Cancer Immunol Immunother (1996) 43: 1–9

PERSPECTIVES

Pekka Uotila

The role of cyclic AMP and oxygen intermediates in the inhibition of cellular immunity in cancer

Received: 28 May 1996 / Accepted: 11 July 1996

Abstract Cell-mediated immunity is often impaired in cancer. This may be partly due to increased amounts of prostaglandin E_2 (PGE_2) and histamine in the blood of cancer patients, since PGE_2 and histamine possess inhibitory effects on cellular immunity. These effects are mediated by cyclic AMP (cAMP), which is increased in leukocytes by PGE_2 through EP2 and by histamine through H2 receptors and also by epinephrine through β2-adrenergic receptors. Increased cAMP activates protein kinase A, which inhibits the formation of interleukin 2 (IL-2) in T cells. The formation of interferon γ is concomitantly decreased, and cellular immunity is attenuated. In monocyte/macrophages the formation of IL-1β, IL-12 and tumor necrosis factor α is decreased by cAMP or through the increased formation of IL-10, which is up-regulated by cAMP. This attenuates cellular immunity. In monocytes histamine may decrease the formation of oxygen intermediates, which can induce apoptosis of natural killer cells and thus inhibit immunity. The superoxide anion is a potent inducer of the cyclooxygenase-2 enzyme, which is up-regulated in colorectal cancer. Cyclooxygenase-2 catalyzes the formation of PGE_2, e.g. in cancer cells. Thus the inhibition of cellular immunity in cancer may be at least partly mediated by cAMP and oxygen intermediates. This may offer new options for cancer immunotherapy.

Key words Cancer immunology · Cyclic AMP · Oxygen intermediates · Prostaglandin E_2 · Histamine

Introduction

The cell-mediated immunity of cancer patients is often impaired and the defense system is not able to kill cancer cells [35, 98]. The leukocytes of cancer patients can, however, be stimulated in vitro to obtain normal cytotoxicity [104]. This indicates that some factors in the blood of cancer patients might prevent the normal activation and function of the defense system.

P. Uotila
Departments of Physiology and Clinical Physiology,
University of Turku, Kiinamyllynkatu 10,
SF-20520 Turku, Finland
Fax: +358 2 2502610; e-mail: pekka.uotila@utu.fi

Activation of the defense system

The human defense system is divided into humoral (antibody-dependent) and cell-mediated immunity. The antitumor activity of the defense system is mainly mediated by cellular immunity. The activity of both the antibody- and the cell-mediated defense systems is regulated by cytokines (interleukins, interferons and tumor necrosis factors) secreted mainly from helper T cells and monocyte/macrophages. Humoral immunity is stimulated by interleukin 4 (IL-4) from helper T cells and is inhibited by interferon γ (IFNγ) [88]. Cell-mediated immunity is stimulated by IL-1β and IL-12 from monocyte/macrophages and by IL-2 and IFNγ from helper T cells [20, 88, 100, 112]. Because IL-4 inhibits the formation of IL-1β and tumor necrosis factor α (TNFα), IL-4 and IFNγ have opposite effects: IL-4 stimulates humoral and inhibits cell-mediated immunity, whereas IFNγ stimulates cell-mediated and inhibits humoral immunity [23, 27, 40, 88, 90].

The cell-mediated defense is activated when a macrophage presents an antigen to helper T cells [26]. This can stimulate macrophages to secrete IL-1β and helper T cells to secrete IL-2 [20, 102]. IL-1β enhances the formation of IL-2 in T cells (Fig. 1) [20] and IL-2 stimulates helper T cells to divide and to form IFNγ [22, 102]. IL-2 stimulates cytotoxic T and natural killer (NK) cells directly and through the formation of IFNγ [18, 66, 102].

IFNγ augments the formation of IL-1β, IL-12 and TNFα and thus the cytotoxicity of monocyte/macrophages (Fig. 1) [4, 11, 41, 81, 112, 113]. IL-12 increases the formation of IFNγ in T and NK cells and stimulates the cytotoxicity of NK cells (Fig. 1) [14, 60, 100, 112, 114]. IL-1β is also needed for the optimal formation of IFNγ [30, 100]. Thus

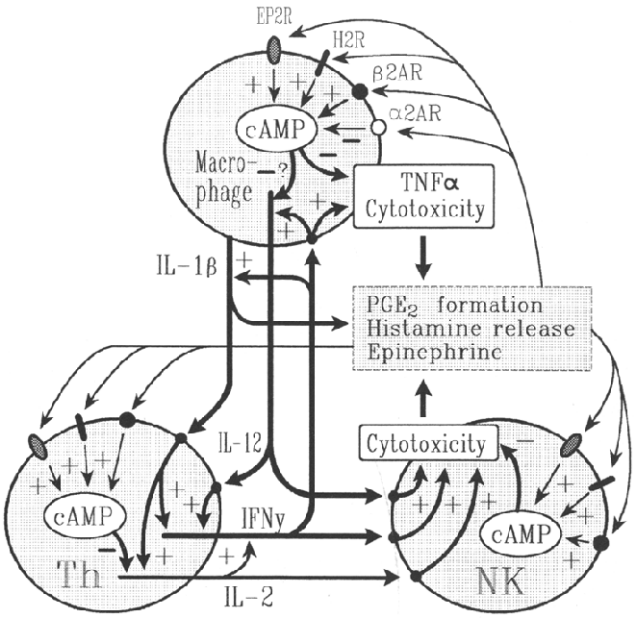

Fig. 1 The activation of the cell-mediated defense and its inhibition by feedback mediators. Interleukin-1β (*IL-1β*) stimulates the formation of IL-2 and interferon γ (*IFNγ*) in helper T cells (*Th*). IFNγ formation is also increased by IL-2 and IL-12. IFNγ stimulates the formation of IL-1β, IL-12 and tumor necrosis factor α (*TNFα*) in monocyte/macrophages and the cytotoxicity of these cells. The cytotoxicity of natural killer cells (*NK*) is enhanced by IL-2, IFNγ and IL-12. Cellular immunity is inhibited by prostaglandin E_2 (*PGE_2*), histamine and epinephrine, which enhance cAMP in macrophages, T and NK cells. Increased cAMP inhibits the formation of IL-2, IFNγ, TNFα and IL-12 and the cytotoxicity of macrophages and NK cells. The cAMP-enhancing effects of PGE_2 are mediated through EP2 or EP4 receptors and those of histamine by H2 receptors (*H2R*). β2-Adrenergic receptors (*β2AR*) mediate the cAMP-enhancing effect of epinephrine. In monocyte/macrophages the cAMP-decreasing effects of epinephrine and norepinephrine are mediated through α2-adrenergic receptors (*α2AR*). + a stimulating effect; – an inhibitory effect

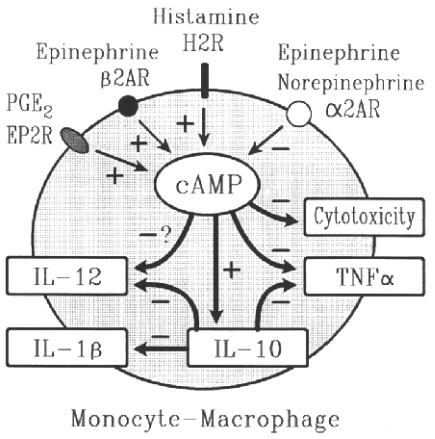

Fig. 2 The regulation of cytokine formation by cAMP in monocytes and macrophages. cAMP in monocyte/macrophages is increased by PGE_2 through EP2 (or EP4) and by histamine through H2 receptors. Epinephrine can increase cAMP through β2-adrenergic receptors and decrease it with norepinephrine through α2-adrenergic receptors (*α2AR*). Increased cAMP stimulates the formation of IL-10, which inhibits the formation of IL-1β, IL-12 and TNFα. Increased cAMP may also decrease the formation of TNFα and IL-12 directly. Increased cAMP attenuates the cytotoxicity of monocyte/macrophages

the cell-mediated cytotoxicity is activated by a positive-feedback chain: IL-1β, IL-2, IFNγ and IL-12 (Fig. 1).

