Environmental Relevant Metal and Transition Metal Ions Enhance FceRI-Mediated Mast Cell Activation
Aurelia Walczak-Drzewiecka,1 Janina Wyczółkowska,1 and Jaroslaw Dastych2

1Department of Biogenic Amines, Polish Academy of Sciences, Lodz, Poland; 2Laboratory of Molecular Immunology, International Institute of Molecular and Cell Biology in Warsaw, Warsaw, Poland

Upon contact with allergen, sensitized mast cells release highly active proinflammatory mediators. Allergen-mediated mast cell activation is an important mechanism in the pathogenesis of atopic asthma. Asthmatic patients are especially susceptible to air pollution. Epidemiologic studies found a positive correlation between severity of symptoms among asthmatic patients and the level of particulate matter (PM) in the air. Among the constituents of PM are metals and transition metals, which could mediate some of its adverse effects on human health. We sought to determine the effect of metal and transition metal ions on allergen-mediated mast cell activation. We observed that several metal and transition metal ions activated mast cells and enhanced allergen-mediated mast cell activation. Thus, Al3+, Cd2+, and Sr2+ induced release of granule-associated N-acetyl-β-d-hexosaminidase, and Al3+ and Ni2+ enhanced antigen-mediated release. Metal and transition metal ions also induced significant secretion of interleukin (IL)-4 and increased antigen-mediated IL-4 secretion in mast cells. These effects of metal and transition metal ions on mast cells were observed at concentrations that do not result in direct cytotoxicity and might be relevant for environmental exposure. Thus, metals and transition metals could increase the level of allergen-mediated mast cell activation, which might be one of the mechanisms mediating exacerbation of allergen-driven asthma symptoms by air pollution. Key words: allergy, asthma, mast cell, IL-4, metals, PM, particulate matter, transition metals. Environ Health Perspect 111:708–713 (2003). doi:10.1289/ehp.5960 available via http://dx.doi.org/ [Online 21 January 2003]

Environmental or occupational exposures to metal and transition metal compounds have been linked to adverse health effects in humans, including dysfunctions of the immune system such as allergic and autoimmune diseases (Bigazzi 1999; Domingo 1994; Kanerva et al. 2000; Norseth 1988; Rondeau et al. 2000; Stejskal and Stejskal 1999). One of the possible sources of exposure to metal and transition metal ions in a nonoccupational environment is the particulate matter (PM) present in the air. The mass of particles of a certain diameter [PM ≤ 10 µm (PM10) or PM ≤ 2.5 µm (PM2.5)] is a standard measure for level of air pollution (Donaldson and MacNee 2001). Among the constituents of PM10 and PM2.5 are metals and transition metals such as nickel, lead, ferrite, ferrous, chromium, manganese, and aluminum (Balachandran et al. 2000; Hrask et al. 2000; Ozkaynak et al. 1996). A correlation between some biological effects of residual oil fly ash observed in vitro and its metal and transition metal content has been reported (Lambert et al. 2000; Samet et al. 1997).

An increase in prevalence of allergic diseases, including allergic asthma, among populations of several industrialized countries has been reported (Holgate 1999). The influence of environmental factors is the most likely explanation for this increase, and air pollution has been considered one of these factors (Heinrich et al. 1999). Two types of possible links between air pollution and allergic asthma have been sought. One hypothesis proposes that exposure to air pollution increases the probability of developing allergic asthma (Donaldson et al. 2000; Heinrich et al. 1999). This causative link cannot be ruled out, but several epidemiologic studies did not find a correlation between the number of allergic asthma patients and the level of exposure to air pollution in a given population (Donaldson et al. 2000). However, several independent epidemiologic studies support a positive correlation between severity of symptoms among asthmatic patients and PM10 concentration (Donaldson et al. 2000; Gavett and Koren 2001). Thus, air pollution seems to precipitate and worsen asthma attacks among people with already existing disease. It is not clear which component of airborne pollutants constitutes the greatest health risk for asthmatic patients, but metal ions are considered one of the likely culprits (Costa and Dreher 1997).

