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# Inhibition of prostaglandin $E_2$ formation and histamine action in cancer immunotherapy

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**Abstract.** The activity of cell-mediated defense systems is stimulated by consecutive formation of interleukin-1β (IL-1β), interleukin-2 (IL-2) and interferon γ (IFNγ). The system is inhibited by interleukin-4 (IL-4) and also by prostaglandin $E_2$ ($PGE_2$) and histamine, which are released when the immune system is activated. The inhibition is strong in cancer patients, because $PGE_2$ is formed in many cancer cells and its formation is stimulated by IL-1β. The release of histamine is also stimulated by IL-1β. Thus $PGE_2$ and histamine are feedback inhibitors of cell-mediated immunity. This inhibition can be abolished by inhibitors of the cyclo-oxygenase (e.g. indomethacin) and H-2 receptor antagonists (e.g. cimetidine). This may offer a new option to stimulate the immune system to kill cancer cells.

**Key words:** Cancer immunotherapy – Prostaglandin $E_2$ – Histamine – Indomethacin – Cimetidine

## Introduction

The cell-mediated immune system is activated when a macrophage presents an antigen to helper T lymphocytes. This can stimulate macrophages to secrete interleukin-1β (IL-1β) and helper T cells to secrete IL-2 [7, 49]. IL-1β stimulates the formation of IL-2 (Fig. 1) [7]. IL-2 stimulates helper T cells to divide and to form interferon γ (IFNγ) [10, 49], although IL-1β is also needed for the optimal formation of IFNγ [14, 25]. IL-2 stimulates cytotoxic T lymphocytes and natural killer (NK) cells directly or through the formation of IFNγ [26, 49]. IFNγ increases the formation IL-1β and tumor necrosis factor α (TNFα) in monocytes/macrophages (Fig. 1) [3, 20, 40]. Thus the cell-mediated immune system is activated by a stimulating chain: IL-1β, IL-2 and IFNγ (Fig. 1).

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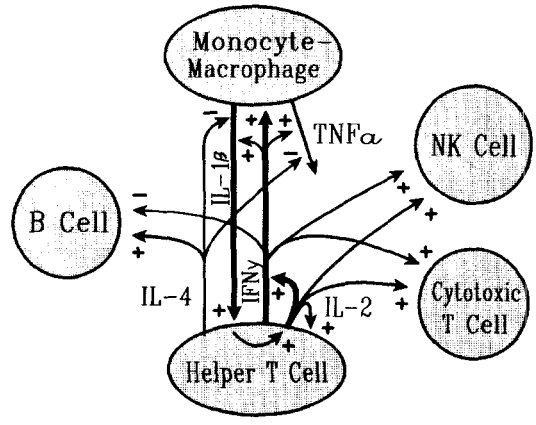


**Fig. 1.** Interleukin-1β (*IL-1β*) stimulates helper T cells to produce IL-2, which increases the formation of interferon γ (*IFNγ*). Because IFNγ stimulates IL-1β formation in monocytes/macrophages, the cell-mediated immune system is activated by a stimulating chain IL-1β, IL-2 and IFNγ, which also activates NK and cytotoxic T cells. IL-4 stimulates B cells and inhibits the formation of IL-1β and TNFα. Thus the effects of IL-4 and IFNγ are opposite. +, A stimulating effect; –, an inhibitory effect

## $PGE_2$ and histamine mediate negative feedback

Cell-mediated defense systems are inhibited by IL-4 formed in helper T cells and by prostaglandin $E_2$ ($PGE_2$) and histamine, which are formed or released when the immune system is activated [13, 38, 42]. Thus $PGE_2$ and histamine mediate negative feedback in the control of cell-mediated defense activity.

IL-4 inhibits the formation of IL-1β and TNFα in monocytes/macrophages and stimulates B cell proliferation and immunoglobulin production [11, 12, 19, 38, 41]. IL-4 inhibits cell-mediated immunity and enhances antibody-mediated immunity and its actions are opposite to those of IFNγ (Fig. 1) [3, 20, 25, 40–42].