Inhibition of cell-mediated immunity by cyclic AMP

The activity of the cell-mediated defense is inhibited by IL-4 and also by other mediators, such as prostaglandin E_2 (PGE_2), histamine and epinephrine [43, 88, 115]. The amounts of PGE_2 and histamine are often increased in cancer [10, 64, 74, 79, 80, 96]. Also some oxygen intermediates possess inhibitory effects on cellular immunity, because they can stimulate PGE_2 formation and induce apoptosis of NK cells (see below).

In monocyte/macrophages and lymphocytes the effects of PGE_2, histamine and epinephrine on cytokine formation are mediated through receptors, which activate adenylate cyclase and thus increase the amount of cyclic AMP in these cells (Fig. 1) [33, 47, 53, 56, 61]. Increased cAMP then down-regulates the formation of TNFα and IL-12 in monocyte/macrophages and the formation of IL-2 and its receptor proteins in helper T cells (Fig. 1) [2, 63, 65, 72, 97, 108, 117]. The formation of IFNγ is concomitantly decreased (Fig. 1) [22].

The cytotoxicity of NK cells is decreased by increased cAMP, because cAMP decreases the ability of NK cells to bind with target cells [94] and because the formation of NK-cell-stimulatory cytokines, IL-2, IFNγ and IL-12, is decreased by cAMP (Fig. 1). In human NK cells IL-12 up-regulates the mRNA of the pore-forming protein perforin and the serine esterase granzyme B, which are important cytotoxic cell granule-associated proteins [6].

The formation of IL-12 was found to be inhibited in human blood cultures by PGE_2 and other cAMP-elevating agents and also by IL-10 (Fig. 2) [117]. Because whole blood was used, it is possible that the inhibition was mediated either by the action of cAMP in monocyte/macrophages or through the decreased formation of IL-2 and IFNγ (Figs. 1, 2). In any case, IL-10 had a direct inhibitory effect on IL-12 formation [117]. IL-10 also decreases the formation of IL-1β and TNFα in monocyte/macrophages (Fig. 2) [18, 19, 29, 93, 117]. The inhibitory effects of IL-10 are also related to cAMP, because the formation of IL-10 is stimulated by increased cAMP (Fig. 2) [107, 117]. Thus cAMP inhibits cytokine formation both directly and through the formation of IL-10.

The cAMP-elevating effects of PGE_2 are mediated through EP2 (or EP4) receptors [16, 47] and those of histamine through histamine-2 receptors (H2R, Figs. 1. 2) [21, 33, 56]. The cAMP-enhancing effects of epinephrine in monocyte/macrophages and lymphocytes are mediated mainly through the β2-adrenergic receptors (β2AR), because most of the β-adrenergic receptors in leukocytes are of the β2 subtype [13, 25, 57, 61]. Because epinephrine is over tenfold more specific a ligand for β2AR than is norepinephrine [25], the ability of norepinephrine to increase cAMP in leukocytes through β2A receptors is limited.

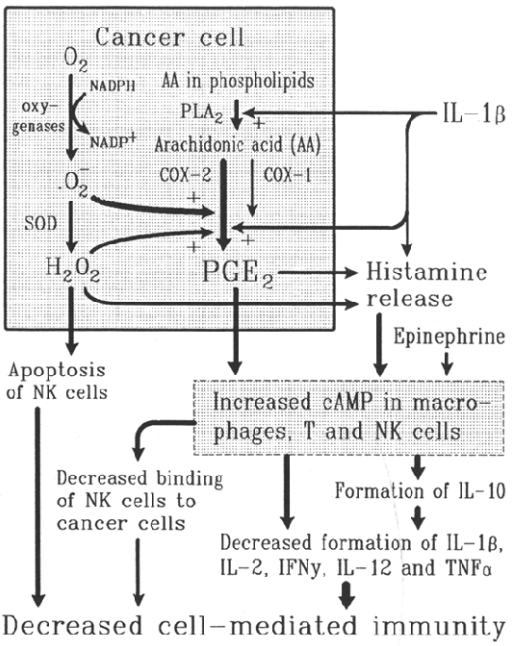

Fig. 3 Cell-mediated immunity may be inhibited in cancer by increased cAMP and oxygen intermediates. IL-1β may increase the formation of eicosanoids, including prostaglandin E_2 (*PGE_2*), by stimulating phospholipase A_2 (*PLA_2*) and cyclooxygenase-2 (*COX-2*) activity. COX-2 may also be up-regulated by superoxide anions ($\cdot O_2^-$) and hydrogen peroxide (*H_2O_2*). The superoxide anion is formed from molecular oxygen by NADPH-dependent reactions catalyzed by different oxygenases and is converted to hydrogen peroxide by superoxide dismutase (*SOD*). Hydrogen peroxide (or its metabolite) can induce apoptosis of NK cells and thus decrease cellular immunity. The blood level of histamine may be increased, because histamine release is stimulated by hydrogen peroxide, IL-1β and PGE_2. The amount of cAMP can be increased by PGE_2, histamine and epinephrine in monocyte/macrophages, T and NK cells. Increased cAMP may inhibit the binding of NK cells to cancer cells and the formation of IL-1β, IL-2, IFNγ, IL-12 and TNFα either directly or through the enhanced formation of IL-10. This should attenuate cell-mediated immunity

EP2, H2 and β2A receptors have similarities in their structures (seven transmembrane domains) and they activate adenylate cyclase when the ligand is bound to the receptor [25, 33, 47, 53, 61]. Adenylate cyclase catalyses the conversion of ATP to cAMP [9, 53]. cAMP activates protein kinase A, which phosphorylates some specific proteins [9, 53].

Monocytes and macrophages also possess α2-adrenergic receptors (α2AR) [105]. The binding of a ligand, such as epinephrine, to α2A receptors inhibits the activity of adenylate cyclase and thus attenuates the formation of cAMP (Fig. 2) [62, 105, 106]. Epinephrine is only about fourfold more specific a ligand for α2A receptors than is norepinephrine [62]. Thus norepinephrine is a relatively more specific ligand for α2- than for β2-adrenergic receptors [25, 62]. Therefore in macrophages the level of cAMP is decreased by norepinephrine (through α2A receptors) and the formation of TNFα is up-regulated [105]. Epinephrine, however, increases the level of cAMP in macrophages (through β2A receptors) and thus decreases the formation of TNFα (Fig. 2) [101, 106]. This effect of epinephrine can be abolished by β2-adrenergic receptor antagonists [101, 106].