IgE-mediated allergic inflammation is the central mechanism involved in the pathogenesis of atopic asthma (Busse and Lemanske 2001). Allergen-mediated activation of immune cells results in release of a number of inflammatory mediators. This in turn leads to the pathological changes in lung tissues, which finally result in airflow obstruction (Maddox and Schwartz 2002). Mast cells are critical effector cells in IgE-mediated allergic inflammation (Hart 2001; Taylor and Metcalfe 2001; Williams and Galli 2000). They accumulate in tissues exposed to the outside environment and are capable of releasing large numbers of highly active mediators such as histamine, serotonin, heparin, prostaglandins, leukotrienes, neutral proteases, and a number of cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-4 (Metcalfe et al. 1997). Antigen-mediated mast cell activation depends on aggregation of high-affinity receptors for IgE (FceR1), which in turn initiates phosphorylation of multiple mast cell proteins on tyrosine (Bemhamou et al. 1990; Hamawy et al. 1995; Kent et al. 1994). This signaling cascade activates exocytosis and upregulates expression of multiple genes, including cytokines such as TNF-α and IL-4 (Brown and Hural 1997; Gordon et al. 1990; Metcalfe et al. 1997).

Heavy-metal ions Hg2+ and Ag+ induce mediator release and enhance allergen-mediated mediator release from mast cells in vitro (Dastych et al. 1999; Suzuki et al. 2001). We decided to expand this observation and investigate effects of several other metal and transition metal ions on allergen-mediated mast cell activation. In this article, we will show that several metal ions activate mast cells in vitro to release granule contents and produce IL-4. Furthermore, some metal ions enhance IgE-mediated mast cell degranulation and IL-4 expression. We observed this effect on mast cell function at concentrations that do not result in a significant level of direct cytotoxicity and might be relevant for environmental exposure. The enhancement of allergen-mediated mast cell activation by metal and transition metal ions could be one mechanism that allows for exacerbation of allergen-driven asthma symptoms by air pollution.

Materials and Methods

Materials. Dulbecco’s modified Eagle’s medium (DMEM), RPMI-1640, fetal calf serum (FCS), HEPES, l-glutamine, 2-mercaptoethanol, penicillin/streptomycin, bovine serum albumin (BSA), dinitrophenyl conjugated human serum albumin (DNP-HSA), p-nitrophenyl-N-acetyl-β-d-glucopyranoside, and neutral red were obtained from Sigma Chemical Company (St. Louis, MO, USA).

Address correspondence to J. Dastych, International Institute of Molecular and Cell Biology in Warsaw, Ks. Trojdena 4, 02-102 Warsaw, Poland. Telephone: (48-22) 668 5095. Fax: (48-22) 668 5288. E-mail: jdadysth@ifimmcb.gov.pl

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We purchased antmurine IL-4 monoclonal antibody (mAb) clone 11B11 from Hazleton (Hazleton, PA, USA); biotin conjugated anti-IL-4 mAb clone BVD6-24G2 from Pharmingen (San Diego, CA, USA); horseradish peroxidase (HRP)-conjugated avidin from ICN Pharmaceuticals Inc. (Costa Mesa, CA, USA); recombinant murine IL-4 from PeproTech (Rocky Hill, NJ, USA); and analytical-grade nickel sulfate, aluminum chloride, strontium chloride, cadmium chloride, and lead nitrate from POCH (Gliwice, Poland). Murine monoclonal dinitrophenyl (DNP)-specific IgE was obtained from the culture of hybridoma Hi-DNP-ε26.82.

Cell culture. C1.MC/C57.1 (C57) (Tsai 1996) mouse mast cells were cultured in DMEM supplemented with 10% heat-inactivated FCS, 4 mM l-glutamine, 25 mM HEPES, 50 µM 2-mercaptoethanol, and 100 µg/mL penicillin/streptomycin (complete DMEM). Cells were cultured at 37°C in a CO2 incubator (5% CO2).