$PGE_2$ is formed from arachidonic acid in monocytes/macrophages, cancer cells and other cells, when arachidonic acid is released from cellular phospholipids [33, 35, 42, 56]. The formation of $PGE_2$ is stimulated by

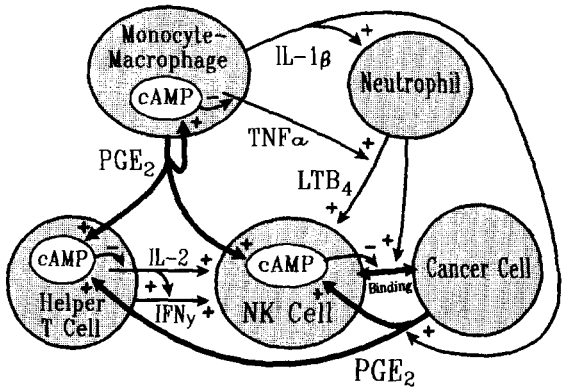


**Fig. 2.** Prostaglandin $E_2$ (*PGE*$_2$), formed in activated monocytes/macrophages and in IL-1β-stimulated cancer cells, inhibits the activation of cell-mediated immunity by increasing the level of cAMP. Increased cAMP in helper T cells inhibits the formation of IL-2. The formation of IFNγ is decreased concomitantly. Elevated cAMP in natural killer (*NK*) cells decreases the conjugation between NK and cancer cells. This conjugation is enhanced by activated neutrophils, which can be stimulated by IL-1β. Tumor necrosis factor α (*TNF*α) can stimulate neutrophils to produce leukotriene $B_4$ (*LTB*$_4$), which can activate NK cells. Increased cAMP in monocytes/macrophages inhibits the formation of TNFα

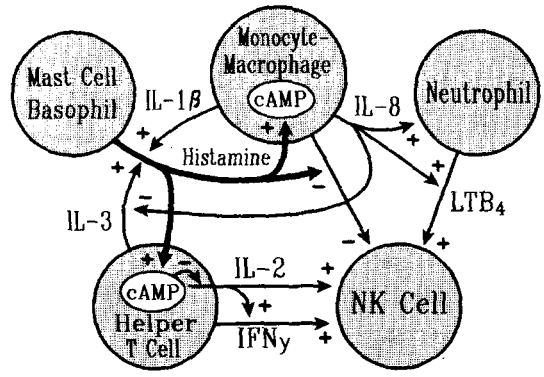


**Fig. 3.** Histamine increases cAMP in monocytes/macrophages and helper T cells through H-2 receptors and thus decreases the formation of IL-2 and concomitantly that of IFNγ. In the circulation, monocytes may inhibit NK cells through a cell-to-cell interaction and this inhibition can be abolished with histamine. IL-8 stimulates neutrophils to secrete $LTB_4$, which activates NK cells. The release of histamine is stimulated by IL-1β and IL-3. IL-8 inhibits IL-3-stimulated release of histamine

several compounds, including histamine, IL-1 (α and β) and TNFα [33, 35, 56]. $PGE_2$ inhibits the formation and receptor expression of IL-2 by increasing the level of cyclic AMP (cAMP) in helper T cells (Fig. 2) [17, 30, 34, 42, 44, 45, 57]. This will concomitantly decrease the formation of IFNγ (Fig. 2) [10].

Histamine can also increase the level of cAMP in helper T cells and thus decrease the formation of IL-2 and IFNγ (Fig. 3) [9, 28]. This effect of histamine is mediated through histamine-2 (H-2) receptors and can be abolished by an H-2 receptor antagonist cimetidine [9, 28].

$PGE_2$ and other cAMP-elevating compounds, like histamine, can decrease TNFα formation in monocytes/macrophages (Figs. 2, 3) [24, 32, 53]. Because TNFα stimulates the formation $PGE_2$ [1, 55], this is a feedback inhibitor of TNFα production.

IL-1 and TNFα can stimulate $PGE_2$ formation in cancer cells [33, 35]. $PGE_2$ inhibits the ability of NK cells to bind with tumor cells by increasing cAMP in the NK cells (Fig. 2) [18, 43]. This decreases tumor cell killing [18, 43].

Thus, when the immune system is stimulated to destroy tumor cells, the killing is prevented because IL-1β stimulates $PGE_2$ formation in tumor cells, which increases cAMP in NK cells and prevents the binding of NK and tumor cells (Fig. 2). The activation of the cell-mediated defense is blocked also because $PGE_2$ increases cAMP in helper T cells and thus inhibits the formation of IL-2 and IFNγ (Fig. 2) [17, 34, 42, 44, 57].

$PGE_2$ is regarded as an immunosuppressive agent [16]. Its formation is blocked by inhibitors of the cyclo-oxygenase such as indomethacin, which is known to stimulate the immune system [16, 56]. Cytotoxic T cells can also produce $PGE_2$, thus inhibiting the activity of NK cells, and this inhibition is abolished by indomethacin [15].