The cytotoxicity of human NK cells is clearly decreased by epinephrine and histamine, and this inhibition is abolished by β2A and H2 receptor antagonists, respectively [43, 55]. PGE_2 inhibits the ability of human NK cells to bind with tumor cells by increasing cAMP in NK cells and thus attenuates tumor cell killing [37, 94].

Increased amounts of prostaglandin E_2 in cancer

The amounts of prostaglandins, such as PGE_2, are increased in colorectal and lung cancer tissues [10, 74, 80, 96]. Increased levels of PGE_2 are also detected in local venous blood draining from colorectal cancer and in peripheral venous blood (from the antecubital vein) of colorectal cancer patients with metastases in liver or lung [64, 80].

The rate of formation of PGE_2 in activated monocyte/macrophages and cytotoxic T cells is high enough to inhibit the activity of NK cells [34, 91]. This inhibition is abolished by indomethacin [34].

PGE_2 and other eicosanoids of the 2 series are formed from arachidonic acid by the cyclooxygenase pathway when arachidonic acid is released from cellular phospholipids by phospholipase A2 (Fig. 3) [116]. Arachidonic acid can be metabolized also by different lipoxygenases to hydroperoxides, hydroxy acids and leukotrienes [116].

There are two different cyclooxygenases: the constitutive cyclooxygenase-1 and the inducible cyclooxygenase-2 [52, 85]. The inducible enzyme is clearly up-regulated in colorectal cancer tissue, but the activity of cyclooxygenase-1 is unchanged or slightly decreased when compared to control tissue [24, 54, 99]. This is in good agreement with reports that the amount of PGE_2 is increased in colorectal cancer tissue and local venous blood.

The inducible cyclooxygenase-2 is less sensitive than cyclooxygenase-1 to the inhibitory effects of many antiinflammatory drugs [75, 78]. The concentration of indomethacin, which is needed for a 50% inhibition in the activity of cyclooxygenase-2, is 50- to 60-fold higher than the IC_{50} value for cyclooxygenase-1 [78]. Therefore high doses of antiinflammatory drugs, such as indomethacin, are needed to inhibit prostaglandin formation in cancer and other cells when cyclooxygenase-2 is stimulated.

IL-1β and TNFα can stimulate the formation of PGE_2 in cancer cells, including chondrosarcoma, fibrosarcoma and carcinoma [67, 76]. The stimulatory effect of IL-1β is very clear (about a tenfold increase) and that of TNFα is weaker (about a twofold increase) [67, 76]. The rate of PGE_2 formation in cancer cells is increased by IL-1β obviously because IL-1β stimulates both phospholipase A2 and cyclooxygenase-2 (Fig. 3) [52, 85, 87]. The activity of cyclooxygenase-1 is not changed by IL-1β [85].

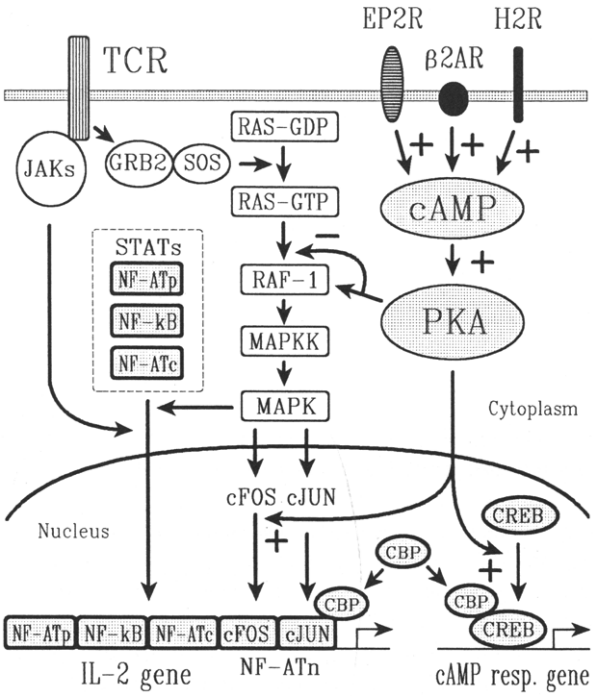

Fig. 4 A proposed mechanism for the inhibition of IL-2 gene expression in helper T cells by cAMP and protein kinase A (*PKA*). In helper T cells cAMP is increased by PGE_2, histamine and epinephrine through EP2, H2 and β2A receptors respectively. Increased cAMP activates PKA, which phosphorylates the regulatory domain of Raf-1 and thus inhibits the binding of activated Ras to Raf-1. Therefore the signal transduction from T cell receptors (*TCR*) through the Ras pathway is inhibited and mitogen-activated protein kinase (*MAPK*) is not activated. Activated MAPK phosphorylates both cytoplasmic signal transducers and activators of transcription (STAT proteins) and nuclear proteins, such as cFos and cJun. This phosphorylation is obviously a necessity for the binding of these transcription factors to the IL-2 gene and thus for gene expression. IL-2 gene expression is therefore inhibited when PKA prevents the activation of MAPK. Activated PKA can stimulate the expression of the cFos gene, but not that of cJun. Because PKA can phosphorylate and activate cAMP-response-element-binding protein (*CREB*), PKA may stimulate the expression of some cAMP-responsive genes when it inhibits the expression of other genes, e.g. that of IL-2 [95]. *CBP* (CREB-binding protein) is a common nuclear factor, which can be bound to phosphorylated cJun and CREB proteins [5]. MAPKK = mitogen-activated protein kinase kinase

Up-regulation of cyclooxygenase-2 by oxygen intermediates

The activity of cyclooxygenase-2 is up-regulated by IL-1β, TNFα, superoxide anion ($\cdot O_2^-$) and hydrogen peroxide (H_2O_2) [28, 52, 85]. Thus IL-1β and TNFα, which stimulate cell-mediated immunity, tend to enhance the formation of PGE_2 by up-regulation of cyclooxygenase-2. On the other hand, cyclooxygenase-2 is down-regulated by IL-4 and IL-10, which inhibit cellular immunity [77, 82]. IL-4 attenuates the stimulated production of superoxide anions and hydrogen peroxide in human monocyte/macrophages [1, 68]. Cyclooxygenase-2 is clearly up-regulated by superoxide anions and only slightly by hydrogen peroxide (Fig. 3) [28]. Since scavengers of reactive oxygen intermediates inhibited cyclooxygenase-2 expression induced by IL-1β and TNFα, reactive oxygen intermediates are probably involved in the up-regulation of this enzyme [28]. Thus oxygen intermediates seem to mediate inhibition in the regulation of cellular immunity.

The superoxide anion is formed from molecular oxygen by NADPH-dependent reactions catalyzed by oxygenases, such as different cytochrome *P*-450 isoenzymes, lipoxygenases and cyclooxygenases (Fig. 3) [31, 38]. When these oxygenases are up-regulated more superoxide anions might be formed than are used in reactions catalyzed by these oxygenases. Therefore the amounts of superoxide anion and other oxygen intermediates are probably increased.

