Transforming growth factor (TGF)-beta can be regarded as the most powerful suppressor of NO production. It has been found to decrease iNOS translation, to destabilise iNOS mRNA, and to accelerate the degradation of iNOS protein in various cell types, including macrophages, smooth muscle cells, and mesangial cells [70-72]. NO-inhibitory effects also are a characteristic feature of granulocyte or macrophage colony-stimulating factors (M-CSF and G-CSF) [73], and IL-13 [74, 75].

ADENOSINE/cAMP PATHWAY AND NITRIC OXIDE-REGULATORY CYTOKINES

The effects of cAMP and adenosine on cytokine production have recently been reviewed [76]. It can be concluded that they may be considered to be up-regulators of the production of Th2 cytokines, whereas down-regulators of the immune-stimulated production of Th1 cytokines. From the point of view of NO production, it is important to mention that the adenosine/cAMP pathways inhibit not only the production of NO-up-regulatory cytokines such as IFN-gamma, TNF-alpha, IL-2, and IL-12, but also the NO-down-regulatory cytokines GM-CSF, TGF-beta1 [77], and IL-4 [78]. On the other hand, both adenosine and cAMP are potent activators of IL-10 production.

MULTIPLE FEEDBACK CIRCUITS

NO affects its own production

Major transcription factors controlling the expression of iNOS are nuclear factor kB (NF-kappaB) and activating protein-1 (AP-1) [21, 79-81]. Once induced by LPS

and/or cytokines, or liberated from NO-donors, NO has been found to modulate the expression and activity of these *cis*-elements. However, both negative [82, 83] and positive [84, 85] regulatory effects on NF-kappaB activity were recorded. Similarly, the AP-1 DNA-binding activity can be either suppressed [86-88] or enhanced [85, 89, 90] by NO. These effects may be a causal background for the autoregulatory influence of NO on its own synthesis. Accordingly, both positive and negative feedback loops have been reported. Thus, while NO itself has no obvious effect on the expression of NOS, it enhances the IL-1beta-induced iNOS activity in mesangial cells [91]. Stimulation of NOS expression by NO was also observed in foetal intrapulmonary artery endothelial cells [92]. It seems that the augmenting effects are bound to low concentrations of NO, because high concentrations inhibit iNOS mRNA expression in mouse macrophage cell line ANA-1 and fetal endothelial cells [92, 93]. The mechanisms of inhibition (in RAW 264.7 cells stimulated with LPS plus IFN-gamma) is independent of the soluble guanylyl cyclase/cyclic GMP pathway [94].

NO affects PG production

A number of studies have documented both stimulatory and inhibitory effects of NO and its metabolic products, such as peroxynitrite, upon formation and maintainance of PG levels. Low amounts of NO stimulate cyclooxygenase (COX) activity in many cell types and tissues [95], and NO at least in part contributes to PG production under various pathological conditions such as inflammation [96] and endotoxemia [97]. Endogenous NO has also been found to stimulate PGF_{2alpha} in human microglial cells, but not in astrocytes [98]. The stimulatory effects of NO may depend greatly on prolonged expression of COX-2 [99]. COX-2 activity can be superinduced in murine macrophages RAW 264.7 after challenge with LPS or IL-1beta [100]. In contrast, high amounts of NO inhibit PG production [101] which is likely to result from decreased COX-2 protein rather than from mRNA [102]. Release of prostacyclins may be inhibited by NO [103].

NO affects cAMP levels

NO inhibits certain types of adenylyl cyclase [104], particularly isoforms 5 and 6 [105]. As expected, activation of iNOS has been observed to decrease the intracellular levels of cAMP upon stimulation of cardiac myocytes with beta-adrenergics, although it had no effect on basal cAMP production [106]. Conversely, NO positively influences formation of cAMP in many cell types.

Probably through the inhibition of cAMP breakdown, NO by itself or in combination with cAMP-elevating compounds, augments the cAMP production in platelets [107], endothelial cells [108], myocytes [109], and in kidney and sphincter cells [110].

NO affects cytokine production

Depending on experimental conditions, NO can both enhance or suppress secretion of a number of cytokines. Its capacity to modulate cytokine responses of macrophages, T cells, endothelial cells, and fibroblasts might result from its potential to affect ion channels, G proteins, protein tyrosine kinases, Janus kinases, and various transcription factors [111, 112]. Production of IL-4, IL-10 [41], TNF-alpha [113, 114], and TGF-beta1 [115] has only been found to be enhanced, while production of IL-2 [116] and IFN-alpha/beta [117] is inhibited by NO. The effects on the secretion of a variety of other cytokines are ambiguous. This concerns all IL-1 [113, 118], IL-6 [113, 119], IL-8 [120, 121], and IL-12 [122, 123]. As a rule, NO inhibits secretion of IFN-gamma [41, 123], but low NO concentrations may stimulate it [123].