Sensitization and stimulation of mast cells. Mast cells were collected by centrifugation; the cell number was adjusted to 106 cells/mL by suspending the cell pellet in complete DMEM. The cell suspension was mixed with anti-DNP IgE containing supernatant in dilution 1:5 (vol:vol), and cells were incubated 2 hr in a CO2 incubator (5% CO2; 37°C). Cells were then washed with medium three times and resuspended in RPMI-1640 without phenol red for 4 hr at 37°C, the reaction was stopped by centrifugation at 37°C, the reaction was stopped by centrifugation at 4°C. We added 20 µL of 1% Triton X-100 to some of the wells to obtain cell lysate (total). We then transferred 50 µL of supernatant from control or assay wells or 60 µL of cell lysate into corresponding wells on a second 96-well plate. We then added 10 µL of 1% Triton X-100 to the wells containing supernatant or control media (blank) to adjust the volume and Triton X-100 concentration. This was followed by the addition of 60 µL 0.08 mM citric buffer, pH 4.5, containing 8 mM p-nitrophenyl-N-acetyl-β-D-glucopyranoside as a chromogenic substrate for N-acetyl-β-D-hexosaminidase, and the plate was incubated for 1.5 hr at 37°C. The reaction was stopped by the addition of 200 µL 0.2 M glycine. The OD at 405 nm was determined with an ELISA reader, and the percentage of the total enzymatic activity was determined as described by Dastrych et al. (1999) and Schwartz et al. (1979). Briefly, 4 × 104 mast cells suspended in RPMI-1640 without phenol red were placed in individual wells on 96-well plates. Increasing concentrations of metal ions dissolved in media with or without indicated concentrations of antigen (DNP-HSA) dissolved in media or media alone were added to selected wells for a final volume of 100 µL. After 15-min incubation at 37°C, the reaction was stopped by centrifugation at 4°C. The percentage of granule-associated N-acetyl-β-D-hexosaminidase (β-Hex) activity released into supernatant was determined, and the spontaneous release (9.8 ± 1.3) was subtracted. Bars represent mean ± SEM from three independent experiments, each performed in triplicate.

Figure 2. Effect of metal and transition metal ions on mast cell viability. C57 mast cells were incubated with (A) AlCl3, (B) CdCl2, (C) NiSO4, (D) SrCl2, or (E) Pb(NO3)2 for 4 hr, washed twice, centrifuged, and then incubated with neutral red for 3 hr. Neutral red incorporation was determined as described in "Materials and Methods." Bars represent means from two independent experiments, each performed in duplicate.
activity released into the supernatant was calculated by using the following formula:

Release = (supernatant – blank) + (total – blank) × 100%.

We tested the possible effect of the presence of NiSO₄, AlCl₃, SrCl₂, CdCl₂, and Pb(NO₃)₂ in the assay buffer on the enzymatic activity of N-acetyl-β-D-hexosaminidase. None of the tested compounds affected N-acetyl-β-D-hexosaminidase enzymatic activity in mast cell lysate at concentrations ≤ 5 × 10⁻⁶ M.

**Cytokine secretion assay.** To measure the amount of IL-4 protein secreted into the supernatant, we suspended mast cells in complete DMEM at a density of 10⁶ cells/mL. Increasing concentrations of metal ions, antigen (DNP-HSA), or a combination of both were added in a final volume of 0.3 mL, and cells were incubated at 37°C for 4 hr. After incubation, cell suspensions were centrifuged at 600 × g for 10 min, and supernatants were collected and stored at -20°C. The ELISA for IL-4 was based on a standard protocol provided by Pharmingen. Briefly, 96-well plates were coated overnight with 11B11 anti–mIL-4 mAb (2 µg/mL). Plates were blocked with 3% BSA dissolved in phosphate-buffered saline (PBS) for 3 hr at room temperature. Wells were rinsed with PBS containing 0.1% Tween-20, samples or standards of rmIL-4 were added, and plates were incubated overnight at 4°C. Each plate was then rinsed with PBS containing 0.1% Tween-20 and incubated 45 min at room temperature with biotinylated anti-IL-4 mAb. This was followed by incubation with HRP-conjugated avidin for 30 min (250 ng/mL) and with α-phenylenediamine as a chromogenic substrate for additional 20 min. We added 3 M H₂SO₄ to stop the reaction; plates were read in an ELISA reader at 450 nm.