Superoxide anions are converted to hydrogen peroxide by superoxide dismutase and also spontaneously [31]. Hydrogen peroxide can be inactivated by catalase or converted by myeloperoxidase to highly reactive hydroxyl radicals or hypochlorous acid [31, 38]. Vitamin E is a lipid-soluble antioxidant and a scavenger of superoxide anions, hydroxyl radicals and other oxygen radicals, such as lipid peroxy radicals [31]. Therefore vitamin E is able to act as a brake on the spontaneous and continuous peroxidation of unsaturated fatty acids [38]. Lipid peroxides are known to stimulate the activity of cyclooxygenase-2 [103], therefore vitamin E might prevent its up-regulation. Ascorbic acid, vitamin C, is a water-soluble antioxidant and a scavenger of superoxide anions and hypochlorous acid [38]. Vitamin C is able to regenerate vitamin E by converting oxidized vitamin E into its active reduced form [38].

Since the activity of COX-2 is often up-regulated in cancer and increased amounts of PGE_2 have been detected in cancer tissue and its local venous blood, the concentration of PGE_2 in the vicinity of cancer cells should be high enough to increase cAMP in lymphocytes and monocyte/macrophages to inhibit cytokine formation and cell-mediated immunity (Fig. 3). Cyclooxygenase-2 may be up-regulated by IL-1β or reactive oxygen intermediates, such as superoxide anions and hydrogen peroxide (Fig. 3). One can assume that in cancer cells the rate of formation of superoxide anions is increased when the basal metabolic rate is enhanced because of the increased rate of mitosis. Significant amounts of hydrogen peroxide are also released from neutrophils and activated monocyte/macrophages [86].

The Janus faces of histamine

The blood level of histamine is increased in patients with solid malignant tumors and it is decreased to the control level after the removal of the tumor [79]. Histamine release from basophils and mast cells is stimulated by antigens and also by other factors such as IL-1β [109]. Prostaglandins of the E series and other eicosanoids, such as leukotrienes, are reported to increase the release of histamine [110, 116]. Hydrogen peroxide can stimulate histamine release from basophils [86].

Histamine has both inhibitory and stimulatory effects on cell-mediated immunity, both effects being mediated

through H2 receptors. Inhibitory effects are mediated by cAMP through decreased formation of cytokines and stimulatory effects through decreased formation of reactive oxygen intermediates.

Histamine decreases the formation of TNFα and IL-2 in human monocytes and T cells respectively [21, 48]. This attenuates cellular immunity. These effects are mediated through increased cAMP and are inhibited by cimetidine, a blocking agent of H2 receptors [21, 48]. The cytotoxicity of NK cells is decreased by histamine through H2 receptors (Fig. 1) [55]. These inhibitory effects of histamine on cellular immunity may also have clinical consequences, because cimetidine is reported to prolong the survival time of gastric cancer patients [111].

The effects of various H2 receptor antagonists are different, since cimetidine increased the cytotoxicity of human NK cells in vitro whereas ranitidine did not [42]. Clear differences have also been detected in animal experiments, since high doses of cimetidine reduced and ranitidine increased pulmonary metastases in mice [45]. This indicates that some effects of cimetidine are mediated by other means than through H2 receptors.

In monocytes histamine decreases the formation of reactive oxygen metabolites, which induce apoptosis of NK cells and thus inhibit the cytotoxicity of NK cells [39, 46]. The formation of these oxygen metabolites is decreased by histamine through H2 receptors and is correspondingly stimulated by a specific H2-receptor-blocking agent ranitidine [44, 46]. Because the formation of these oxygen intermediates is NADPH-dependent [46], they are obviously formed from superoxide anions generated in NADPH-dependent oxygenase reactions. Superoxide anions are then converted to hydrogen peroxides by superoxide dismutase [31].

The rate of hydrogen peroxide formation is inhibited by histamine in monocytes [46]. Hydrogen peroxide inhibits the cytotoxicity of NK cells and stimulates their apoptosis [39, 46]. The suppressive effects of monocytes and hydrogen peroxide on NK cells are readily abolished by catalase and partially prevented by an inhibitor of myeloperoxidase [39, 46]. This indicates that inhibitory oxygen intermediates could be formed from hydrogen peroxide by myeloperoxidase [39].

The NADPH-dependent formation of hydrogen peroxide is decreased in vitro by cimetidine but not by ranitidine [8]. The inhibition is due to the binding of cimetidine to cytochrome *P*-450 isoenzymes [8, 59, 92]. Because cimetidine is an effective inhibitor of several cytochrome *P*-450 isoenzymes, the NADPH-dependent formation of superoxide anions should also be decreased by cimetidine [59, 89]. Ranitidine has about tenfold lower binding activity to cytochrome *P*-450 than has cimetidine [92]; therefore, the activity of cytochrome *P*-450 is not changed significantly by ranitidine [92].

The inhibitory effects of cimetidine are so clear that cytochrome *P*-450-dependent metabolism of several drugs and endogenous compounds is attenuated significantly [32, 92]. Thus it is reasonable to assume that cimetidine would partially inhibit the formation of reactive oxygen intermediates in monocytes when the inhibitory effects of histamine are prevented by the H2 receptor antagonist cimetidine. The inhibitory effects of cimetidine on cytochrome *P*-450 could also explain differences in the effects of cimetidine and ranitidine on cellular immunity.

The role of cyclic AMP and protein kinase A

The amount of cAMP in cells is controlled, on the one hand, by the activity of adenylate cyclase, which catalyses the conversion of ATP to cAMP, and, on the other hand, by phosphodiesterase, which degrades cAMP [53]. Stimulatory signals for adenylate cyclase are transduced from receptors (such as EP2, H2 and β2A receptors) at the cell membrane by stimulatory G-proteins, when ligands (PGE_2, histamine or epinephrine) are bound to the corresponding receptors [53]. Suppressive signals are transduced from inhibitory receptors (e.g. α2A receptors) by inhibitory G-proteins [53]. These stimulatory and inhibitory G-proteins collect stimulatory and inhibitory signals and thus regulate the activity of adenylate cyclase and the level of cAMP in each cell. In cancer tissues the activity of adenylate cyclase and the level of cAMP might be increased, because cyclooxygenase-2 is often up-regulated and the formation of PGE_2 is thus increased, and because the blood level of histamine can be elevated [10, 24, 54, 74, 79, 80, 96, 99].

cAMP executes its effects through the activation of protein kinase A, which phosphorylates differents proteins, such as other kinases or transcription factors, and thus regulates gene expression (Fig. 4) [9, 53]. PGE_2 inhibits the expression of IL-2 and its receptor gene in human T cells through increased cAMP and activation of protein kinase A, since the decrease in gene expression is prevented with an inhibitor of this enzyme [2].

A proposed mechanism for the inhibition of IL-2 formation by protein kinase A in helper T cells is presented in Fig. 4. When ligands are bound to specific T cell receptors, signals for IL-2 gene expression are transduced to the nucleus obviously through the Janus kinase and Ras pathways (Fig. 4). Janus kinases phosphorylate cytoplasmic STAT (signal transducers and activators of transcription) proteins, which are translocated into the nucleus [7, 49]. In the Ras pathway the signal is carried by consecutive phosphorylation and activation of several proteins to mitogen-activated protein kinase (MAPK), which phosphorylates serine in STAT proteins and stimulates the formation and/or activation of cFos and cJun proteins [7, 70].