Cytokines affect production of PGs

The most potent activator of COX-2 expression and PG production is IL-1, the effect thereof can be synergistically augmented by other cytokines such as TNF-alpha [124] or TGF-beta [125]. TNF-alpha on its own stimulates the release of arachidonic acid from cellular phopsholipids and sustained COX-2 gene expression and PGE_2 synthesis [126]. Both IL-1 and TNF-alpha stabilise COX-2 mRNA, although long TNF-alpha treatment has an opposite effect, and simultaneous treatment of human macrophages with TNF-alpha and IL-1 may attenuate induction of COX-2 [127]. Excessive TNF-alpha also reduces PGE_2 expression in murine macrophages [128]. IL-1 enhances release of arachidonic acid [129]. TGF-beta1 activates basal and up-regulates the LPS-induced PGE_2 [130]. Several other cytokines including IFN-gamma [131], IFN-b [132], IL-4, IL-10, and IL-13 [133] inhibit production of PGE_2 triggered by LPS, IL-1, or TNF-alpha.

cAMP affects production of PGs

The bi-directionality of the influence of cAMP stable derivatives and cAMP-elevating compounds depends on the isoform of COX. They stimulate

expression of COX-2 and thus enhance production of PGs [134] in many cell types including human monocytes, granulosa cells, osteoblastic cells, and others. On the other hand, cAMP-elevating compounds exhibit inhibitory effects in cells expressing COX-1, *e.g.* endothelial cells [135]. Formation of PGs can be reduced by enhanced levels of adenosine which suppresses the release of arachidonic acid [136].

PLAUSIBLE MECHANISMS OF THE DUAL EFFECTS OF cAMP ON NITRIC OXIDE PRODUCTION

It can be concluded that the interference of cAMP ranges from no influence to stimulation or inhibition of immune-stimulated biosynthesis of NO. It should be noted, however, that the up-regulatory function prevails. Only enhancing or no effects have been observed when the compounds were applied alone; this may be expected taking into account the fact that iNOS activity is quiescent in immune-non-stimulated cells, and thus, conceivably, any respective inhibitory potential of compounds cannot manifest itself. Incidentally, ambiguous NO-activity is a typical feature of other cAMP-elevating compounds such as phosphodiesterase inhibitors [31, 137], and also of various adenosine receptor agonists [25, 32, 138-140]. Typically, beta-adrenergic agonists [8], direct activators of adenylyl cyclase forskolin [31] and cholera toxin [19], as well as adenosine itself [25, 140] mostly up-regulate NO production. On the other hand, pituitary adenylate cyclase-activating hormone (PACAP) and vasoactive intestinal peptide (VIP), the physiological stimulators of adenylyl cyclase, inhibit production of NO [141, 142]. It is not quite clear what might be the direct, *i.e.* cAMP-independent effects of cAMP-elevating compounds, that could theoretically either synergise or counter-balance the NO-regulating activity of the originating cAMP.

Both transcriptional and post-transcriptional events have been implicated in the up-regulation of NO production stimulated by cAMP. Enhanced steady-state levels of iNOS mRNA result obviously from both increased transcription of the iNOS gene [16] and stabilisation of iNOS mRNA [9, 18]. Presumably, at least some of the effects could be due to an immediate early transciption factor CREB, *i.e.* cAMP response element (CRE)-binding protein, which mediates the cAMP-triggered expression of numerous genes. cAMP derivatives, and cAMP enhancers, such as forskolin, and isoproterenol (a pure beta-adrenergic agonist) are able to phosphorylate CREB [143, 144]. Besides, cAMP induces

transcription of some c-*fos* genes, which depend on the activity of other binding proteins, *e.g.* C/EBP (CCAAT/enhancer-binding protein) [145]. It has been found that cAMP and IL-1beta activate both C/EBPbeta and C/EBPdelta transcription factors that participate in the regulation of iNOS gene expression in rat mesangial cells [146], and together with NF-kappaB and CREB determine iNOS activation in vascular smooth muscle cells [147].

The direction and magnitude of cAMP effects on NO formation may be modified by many experimental conditions such as the type of cells and their tissue origin [148, 149]. They may produce differential amounts of cAMP depending on the expression of various isoforms of mammalian adenylyl cyclase [150], cyclic nucleotide phosphodiesterase [151], and cyclooxygenase [152], as well as on the diversity and distribution of receptors for corresponding cAMP-elevating ligands such as prostaglandins [153, 154], and adenosine itself [155]. The differential effects in cell types also seem to depend on differential regulation of NF-kappaB upon treatment with cAMP stable derivatives [32]. At least some of the controversial results might be attributed to the existence of multiple, both down- and up-regulatory feedback circuits between the initial (cAMP, PGs), intermediate (cytokines) and ultimate (NO) reaction participants (Figure 1) that may be influenced by the kind of primary NO-stimulator (LPS and/or various cytokines), dynamic oscillations in levels of cytokines resulting from timing of experiments, conditions *in vivo* or *in vitro*, etc.

