Interactions of Cytokines and Lipid Mediators in Acute and Chronic Inflammation

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Key Words

Priming
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We analysed the effects of the growth factors granulo-cyte/macrophage-colony-stimulating factor (GM-CSF) and granulocyte-colony-stimulating factor (G-CSF), as well as the cytokines interleukin (IL)-3 and IL-8 on the generation of leukotriene (LT)B₄ and IL-8 from human peripheral blood cells after subsequent stimulation with N-formyl-methionyl-leucyl-phenylalanine (fMLP). The amounts of LTB₄ generated from neutrophils (PMNs) and from the lymphocyte-monocyte-basophil fraction (LMB) from patients with atopic dermatitis (AD), with type 1 allergic diseases or psoriasis (PD) were compared with those of normal donors. Our results demonstrate that the cells from patients with AD [1,2] or type 1 allergy generated significantly higher quantities of inflammatory lipid mediators as compared to cells from normal donors or from psoriatic patients (tables 1-3). Unlike the Ca ionophore A23187, stimulation of PMNs or LMBs with fMLP or fluoride led to a diminished formation of LTB₄ in the presence of cetirizine 2HC1. Furthermore transcellular metabolism of LTA₄ by platelets into LTC₄, D₄, and E₄ was markedly suppressed by cetirizine 2HC1. Costimulation of PMN/platelet or LMB/platelet suspensions from normal and atopic donors also led to a suppression for leukotriene and IL-8 release in the presence of cetirizine. Since cetirizine inhibited receptor-mediated cell

Table 1. Formation of LTB₄ (ng/l×10⁷ PMNs) after priming with IL-3, IL-8, and GM-CSF without or with LTA₄

PMNs (1×10⁷/500 µl) were incubated for 20 min with the various cytokines [IL-3 (40 pg/ml), IL-8 (10 ng/ml), GM-CSF (10 ng/ml)] in the presence and absence of LTA₄ (5 µM) at 37°C in the presence of calcium (1 mM) and magnesium (0.5 µM). Leukotrienes were analysed by reverse-

phase HPLC. Results are the means $\pm$ SD of at least seven independent experiments in each group. * = Significant compared to the group of normal donors (ND).

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fMLP

Table 2. Release of IL-8 (pg/l $\times$ 10⁷ PMNs) after cytokine priming

ND

PD

AD

Type I

Buffer

GM-CSF

G-CSF

IL-3

1,220 $\pm$ 291

2,573 $\pm$ 501 1,115 $\pm$ 356

1,395 $\pm$ 271* 4,618 $\pm$ 254* 1,286 $\pm$ 231*

801 $\pm$ 255

1,765 $\pm$ 343

797 $\pm$ 361

2,077 $\pm$ 243* 4,469 $\pm$ 291* 2,342 $\pm$ 217*

834 $\pm$ 499 1,540 $\pm$ 436 2,189 $\pm$ 199* 1,401 $\pm$ 245

PMNs (1 $\times$ 10⁷/ml) were incubated for 60 min with the various cy-tokines [IL-3 (40pg/ml), G-CSF (10ng/ml), GM-CSF (10ng/ml)] in the presence of calcium (1 mM) and magnesium (0.5 μ M) at 37°C. IL-8 was measured by a specific sandwich ELISA. Results are the means $\pm$ SD of at least seven independent experiments in each group.

* = Significant compared to the group of normal donors (ND).

Table 3. Release of histamine (%) from basophils after stimulation with the different cytokines without or with fMLP

ND

PD

AD

Type 1

LMBs (1 $\times$ 10⁷) were primed with the indicated cytokines [GM-CSF (10 ng/ml), G-CSF (10 ng/ml), IL-3 (40 pg/ml), 30 min] and subsequently stimulated with fMLP (10⁻⁶ M, 60 min) at 37°C in the presence of calcium (1 mM) and magnesium (0.5 mM). Results are the means $\pm$ SD of at least seven independent experiments in each group.

* = Significant compared to the group of normal donors (ND).

activation, an analysis of G protein involvement was carried out. Cetirizine modulates GTPase activities as well as Gpp (NH)p binding of G proteins in PMNs. It affects the phos-phorylation pattern and ADP ribosylation of low-molecular-weight G proteins. Cetirizine suppresses, time depend-ently, IL-8 mRNA in LMBs, as assessed by Northern blot analysis. Thus, our studies show an enhanced mediator release from cells of allergic patients, and an inhibitory effect of cetirizine on mediator release (leukotrienes, IL-8) from

normal as well as atopic cells, presumably by interfering with defined components of signal transduction pathways. Thus, in addition to having therapeutic properties, $\frac{1}{8}$ antagonists may serve as cell-biological probes.

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