Nuclear factors necessary for IL-2 gene expression include both cytoplasmic STAT proteins (e.g. NF-ATp, NF-ATc and NF-kB) [50, 69, 73, 84] and the nuclear component of nuclear factors (NF-ATn), which includes cFos and cJun proteins (Fig. 4) [49, 51, 58, 83]. The signal transduction through the Ras-Raf-MAPKK-MAPK cascade may be inhibited by protein kinase A, because activated protein kinase A phosphorylates the regulatory domain of Raf-1 and thus inhibits its binding to Ras (Fig. 4) [17, 71,

118]. This prevents the activation of MAPK. Therefore STAT, cFos and cJun proteins are not phosphorylated by MAPK and IL-2 expression is inhibited.

Activated protein kinase A may, however, stimulate expression of the cFos gene directly [12, 15, 95]. Therefore cFos is formed, but cJun is not. The expression of the IL-2 gene is, however, not stimulated, because cJun is necessary for an active NF-ATn, since only diheteromers of cFos and cJun or dihomomers of cJun are good transactivators of the IL-2 gene [3]. Thus increased cAMP inhibits IL-2 gene expression through the activation of protein kinase A (Fig. 4). cAMP is increased in helper T cells by PGE_2, histamine and epinephrine through EP2, H2 and β2A receptors (Fig. 4).

Therapeutic implications

Cell-mediated immunity is decreased in cancer by oxygen intermediates and other factors, such as PGE_2 and histamine, which mediate their inhibitory effects through their receptors, which activate adenylate cyclase e.g. in leukocytes and thus increase the amount of cAMP (Figs. 1–3). The known inhibitory effects of oxygen intermediates on immunity are due to the up-regulation of cyclooxygenase-2 and the induction of apoptosis in NK cells.

Increased cAMP activates protein kinase A, which inhibits the expression of the genes for several cytokines either directly or through the increased formation of IL-10 (Figs. 2, 4). The formation of cytokines, which stimulate cellular immunity, is thus attenuated [2, 63, 65, 72, 97, 108, 117]. Also the binding of NK cells to tumor cells is decreased (Fig. 3) [94]. Therefore the activity of the cell-mediated defense is attenuated and cancer cells may not be destroyed.

The inhibition of immunity by cAMP is a part of the normal regulation of cell-mediated defense. In cancer patients this inhibition may, however, be exceptionally strong especially in the vicinity of cancer cells, since cancer cells may produce large amounts of PGE_2 and the blood level of histamine may also be increased (Fig. 3) [10, 64, 67, 74, 76, 79, 80]. Therefore the defense may not be able to destroy cancer cells.

The formation of PGE_2 can be blocked by inhibitors of the cyclooxygenases. The doses of traditional inhibitors, such as indomethacin, should be high, because cyclooxygenase-2 is often up-regulated in cancer and because high concentrations of traditional inhibitors are needed to inhibit the enzyme [52, 75, 78, 85].

When the cyclooxygenase pathway is inhibited, the formation of leukotrienes may be increased and they may stimulate histamine release, which is enhanced also by oxygen intermediates and IL-1β (Fig. 3) [86, 109, 116]. Because the histamine concentration may be increased, it could be useful to prevent the cAMP-elevating effect of histamine by a H2 receptor antagonist, such as cimetidine, which prevents the effects of histamine on cytokine formation and thus stimulates cellular immunity.

Blocking H2 receptors may increase in monocytes the formation of hydrogen peroxide, which (or its metabolite) may induce apoptosis of NK cells and thus attenuate cellular immunity [46]. Cimetidine, however, obviously inhibits hydrogen peroxide formation because it inhibits several cytochrome *P*-450 isoenzymes and thus attenuates the formation of superoxide anions and hydrogen peroxide [8, 59, 89]. Therefore cimetidine seems to be more suitable for cancer immunotherapy than ranitidine, for example, which does not have any significant inhibitory effect on cytochromes *P*-450 [92].

Because cimetidine attenuates the gastrointestinal side-effects of indomethacin, a long-term treatment with high doses of indomethacin should be possible to stimulate the cell-mediated defense to destroy cancer cells. The activity of the cell-mediated cytotoxicity can further be enhanced by a β2-adrenergic receptor antagonist, which removes the cAMP-enhancing effects of epinephrine, but leaves the cAMP-decreasing α2-adrenergic receptors intact. In addition cellular cytotoxicity may be stimulated also by agonists of α2-adrenergic receptors, such as clonidine [36], which decreases the level of cAMP.

Thus the cell-mediated immunity is probably stimulated in cancer by a combination of (a) an inhibitor of the cycloogenases (e.g. indomethacin), (b) an H2 receptor antagonist (e.g. cimetidine), (c) a β2-adrenergic-receptor-blocking agent and (d) an agonist of α2-adrenergic receptors (e.g. clonidine). Since the elimination half-life of cimetidine is only 2 h [92], the cimetidine dosage should be rather high and it should be divided into several daily doses to inhibit cytochrome *P*-450 isoenzymes so that the formation of oxygen intermediates is attenuated.

Experimental work

The author has successfully used this therapy for pulmonary metastases of chondrosarcoma now for 8 years. During the first 5 years both indomethacin (usually 200 mg daily) and cimetidine (earlier 1.6 g daily, recently 3.2 g) were used [115]. Later these drugs were combined with a β2-adrenergic-blocking agent, sotalol, and an α2-adrenergic receptor agonist, clonidine [36]. Vitamins C and E are used to decrease the amounts of oxygen intermediates [38]. Clinical trials are needed to assess the efficiency of this kind of treatment.

References

1. Abramson SL, Gallin JI (1990) IL-4 inhibits superoxide production by human mononuclear phagocytes. J Immunol 144: 625
2. Anastassiou ED, Paliogianni F, Balow JP, Yamada H, Boumpas DT (1992) Prostaglandin E_2 and other cyclic AMP-elevating agents modulate IL-2 and IL-2Rα gene expression at multiple levels. J Immunol 148: 2845