In general, cAMP is a potent inhibitor of the production of a number of cytokines, including IFN-gamma and TNF-alpha, the crucial requirements for activation of iNOS. On the other hand, IL-10 has been uniformly found to be stimulated by cAMP [76]. From this point of view, the dominant positive influence of cAMP on NO production might rather seem to be a puzzle. In order to reconcile the opposing data on the interference of cAMP with NO production, several important facts should be taken into account. IL-10 is known to be a pleiotropic molecule with a plethora of immunostimulatory activities. For example, in combination with IL-2 it enhances the *in vitro* lymphokine-activated killer activity [156], up-regulates expression of IL-2 receptor alpha-chain (IL-2Ralpha) [157], soluble p75 TNF-R [158], IL-1 receptor antagonist (IL-1Ra) [159], and the Fc receptor for monomeric IgG (FcgammaRI) CD64 [160]. It also stimulates *in vitro* production of immunoglobulins [161], and similar to interferons, IL-10 activates the Jak/STAT pathway [162], and may stimulate expression of NF-kappaB [163], the factors which are important in iNOS transcription [79, 164]. Importantly, IL-10

has been found not only to inhibit the NO production [61, 62, 64, 65, 165-167], but also to stimulate it, especially in the presence of LPS, TNF-alpha and IFN-gamma [66, 67, 167-173]. In this context, it remains to be firmly established what is its NO-regulating role under the conditions of enhanced cAMP levels. It is important to note that the degree of suppression of TNF-alpha following treatment of cells with distinct cAMP-augmenting agents or cAMP derivatives is not necessarily complete; it depends on the type and concentration of an agent [174-176], and is in a dose-dependent manner inversely correlated with the increase in IL-10 secretion [177, 178]. Similarly, secretion of IFN-gamma may be completely or only moderately suppressed by various cAMP-enhancers [78, 137, 179]. Thus, the positive or negative regulation of NO production by cAMP could primarily be controlled by the ratio of enhanced levels IL-10 with respect to the differentially suppressed levels of NO up-regulatory cytokines, such as TNF-alpha, IFN-gamma. IL-1beta is unlikely to participate in this mechanism because it is much less affected by cAMP [76]. Expressed simply, the model presumes that mildly to moderately suppressed TNF-alpha and IFN-gamma can still activate iNOS expression, whereas their suppression can rather inhibit it. This hypothesis is supported by the fact that cAMP acts in a concentration-dependent biphasic manner: small elevations of cAMP stimulate, whereas high or sustained increase in cAMP inhibits production of NO [12, 35]. Incidentally, the ratio of IL-10 to IFN-gamma or IL-2 also influences the pro- or anti-inflammatory function of Th1 cells [180]. Although a synergistic co-operation of some, as yet undiscovered cAMP-activated factor cannot be ruled out, there seem to be presently no data that would endorse this possibility. Anyhow, this hypothetical factor could help to explain the fact that both cAMP derivatives and cAMP-elevating agents can, in some cases, elicit the NO expression on their own.

CONCLUSION

Cyclic AMP is a potent dual modulator of NO production. The influence, if any, is only stimulatory in immune-non-stimulated cells. Applied together with major immune activators such as LPS and/or cytokines, cAMP mostly stimulates NO, although exceptions frequently occur showing either no or inhibitory modulation. The effects seem to result from a highly integrated complex of underlying mechanisms, regulating the ultimate concentrations of cytokines. It is suggested that the crucial factor determining the direction of the action is the ratio of IL-10 with respect to other NO-regulatory cytokines (TNF-alpha, IFN-gamma) that are inversely influenced by cAMP.

Activation or suppression of NO production may be both beneficial or harmful to the host, depending on pathogenesis and actual state of a disease. As far as this important signaling and effector molecule is produced under *in vivo* conditions in man, these facts should carefully be considered in therapeutic targeting the cAMP levels.