**Western blotting.** Cells were collected by centrifugation and lysed in buffer containing 50 mM Tris-HCl (pH 8.0), 1% nonionic detergent IGEPA (Sigma Chemical Company), 20 mM ethylenediaminetetraacetic acid, 150 mM sodium chloride, 1 mM magnesium chloride, 10 mM tetrasodium pyrophosphate, 100 mM sodium fluoride, 2 mM sodium orthovanadate, 10 µg/mL leupeptin, 10 µg/mL aprotinin, and 1 mM phenylmethylsulfonyl fluoride. After 30-min incubation at 4°C, lysates were centrifuged at 10,000 × g for 15 min at 4°C. Supernatants were mixed with loading buffer containing sodium dodecylsulfate (SDS) and 2-mercaptoethanol, boiled for 5 min, and separated with SDS-polyacrylamide gel electrophoresis (4–12% gradient gels). Proteins were electrotransferred to nitrocellulose and immunoblotted with the HRP-conjugated PY20 antiphosphotyrosine antibody, and specific bands were detected with chemiluminescence (SuperSignal Substrate; Pierce Biotechnology Inc, Rockford, IL, USA). Next, the nitrocellulose membrane was stripped and reblotted with antiactin antibody followed by secondary HRP-conjugated antibody, and specific bands were detected with chemiluminescence. Optical densities associated with specific bands were measured using Quantity One software (BioRad Laboratories, Hercules, CA, USA).

**Statistical analysis.** Statistical significance of observed differences was determined using one-way analysis of variance followed by Dunnett test.

**Results**

The level of mast cell degranulation was determined by the percentage of release of granule-associated N-acetyl-β-D-hexosaminidase activity into supernatant (Dastych et al. 1997). The majority of N-acetyl-β-D-hexosaminidase in mast cells is stored in mast cell granules (Schwartz and Austen 1980) and is released upon mast cell activation in parallel with other preformed mediators such as β-glucuronidase, β-D-galactosidase, mast cell-specific proteases, chondroitin sulfate E proteoglycan, and histamine (Razin et al. 1983; Schwartz and Austen 1980; Schwartz et al. 1979, 1981). The release of N-acetyl-β-D-hexosaminidase is associated with the extrusion of exocytotic granules, which can be visualized with specific staining (Demo et al. 1999). To determine if some metal and transition metal ions expected to be present in PM of ambient air could cause mast cell degranulation, mouse mast cells C57.1 were exposed to 10⁻⁷ M SrCl₂, NiSO₄, CdCl₂, or AlCl₃, or to the mixture containing 10⁻² M of each compound. As shown in Figure 1, incubation with such concentrations of NiSO₄, AlCl₃, SrCl₂, or CdCl₂ resulted in a low (2–5%) release of granule-associated N-acetyl-β-D-hexosaminidase in nonsensitized mast cells. Interestingly, a mixture of these compounds induced a much higher release (11%), which suggests that the effects of exposure to metal and transition metal ions at these concentrations could be additive. We next

![Figure 3](image-url)
decided to systematically test the effect of increasing concentrations of NiSO$_4$, AlCl$_3$, SrCl$_2$, CdCl$_2$, or Pb(NO$_3$)$_2$ present in incubation media on mast cell function. First, the direct cytotoxic effects of increasing concentrations of these compounds have been determined. As shown in Figure 2, incubation of C57 mast cells for 4 hr in medium containing 10$^{-7}$-5 × 10$^{-6}$ M NiSO$_4$, AlCl$_3$, SrCl$_2$, CdCl$_2$, or Pb(NO$_3$)$_2$ did not result in a decrease in neutral red uptake compared with control. Thus, exposure of mast cells to metal and transition metal salts at concentrations and incubation time employed did not result in a decrease in cell viability.