3. Angel P, Karin M (1991) The role of Jun, Fos and AP-1 complex in cell-proliferation and transformation. Biochim Biophys Acta 1072: 129
4. Arend WP, Gordon DF, Wood WM, Janson RW, Joskin FG, Jameel S (1989) IL-1β production in cultured human monocytes is regulated at multiple levels. J Immunol 143: 118
5. Arias J, Alberts AS, Brindle P, Claret FX, Smeal T, Karin M, Feramisco J, Montminy M (1994) Activation of cAMP and mitogen responsive genes relies on a common nuclear factor. Nature 370: 226
6. Aste-Amezaga M, D'Andrea A, Kubin M, Trinchieri G (1994) Cooperation of natural killer cell stimulatory factor/interleukin-12 with other stimuli in the induction of cytokines and cytotoxic cell-associated molecules in human T and NK cells. Cell Immunol 156: 480
7. Barinaga M (1995) Two major signaling pathways meet at MAP-kinase. Science 269: 1673
8. Bast A, Savenije-Chapel EM, Kroes BH (1984) Inhibition of mono-oxygenase and oxidase activity of rat-hepatic cytochrome *P*-450 by H_2-receptor blockers. Xenobiotica 14: 399
9. Bauman GP, Bartik MM, Brooks WH, Roszman TL (1994) Induction of cAMP-dependent protein kinase (PKA) activity in T cells after stimulation of the prostaglandin E_2 or the β-adrenergic receptors: relationship between PKA activity and inhibition of anti-CD3 monoclonal antibody-induced T cell proliferation. Cell Immunol 158: 182
10. Bennet A, Civier A, Hensby CN, Melhuish PB, Stamford IF (1987) Measurement of arachidonate and its metabolites extracted from human normal and malignant gastrointestinal tissues. Gut 28: 315
11. Beutler B, Van Huffel C (1994) Unraveling function in the TNF ligand and receptor families. Science 264: 667
12. Bravo R, Nueberg M, Burckhardt J, Almendral J, Wallich R, Müller R (1987) Involvement of common and cell type-specific pathways in c-fos gene control: Stable induction by cAMP in macrophages. Cell 48: 251
13. Brodde O-E, Engel G, Hoyer D, Bock KD, Weber F (1981) The β-adrenergic receptor in human lymphocytes: subclassification by the use of a new radioligand (+)-^{125}iodocyanopindolol. Life Sci 29: 2189
14. Chan SH, Perussia B, Gupta JW, Kobayashi M, Pospisil M, Young HA, Wolf SF, Young D, Clark SC, Trinchieri G (1991) Induction of interferon γ production by natural killer cell stimulatory factor: characterization of the responder cells and synergy with other inducers. J Exp Med 173: 869
15. Chiu R, Angel P, Karin M (1989) Jun-B differs in its biological properties from, and is a negative regulator of, cJun. Cell 59: 979
16. Coleman RA, Smith WL, Narumiya S (1994) VIII International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. Pharmacol Rev 46: 205
17. Cook SJ, McCormick F (1993) Inhibition by cAMP of Ras-dependent activation of Raf. Science 262: 1069
18. D'Andrea A, Aste-Amezaga M, Valiante NM, Ma X, Kubin M, Trinchieri G (1993) Interleukin 10 (IL-10) inhibits human lymphocyte interferon γ-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. J Exp Med 178: 1041
19. De Waal Malefyt R, Abrams J, Bennett B, Figdor CG, De Vries JE (1991) Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. J Exp Med 174: 1209
20. Di Giovine F, Duff GW (1990) Interleukin 1: the first interleukin. Immunol Today 11: 13
21. Dohlsten M, Sjögren HO, Carlsson R (1987) Histamine acts directly on human T cells to inhibit interleukin-2 and interferon-γ production. Cell Immunol 109: 65
22. Dohlsten M, Hedlund G, Fischer H, Sjögren HO, Carlsson R (1989) Proliferation of human $CD4^+45R^+$ and CD^+45R^- T helper cells is promoted by both IL-2 and IL-4 while interferon-gamma production is restricted to IL-2 activated $CD4^+45R^-$ T cells. Immunol Lett 20: 29
23. Donnelly RP, Fenton MJ, Kaufmann JD, Gerrard TL (1991) IL-1 expression in human monocytes is transcriptionally and posttranscriptionally regulated by IL-4. J Immunol 146: 3431
24. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, Dubois RN (1994) Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 107: 1183
25. Emorine LJ, Marullo S, Delavier-Klutchko C, Kaveri SV, Durieu-Trautmann O, Strosberg AD (1987) Structure of the gene for human β_2-adrenergic receptor: expression and promoter characterization. Proc Natl Acad Sci USA 84: 6995
26. Engelhard VH (1994) How cells process antigens. Sci Am 271: 44
27. Essner R, Rhoades K, McBride WH, Morton DL, Economou JS (1989) IL-4 down-regulates IL-1 and TNF gene expression in human monocytes. J Immunol 142: 3857
28. Feng L, Xia Y, Garcia GE, Hwang D, Wilson CB (1995) Involvement of reactive oxygen intermediates in cyclooxygenase-2 expression induced by interleukin-1, tumor necrosis factor-α, and lipopolysaccharide. J Clin Invest 95: 1669
29. Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A (1991) IL-10 inhibits cytokine production by activated macrophages. J Immunol 147: 3815
30. Fischer H, Hedlund G, Kalland T, Sjögren HO, Dohlsten M (1990) Independent regulation of IFN-γ and tumor necrosis factor by IL-1 in human T helper cells. J Immunol 145: 3767
31. Freeman BA, Crapo JD (1982) Biology of disease: free radicals and tissue injury. Lab Invest 47: 412
32. Galbraith RA, Michnovicz JJ (1989) The effects of cimetidine on the oxidative metabolism of estradiol. N Engl J Med 321: 269
33. Gantz I, Munzert G, Tashiro T, Schäffer M, Wang L, DelValle J, Yamada T (1991) Molecular cloning of human histamine H2 receptor. Biochem Biophys Res Commun 178: 1386
34. Garcia-Penarrubia P, Bankhurst AD, Koster FT (1989) Prostaglandins from human T suppressor/cytotoxic cells modulate natural killer antibacterial activity. J Exp Med 170: 601
35. Gastl G, Niederwieser D, Marth C, Huber H, Egg D, Schuler G, Margreiter R, Braunsteiner H, Huber C (1984) Human large granular lymphocytes and their relationship to natural killer cell activity in various disease states. Blood 64: 288
36. Goodman Gilman A, Rall TW, Nies AS, Taylor P (1990) Goodman and Gilman's The pharmacological basis of therapeutics, 8th edn. Pergamon, New York
37. Goto T, Herberman RB, Maluish A, Strong DM (1983) Cyclic AMP as a mediator of prostaglandin E-induced suppression of human natural killer cell activity. J Immunol 130: 1350
38. Halliwell B, Gutteridge JMC (1991) Free radicals in biology and medicine, 2nd edn. Clarendon, Oxford
39. Hansson M, Asea A, Ersson U, Hermodsson S, Hellstrand K (1996) Induction of apoptosis in NK cells by monocyte-derived reactive oxygen metabolites. J Immunol 156: 42
40. Hart PH, Vitti GF, Burgess DR, Whitty GA, Piccoli DS, Hamilton JA (1989) Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor α, interleukin 1, and prostaglandin E_2. Proc Natl Acad Sci USA 86: 3803
41. Hart PH, Whitty GA, Piccoli DS, Hamilton JA (1989) Control by IFN-γ and PGE_2 of TNFα and IL-1 production by human monocytes. Immunology 66: 376
42. Hellstrand K, Hermodsson S (1987) Differential effects of histamine receptor antagonists on human natural killer cell activity. Int Arch Allergy Appl Immunol 84: 247
43. Hellstrand K, Hermodsson S (1989) An immunopharmacological analysis of adrenaline-induced suppression of human natural killer cell cytotoxicity. Int Arch Allergy Appl Immunol 89: 334
44. Hellstrand K, Hermodsson S (1990) A cell-to-cell mediated interaction involving monocytes and non-T/CD16+ natural killer (NK) cells is required for histamine H_2-receptor-mediated NK-cell activation. Scand J Immunol 31: 631
45. Hellstrand K, Asea A, Hermodsson S (1990) Role of histamine in natural killer cell-mediated resistance against tumor cells. J Immunol 145: 4365

