Interferon and Antiallergic Drug Regulation of Histamine and Tumor Necrosis Factor- α in Rat Mast Cell Subsets

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Key Words

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Abstract

We have further characterized the heterogeneity of mast cells (MCs) by comparing the ability of rat peritoneal MCs (PMCs) and intestinal mucosal MCs (IMMCs) to produce tumor necrosis factor (TNF)- α and by investigating its regulation by interferon (IFN) and the antiallergic drugs nedocromil sodium (NED) and sodium cromoglycate (SCG). Although IMMCs store less TNF- α than PMCs, they produced comparable amounts of TNF- α in cytotoxic assays. Just as SCG and NED inhibit histamine secretion from PMCs but not IMMCs, IFN exhibited a similar differential effect on histamine release from these cells. However, SCG, NED, and IFN inhibit TNF- α -dependent cytotoxicity by both PMCs and IMMCs and reduce the **steady-state** levels of mRNA for TNF- α in PMCs. Thus, the modulation of MC mediator release depends upon the MC population and mediator studied. The inhibitory effect of SCG and NED on TNF- α release from MCs may explain some of their **anti-inflammatory** and therapeutic effects.

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Introduction

The heterogeneity of mast cells (MCs) in the rat has been well characterized. Connective tissue MCs, often represented by peritoneal MCs (PMCs), and the intestinal mucosal MCs (IMMCs) exhibit many differences in mediator content and responsiveness to secretagogues and antiallergic drugs [1-3], but nothing is known about the regulation of recently identified cytokines in MCs. To further define this heterogeneity, we investigated the ability of PMCs and IMMCs to produce tumor necrosis-factor (TNF)- α and the ability of interferon (IFN)- α/β and - γ and the antiallergic drugs nedocromil sodium (NED) and sodium cromoglycate (SCG) to regulate the TNF- α activity of MCs.

Materials and Methods

PMCs and IMMCs were isolated and purified according to previously described protocols [4]. MC TNF- α activity was measured using a cytotoxic assay as previously described [5]. Rat IFN- α/β and - γ were purchased from Lee Biomolecular (San Diego, Calif, USA) and Holland Biotechnology (Leiden, The Netherlands), respectively. NED and SCG were generously provided by Fisons Pharmaceuticals, UK.

Results

Both PMCs and IMMCs express TNF- α -dependent cytotoxicity. Isolated IMMCs (71% purity) exhibited 118 ± 9 LI $\frac{1}{\%}$ /106 MCs, approximately 89% of the cytotoxic activity of PMCs (132 ± 11 LU20/106 MCs) collected from the same animal and subjected to the enzymatic cell dispersion

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Table 1. Modulation of antigen-induced

Table 2. Modulation of TNF- α activity of mast cells by IFN and

n = 3-6; * p < 0.05 versus sham treatments.

TNF- α was assayed by cytotoxicity to the tumor target, WE-HI-164. n = 4-6; *p < 0.05, **p < 0.01 versus sham treatments.

procedure used for IMMC isolation. However, the preformed TNF- α content in PMC is 5-fold higher than that of IMMC (0.89 fg/cell and 0.17 fg/cell, respectively) and corresponds to about 45% of PMC cytotoxic activity, whereas the newly synthesized TNF- α is responsible for about 55%. Thus, IMMCs store less TNF- α than PMCs, but when stimulated with WEHI-164 target cells, IMMCs exhibited comparable levels of TNF- α activity to PMCs.

The modulation of MC TNF- α release is not as well characterized as histamine release.

Antiallergic drugs such as NED and SCG are well known to inhibit histamine secretion of PMCs but not of IMMCs (table 1). In these experiments, SCG was added concurrently with the stimulating antigen, whereas pretreatment with SCG caused tachyphylaxis. In contrast, the addition of NED or SCG concurrently with WEHI-164 did not modify MC TNF- α activity. Pretreatment of MCs with SCG or NED for at least 2 h was required to significantly reduce MC TNF- α activity. Furthermore, 4 h pretreatment with NED and SCG reduced TNF- α activity of both PMCs and IMMCs equally well (table 2). Similar data were obtained with IFN treatment (4 h) where IFN- α/β and - γ inhibited TNF- α release of both PMCs and IMMCs (table 2).

Furthermore, treatment with IFN- α/β and - γ for up to 24 h inhibited histamine release from PMCs, but had no effect on that from IMMCs (table 1).

The inhibitory effect of IFN and antiallergic drugs on TNF- α release required new protein and RNA synthesis. When MCs were treated with 0.5 μ g/ml actinomycin D (RNA synthesis inhibitor) and 5 μ g/ml cycloheximide (protein synthesis inhibitor) 1 h before the addition of IFN and antiallergic drugs, no additional inhibition of TNF- α release was observed. Furthermore, IFN (800 U/ml) and NED (1 μ M) treatment (24 h) reduced the steady-state levels of mRNA for TNF- α by 87 and 71%, respectively.

Discussion

The release of mediators from MCs is modulated differently depending on the MC type and the mediator studied. IFN- α/β , IFN- γ , NED and SCG inhibit histamine release of PMCs but not IMMCs. Similar treatments inhibit TNF- α release from both PMCs and IMMCs. It is intriguing to down-regulate the release of one mediator but not the release of others in the same cell. Our observations suggest that the intracellular pathways which regulate the release of histamine and TNF- α from MCs are distinct and, moreover, the regulation of histamine release from IMMCs and PMCs differs. Definition of these pathways may lead to new strategies for the therapeutic regulation of allergic diseases.

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