Mast cells sensitized in vitro with IgE respond to antigen by degranulation and cytokine secretion. To determine how the presence of noncytotoxic concentrations of metal ions affects the antigen-mediated degranulation, we incubated sensitized mast cells with concentrations of tested metal ions or antigen (DNP-HSA) or a combination of both. As shown in Figure 3, incubation of mast cells in the presence of some metal and transition metal ions resulted in release of a significantly higher percentage of N-acetyl-$\beta$-D-hexosaminidase compared with spontaneous release. The maximum N-acetyl-$\beta$-D-hexosaminidase release of about 8.5% was observed with 5 × 10$^{-6}$ M Al$_3^+$ and Cd$_2^+$. A lower but significant release (5%) was observed with 5 × 10$^{-6}$ M Sr$_2^+$, but not with Ni$_2^+$ and Pb$_2^+$. Interestingly, the percentages of released N-acetyl-$\beta$-D-hexosaminidase observed with Sr$_2^+$ and Al$_3^+$ in sensitized mast cells (Figure 3) differed from those observed in nonsensitized cells (Figure 1).

Metal ions in combination with optimal concentrations of antigen resulted in greater N-acetyl-$\beta$-D-hexosaminidase release compared with antigen alone. For example, mast cells challenged with antigen (100 ng/mL) and 10$^{-7}$ M AlCl$_3$ released 23% of N-acetyl-$\beta$-D-hexosaminidase, whereas mast cells incubated with antigen alone released 11% of N-acetyl-$\beta$-D-hexosaminidase. Similar effects were observed with 10$^{-7}$ M NiSO$_4$. For these two transition metal ions, the combination of antigen and ions resulted in a release of the amount of mediator higher than the sum of the amounts released with each of these stimuli acting separately. Cd$_3^+$, Sr$_3^+$, and Pb$_{3}^+$ also enhanced the antigen-mediated mediator release, but to a lesser extent. For Ni$_{3}^+$, Al$_{3}^+$, Sr$_{3}^+$, and Cd$_{3}^+$ ions, there was a direct relation between the concentration and the effect on antigen-mediated N-acetyl-$\beta$-D-hexosaminidase release. Thus, noncytotoxic concentrations of metal and transition metal ions stimulated mediator release and enhanced antigen-mediated mediator release in mast cells.

Mast cell activation is regulated by a complex signal transduction process that is initiated by phosphorylation of multiple mast cell proteins on tyrosine residues (Benhamou et al. 1990; Hamawy et al. 1995; Kent et al. 1994). To determine if transition metal and metal ions affect this signal transduction process, mast cells were activated with the optimal dose of antigen in the absence or presence of NiSO$_4$, AlCl$_3$, or Pb(NO$_3$)$_2$, and mast cell proteins were analyzed with Western blot using antiphosphotyrosine specific antibodies. As expected, addition of antigen induced phosphorylation of multiple proteins in C57 mast cells, resulting in the increased intensity of several electrophoretic bands and the appearance of additional bands, which were not observed in resting mast cells (Figure 4). The presence of Ni$_{2}^+$, Pb$_{2}^+$, and Al$_{3}^+$ in incubation media resulted in different intensity of several electrophoretic bands compared with mast cells activated with antigen in the absence of these metal ions. Ni$_{2}^+$ and Pb$_{2}^+$ mediated an increase in the amount of several phosphorylated proteins at certain time points. In contrast, Al$_{3}^+$ mediated a decrease in the level of phosphorylation of multiple proteins compared with control. To assess quantitative differences in the level of protein phosphorylation, we analyzed densitometrically three protein bands, approximately 33, 37, and 56 kD in molecular weight, that were upregulated after antigen challenge in all Western blot experiments. We then normalized resultant optical densities to actin to control for differences in loading. As shown in Figure 4, all three protein bands from mast cells activated with antigen in the presence of Ni$_{2}^+$ were phosphorylated to a greater extent and with different kinetics compared with control. Addition of Pb$_{2}^+$ resulted in increased phosphorylation of 33 and 37 kD bands, whereas the 56 kD band was phosphorylated to an extent similar to control. The presence of Al$_{3}^+$ in incubation media resulted in a decrease in the level of antigen-mediated phosphorylation of 56 and 37 kD bands. Interestingly, despite the overall inhibition of protein phosphorylation observed with this transition metal ion, the 33 kD band shows a greater level of phosphorylation than those observed in control cells.