46. Hellstrand K, Asea A, Dahlgren C, Hermodsson S (1994) Histaminergic regulation of NK cells. Role of monocyte-derived reactive oxygen metabolites. J Immunol 153: 4940
47. Honda A, Sugimoto Y, Namba T, Watabe A, Irie A, Negishi M, Narumiya S, Ichikawa A (1993) Cloning and expression of a cDNA for mouse prostaglandin E receptor EP_2 subtype. J Biol Chem 268: 7759
48. Hotermans G, Bury T, Radermecker MF (1991) Effect of histamine on tumor necrosis factor production by human monocytes. Int J Allergy Appl Immunol 95: 278
49. Ihle JN, Witthuhn BA, Quelle FW, Yamamoto K, Thierfelder WE, Kreider B, Silvennoinen O (1994) Signaling by the cytokine receptor superfamily; JAKs and STATs. Trends Biochem Sci 19: 222
50. Israel A (1994) NF-AT comes under control. Nature 369: 443
51. Jain J, McCaffrey PG, Valge-Archer VE, Rao A (1992) Nuclear factor of activated T cells contains Fos and Jun. Nature 356: 801
52. Jones DA, Carlton DP, McIntyre TM, Zimmerman GA, Prescott SM (1993) Molecular cloning of human prostaglandin endoperoxide synthase Type II and demonstration of expression in response to cytokines. J Biol Chem 268: 9049
53. Kammer GM (1988) The adenylate cyclase-cAMP-protein kinase A pathway and regulation of the immune response. Immunol Today 9: 222
54. Kargman SL, O'Neill GP, Vickers PJ, Evans JF, Mancini JA, Jothy S (1995) Expression of prostaglandin G/H synthase-1 and -2 protein in human colon cancer. Cancer Res 55: 2556
55. Katz P, Zaytoun AM, Fauci AS (1982) Mechanisms of human cell-mediated cytotoxicity. I. Modulation of natural killer cell activity by cyclic nucleotides. J Immunol 129: 287
56. Khan MM, Sansoni P, Engleman EG, Melmon KL (1985) Pharmacologic effects of autacoids on subsets of T cells. J Clin Invest 75: 1578
57. Khan MM, Sansoni P, Silverman ED, Engleman EG, Melmon KL (1986) Beta-adrenergic receptors on human suppressor, helper, and cytolytic lymphocytes. Biochem Pharmacol 35: 1137
58. Kishimoto T, Taga T, Akira S (1994) Cytokine signal transduction. Cell 76: 253
59. Knodell RG, Browne DG, Gwozdz GP, Brian WR, Guengerich FP (1991) Differential inhibition of individual human liver cytochromes *P*-450 by cimetidine. Gastroenterology 101: 1680
60. Kobayaski M, Fitz L, Ryan M, Hewick RM, Clark SC, Chan S, Loudon R, Sherman F, Perussia B, Trinchieri G (1989) Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biological effects on human lymphocytes. J Exp Med 170: 827
61. Kobilka BK, Dixon RA, Frielle T, Dohlman HG, Bolanowski MA, Sigal IS, Yang-Feng TL, Francke U, Caron MG, Lefkowitz RJ (1987) cDNA for the human β_2-adrenergic receptor: a protein with multiple membrane-spanning domains and encoded by a gene whose chromosomal location is shared with that of the receptor for platelet-derived growth factor. Proc Natl Acad Sci USA 84: 46
62. Kobilka BK, Matsui H, Kobilka TS, Yang-Feng TL, Francke U, Caron MG, Lefkowitz RJ, Regan JW (1987) Cloning, sequencing, and expression of the gene coding for the human platelet α_2-adrenergic receptor. Science 238: 650
63. Krause DS, Deutsch C (1991) Cyclic AMP directly inhibits IL-2 receptor expression in human T cells: expression of both p55 and p75 subunits is affected. J Immunol 146: 2285
64. Kubota Y, Sunouchi K, Ono M, Sawaka T, Muto T (1992) Local immunity and metastasis of colorectal carcinoma. Dis Colon Rectum 35: 645
65. Kunkel SL, Spengler M, May MA, Spengler R, Larrick J, Remick D (1988) Prostaglandin E_2 regulates macrophage-derived tumor necrosis factor gene expression. J Biol Chem 263: 5380
66. Kärre K, Hansson M, Kiessling R (1991) Multiple interactions at the natural killer workshop. Immunol Today 12: 343
67. Last-Barney K, Homon CA, Faanes RB, Merluzzi VJ (1988) Synergistic and overlapping activities of tumor necrosis factor-α and IL-1. J Immunol 141: 527
68. Lehn M, Weiser WY, Engelhorn S, Gillis S, Remold HG (1989) IL-4 inhibits H_2O_2 production and antileishmanial capacity of human cultured monocytes mediated by IFN-γ. J Immunol 143: 3020
69. Liou H-C, Baltimore D (1993) Regulation of the NK-kB/rel transcription factor and IkB inhibitor system. Curr Opin Cell Biol 5: 477
70. Marx J (1993) Forging a path to the nucleus. Science 260: 1588
71. Marx J (1993) Two major signal pathways linked. Science 262: 988
72. Mary D, Aussel C, Ferrua B, Fehlmann M (1987) Regulation of interleukin2 synthesis by cAMP in human T cells. J Immunol 139: 1179
73. McCaffrey PG, Luo C, Kerppola TK, Jain J, Badalian TM, Ho AM, Burgeon E, Lane WS, Lambert JN, Curran T, Verdine GL, Rao A, Hogan PG (1993) Isolation of cyclosporin-sensitive T cell transcription factor NFATp. Science 262: 750
74. McLemore TL, Hubbard WC, Litterst CL, Liu MC, Miller S, McMahon NA, Eggleston JC, Boyd MR (1988) Profiles of prostaglandin biosynthesis in normal lung and tumor tissue from lung cancer patients. Cancer Res 48: 3140
75. Meade EA, Smith WL, DeWitt DL (1993) Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal antiinflammatory drugs. J Biol Chem 268: 6610
76. Merluzzi VJ, Faanes RB, Czajkowski M, Last-Barney K, Harrison PC, Kahn J, Rothlein R (1987) Membrane-associated interleukin 1 activity on human U937 tumor cells: stimulation of PGE_2 production by human chondrosarcoma cells. J Immunol 139: 166
77. Mertz PM, DeWitt DL, Stetler-Stevenson WG, Wahl LM (1994) Interleukin 10 suppression of monocyte prostaglandin H synthase-2. J Biol Chem 269: 21322
78. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR (1993) Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci USA 90: 11693
79. Moriarty CM, Stucky JL, Hamburger KW, Patil KD, Foley JF, Koefoot RR (1988) Blood histamine and solid malignant tumors. J Cancer Res Clin Oncol 114: 588
80. Narisawa T, Kusaka H, Yamazaki Y, Takahashi M, Koyama H, Koyama K, Fukaura Y, Wakizaka A (1990) Relationship between blood plasma prostaglandin E_2 and liver and lung metastases in colorectal cancer. Dis Colon Rectum 33: 840
81. Newton RC (1985) Effect of interferon on the induction of human monocyte secretion of interleukin-1 activity. Immunol 56: 441
82. Niiro H, Otsuka T, Tanabe T, Hara S, Kuga S, Nemoto Y, Tanaka Y, Nakashima H, Kitajima S, Abe M, Niho Y (1995) Inhibition by interleukin-10 of inducible cyclooxygenase expression in lipopolysaccharide-stimulated monocytes: its underlying mechanism in comparison with interleukin-4. Blood 85: 3736
83. Northrop JP, Ullman KS, Crabtree GR (1993) Characterization of the nuclear and cytoplasmic components of the lymphoid-specific nuclear factor of activated T cells (NF-AT) complex. J Biol Chem 268: 2917
84. Northrop JP, Ho SN, Chen L, Thomas DJ, Timmerman LA, Nolan GP, Admon A, Crabtree GR (1994) NF-AT components define a family of transcription factors targeted in T-cell activation. Nature 369: 497
85. O'Banion MK, Winn VD, Young DA (1992) cDNA cloning and functional activity of glucocorticoid-regulated inflammatory cyclooxygenase. Proc Natl Acad Sci USA 89: 4888
86. Ogasawara H, Fujitani T, Drzewiecki G, Middleton E (1986) The role of hydrogen peroxide in basophil histamine release and the effect of selected flavonoids. J Allergy Clin Immunol 78: 321
87. Ozaki M, Morii H, Qvist R, Watanabe Y (1994) Interleukin-1β induces cytosolic phospholipase A2 gene in rat C6 glioma cell line. Biochem Biophys Res Commun 205: 12
88. Paul WE, Seder RA (1994) Lymphocyte responses and cytokines. Cell 76: 241