## $LTB_4$, IL-8 and neutrophils

Arachidonic acid is metabolized by the cyclo-oxygenase and different lipoxygenases [47, 56]. The 5-lipoxygenase is usually inactive in macrophages and neutrophils, but when activated it can produce leukotrienes such as leukotriene $B_4$ ($LTB_4$) [47]. The products of the 5-lipoxygenase enhance the cytotoxicity of NK cells, because the inhibition of this pathway decreases and the addition of 5-lipoxygenase products restores NK cell cytotoxicity [5, 46].

When the cyclo-oxygenase is inhibited with indomethacin, the formation of leukotrienes may be increased because more arachidonic acid is metabolized by the 5-lipoxygenase. This can activate NK cells and draw neutrophils to the tumor site, because $LTB_4$ is chemotactic for leukocytes [47]. Activated neutrophils can stimulate NK cells and increase their binding to target cells (Fig. 2) [58]. IL-1β and TNFα stimulate phagocytic activity of neutrophils [39] and TNFα enhances $LTB_4$ generation in neutrophils (Fig. 2) [37].

Interleukin-8 (IL-8) is formed in monocytes/macrophages and neutrophils. Its formation is stimulated by IL-1β and TNFα and inhibited by IL-4 [51, 52]. IL-8 is chemotactic for neutrophils and it activates the 5-lipoxygenase in neutrophils thus stimulating $LTB_4$ formation, which may stimulate NK cells (Fig. 3) [48, 52]. IL-8 inhibits histamine release from basophils (Fig. 3) [31].

Thus polymorphonuclear neutrophils and $LTB_4$ have an important role in the activation of NK cells [Figs. 2, 3). Because leukotrienes may stimulate the release of histamine, it is important to prevent its cAMP-elevating action with H-2 receptor antagonists when the cell-mediated immunity is stimulated with inhibitors of the cyclo-oxygenase.

## Histamine and H-2 receptor antagonists

Histamine release from basophils and mast cells is stimulated by antigens and many compounds including IL-1β

[27, 54]. Histamine has both inhibitory and stimulating effects on immunity. The inhibitory effect is due to its cAMP-enhancing effect in helper T cells and monocytes/macrophages, which decreases the formation of IL-2, IFNγ and TNFα (Fig. 3). This effect is abolished by the H-2 receptor antagonist cimetidine [8, 9, 24, 28].

Monocytes may have inhibitory effects on NK cells. This is partly due to $PGE_2$, because some of the inhibition is abolished with indomethacin [29]. It is also partly due to a cell-to-cell-mediated interaction between non-adherent monocytes and NK cells and this inhibition can be removed with histamine through H-2 receptors [22] (Fig. 3).

The effects of various H-2 receptor antagonists are different, since cimetidine increased the cytotoxicity of human NK cells in vitro whereas ranitidine did not [21]. Clear differences have also been detected in animal experiments [23]. Therefore it is possible that some effects of cimetidine are mediated by other means than through H-2 receptors.

Cimetidine increased the counts of helper T cells, B lymphocytes and immunoglobulins in blood of healthy volunteers who ingested 1600 mg cimetidine daily for 3 weeks [6]. Cimetidine (1200 mg daily) increased the activity of NK cells in blood of patients with B cell chronic lymphocytic leukemia [2]. In some cases a regression of cancer has been seen during cimetidine treatment [4, 50]. Regression of melanona was also detected in some patients treated with indomethacin and ranitidine [36].

## Concluding remarks

Many cancer cells produce $PGE_2$ which inhibits the cell-mediated defense system at several points and thus inhibits the killing of cancer cells. This inhibition becomes stronger when the immune system is activated to destroy tumor cells, because IL-1β stimulates $PGE_2$ formation in such cells, which are therefore not killed by the defense system. The formation of $PGE_2$ can be blocked with cyclo-oxygenase inhibitors, such as indomethacin, which may increase leukotriene formation. Leukotrienes may activate NK cells and stimulate the release of histamine, which prevents helper-T-cell-dependent activation of monocytes/macrophages, NK and cytotoxic T cells. This inhibition can be blocked with the histamine-2 receptor antagonist cimetidine, which also removes the gastrointestinal side-effects of indomethacin. Therefore a long-term treatment with indomethacin and cimetidine should activate the cell-mediated defense system to destroy cancer cells. The author has successfully used this therapy for pulmonary metastases of chondrosarcoma now for 5 years.

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