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Figures

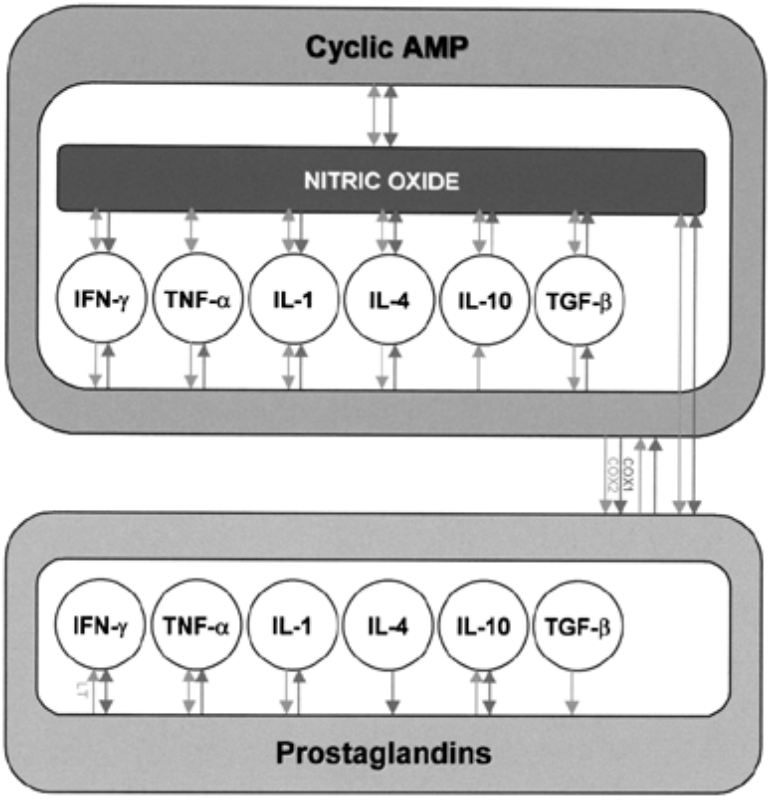


Figure 1

Multiple feedback circuits.

The scheme shows multiple functional interactions between cAMP, prostaglandins, cytokines, and nitric oxide. Involvement of prostaglandins is shown separately because it is not completely known whether their role within the system depends on their cAMP-enhancing effects, solely. The green arrows represent up-regulatory, red arrows down-regulatory activities. Ineffectiveness is not depicted.

Table 1
Dual interference of cAMP with NO production (reference list)

Compounds	Compounds alone		Compounds + immune stimuli		
	No effect	Stimulation	No effect	Stimulation	Suppression
cAMP stable derivatives	[8-12]	[14-17, 19, 20, 22]	[30, 34]	[8-12, 19, 23-26, 29-31]	[12, 33, 34]
Arachidonic acid metabolites	[12, 35, 46]	[36-39]	[43-45]	[12, 31, 40, 41]	[33, 35, 42, 43]

Authors

Z. Zidek

Laboratory of Molecular Immunopharmacology, Institute of Pharmacology, Academy of Sciences, Vídenská 1083, 14220 Prague, Czech Republic.

In this issue

Regulation of interferon-g receptor (INF-gR) chains: a peculiar way to rule the life and death of human lymphocytes.

P. Bernabei, A. Allione, L. Rigamonti, M. Bosticardo, G. Losana, I. Borghi, G. Forni, F. Novelli
human, IFN-g, IFN-g receptor, signal transduction, cellular proliferation, apoptosis.

The interleukin-6 cytokine system in embryonic development, embryo-maternal interactions and cardiogenesis.

P. Seiler, G. Plenz, M.C. Deng
interleukin-6, embryo, blastocyst, endometrium, heart, gp130.

Role of cytokines in the modulation of nitric oxide production by cyclic AMP.

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cyclic AMP, prostaglandins, nitric oxide, interleukin-10, tumor necrosis factor-a, interferon-g.

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TNF-a, idiopathic pulmonary fibrosis, polymorphism.

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interferon-g, cytokines, host defense, Pseudomonas aeruginosa, pneumonia.

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F.M. Becke, T. Hehlgans, G. Brockhoff, D.N. Männel
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interleukin-6, cord blood, gene polymorphism, inflammatory mediators.

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HCV-RNA, interleukin-10, H9 T cells, CD81, capsid mutation, protein kinase C.

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TNF, cytokine, LPS.

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apoptosis, caspases, Hsp27, Hsp70, T lymphocytes.

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MHC class II antigens, murine macrophages, c-Fos.

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MRC5, fibroblasts, TNF receptor, RT-PCR, binding, flow cytometry.

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cytokines, lipid mediators, macrophages, rat.

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apoptosis, interleukin-1, caspases, polymorphonuclear leukocytes, ICE.

Rat interleukin-10: production and characterisation of biologically active protein in a recombinant bacterial expression system.

V. Ball, S. Vigues, C.K. Gee, S. Poole, A.F. Bristow
IL-10, recombinant, rat, cytokines.

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