89. Pelkonen O, Breimer DD (1994) Role of environmental factors in the pharmacokinetics of drugs: considerations with respect to animal models, *P*-450 enzymes, and probe drugs: In: Welling PG, Balant LP (eds) Handbook of experimental pharmacology, vol 110. Pharmacokinetics of drugs. Springer, Berlin Heidelberg New York, pp 289
90. Pene J, Rousset F, Briere F, Chretien I, Paliard X, Banchereau J, Spits H, De Vries JE (1988) IgE production by normal human B cells induced by alloreactive T cell clones is mediated by IL-4 and suppressed by IFN-γ. J Immunol 141: 1218
91. Phipps RP, Stein SH, Roper RL (1991) A new view of prostaglandin E regulation of the immune response. Immunol Today 12: 349
92. Powell JR, Donn KH (1984) Histamine H_2-antagonist drug interactions in perspective: mechanistic concepts and clinical implications. Am J Med 77 [Suppl 5B]: 57
93. Ralph P, Nakoinz I, Sampson-Johannes A, Fong S, Lowe D, Min H-Y, Lin L (1992) IL-10, T lymphocyte inhibitor of human blood cell production of IL-1 and tumor necrosis factor. J Immunol 148: 808
94. Ramstedt U, Ng J, Wigzell H, Serhan CN, Samuelsson B (1985) Action of novel eicosanoids lipoxin A and B on human natural killer cell cytotoxicity: effects of intracellular cAMP and target cell binding. J Immunol 135: 3434
95. Riabowol KT, Fink JS, Gilman MZ, Walsh DA, Goodman RH, Feramisco JR (1988) The catalytic subunit of cAMP-dependent protein kinase induces expression of genes containing cAMP-responsive enhancer elements. Nature 336: 83
96. Rigas B, Goldman IS, Levine L (1993) Altered eicosanoid levels in human colon cancer. J Lab Clin Med 122: 518
97. Rincon M, Tugores A, Lopez-Rivas A, Silva A, Alonso M, De Landazuri MO, Lopez-Botet M (1988) Prostaglandin E_2 and the increase of intracellular cAMP inhibits the expression of interleukin-2 receptors in human T cells. Eur J Immunol 18: 1791
98. Ruco LP, Procopio A, Maccallini V, Calogero A, Uccini S, Annino L, Mandelli F, Baroni CD (1983) Severe deficiency of natural killer activity in the peripheral blood of patients with hairy cell leukemia. Blood 61: 1132
99. Sano H, Kawahito Y, Wilder RL, Hashiramoto A, Mukai S, Asai K, Kimura S, Kato H, Kondo M, Hla T (1995) Expression of cyclooxygenase-1 and -2 in human colorectal cancer. Cancer Res 55: 3785
100. Scott P (1993) IL-12: initiation cytokine for cell-mediated immunity. Science 26: 496
101. Severn A, Rapson NT, Hunter CA, Liew FY (1992) Regulation of tumor necrosis factor production by adrenaline and β-adrenergic agonists. J Immunol 148: 3441
102. Smith KA (1990) Interleukin-2. Sci Am 262: 26
103. Smith WL, Marnett LJ (1991) Prostaglandin endoperoxide synthase: structure and catalysis. Biochim Biophys Acta 1083: 1
104. Soiffer RJ, Robertson MJ, Murray C, Cochran K, Ritz J (1993) Interleukin-12 augments cytolytic activity of peripheral blood lymphocytes from patients with hematologic and solid malignancies. Blood 82: 2790
105. Spengler RN, Allen RM, Remick DG, Strieter RM, Kunkel SL (1990) Stimulation of α-adrenergic receptor augments the production of macrophage-derived tumor necrosis factor. J Immunol 145: 1430
106. Spengler RN, Chensue SW, Giacherio DA, Blenk N, Kunkel SL (1994) Endogenous norepinephrine regulates tumor necrosis factor-α production from macrophages in vitro. J Immunol 152: 3024
107. Strassmann G, Patil-Koota V, Finkelman F, Fong M, Kambayashi T (1994) Evidence for the involvement of interleukin 10 in the differential deactivation of murine peritoneal macrophages by prostaglandin E_2. J Exp Med 180: 2365
108. Strieter RM, Remick DG, Ham JM, Colletti LM, Lynch JP, Kunkel SL (1990) Tumor necrosis factor-alpha gene expression in human blood. J Leukoc Biol 47: 366
109. Subramanian N, Bray MA (1987) Interleukin 1 releases histamine from human basophils and mast cells in vitro. J Immunol 138: 271
110. Theoharides TC, Kops SR, Bondy PK, Askenase PW (1985) Differential release of serotonin without comparable histamine under diverse conditions in the rat mast cell. Biochem Pharmacol 34: 1389
111. Tønnesen H, Knigge U, Bülow S, Damm P, Fischerman K, Hesselfeldt P, Hjortrup A, Pedersen IK, Pedersen VM, Siemssen OJ, Svendsen LB, Christiansen PM (1988) Effect of cimetidine on survival after gastric cancer. Lancet 2: 990
112. Trinchieri G (1993) Interleukin-12 and its role in the generation of Th1 cells. Immunol Today 14: 335
113. Trinchieri G, Wysocka M, D'Andrea A, Rengaraju M, Aste-Amezaga M, Kubin M, Valiante NM, Chehimi J (1992) Natural killer cell stimulatory factor (NKSF) or interleukin-12 is a key regulator of immune response and inflammation. Prog Growth Factor Res 4: 355
114. Trinchieri G, Scott P (1994) The role of interleukin 12 in the immune response, disease and therapy. Immunol Today 15: 460
115. Uotila P (1993) Inhibition of prostaglandin E_2 formation and histamine action in cancer immunotherapy. Cancer Immunol Immunother 37: 251
116. Uotila P, Vapaatalo H (1984) Synthesis, pathways and biological implications of eicosanoids. Ann Clin Res 16: 226
117. Van der Pouw Kraan TCTM, Boeije LCM, Smeenk RJT, Wijdenes J, Aarden LA (1995) Prostaglandin-E2 is a potent inhibitor of human interleukin 12 production. J Exp Med 181: 775
118. Wu J, Dent P, Jelinek T, Wolfman A, Weber MJ, Sturgill TW (1993) Inhibition of the EGF-activated AMP kinase signaling pathway by adenosine 3′,5′-monophosphate. Science 262: 1065