![Figure 4](image-url)
Mast cells challenged with antigen express and secrete to supernatant several proinflammatory cytokines including IL-4. To determine if metal ions change the level of expression of IL-4 in antigen-activated mast cells, we sensitized mast cells with IgE and challenged them with antigen in the presence or absence of increasing concentrations of NiSO₄, AlCl₃, SrCl₂, CdCl₂, or Pb(NO₃)₂. As shown in Figure 5, the addition of antigen resulted in accumulation of IL-4 in the supernatant, with maximum accumulation observed at an optimal concentration of 10–100 ng/mL antigen. Higher antigen concentrations resulted in significantly lower IL-4 secretion (data not shown). Incubation of C57 mast cells with NiSO₄, AlCl₃, and CdCl₂ at the lowest concentration tested (10⁻⁷ M) resulted in a significant secretion of IL-4 into the supernatant compared with control. For example, mast cells incubated with 10⁻⁷ M NiSO₄ secreted 200 pg/mL IL-4 compared with 80 pg/mL in control. In contrast, Ni²⁺ did not increase the amount of secreted IL-4 above the level observed with optimal dose of antigen alone. Thus, at certain concentrations, all tested metal and transition metal ions either induced IL-4 secretion or enhanced antigen-driven IL-4 secretion from mast cells.

**Discussion**

In this article we have shown that several metal and transition metal ions induced mediator release and enhanced antigen-mediated mediator release in mast cells (Figures 1 and 3). Mediator release did not result from direct cytotoxicity, as it occurred at ion concentrations that did not cause cell death (Figure 2). Some effects of transition metal and metal ions on the level of tyrosine phosphorylation of proteins in antigen-activated mast cells were observed (Figure 4). This is consistent with the hypothesis that these ions affect antigen-mediated signal transduction processes. Furthermore, mast cell degranulation was associated with IL-4 secretion (Figure 5), which requires de novo transcription and translation (Dastych et al. 1999). All these observations are consistent with the hypothesis that metal and transition metal compounds, at certain concentrations, are capable of activating mast cells and enhancing antigen-mediated activation.

Metal and transition metal compounds can affect functions of multiple cell types (Ghio et al. 1998; Klein et al. 1994; McCabe and Lawrence 1990). There are, however, some unique characteristics of mast cells that affect how they respond to metal ions and how such responses affect human health. Mast cells are present in large numbers in tissues exposed to the outside environment (Metcalfe et al. 1997). It has been previously shown in animal models that mast cells mediate proinflammatory and immunomodulatory effects of such environment factors as the midrange spectrum of ultraviolet light (Ikai et al. 1985), ozone (Kleeberger et al. 2001), and heavy metals (Kiely et al. 1997). Several mast cell-derived mediators possess strong immunomodulatory activities (Taylor and Metcalfe 2001). For example, IL-4 is a prototypic immunomodulatory cytokine expressed only in few cell types, which supports the Th2 type of immune response and IgE production (Brown and Hural 1997). There is evidence that metals and transition metals stimulate Th2-driven immune responses (Heo et al. 1997; McCabe and Lawrence 1991; Probst et al. 1995; Szepietowski et al. 1997) and induce IgE production (Kirala 1994; Lutz et al. 1999; Murdoch et al. 1986; Prouvost-Danon et al. 1988; Revolletta and Ovary 1969) in humans and in experimental animals. Thus, mast cell activation could be involved in metal- and transition metal-mediated immunomodulation.

The effects of metal and transition metal ions on mast cells were observed at concentrations relevant for occupational and environmental exposure. For example, the concentration of Ni²⁺ (10⁻⁷ M) that induced IL-4 secretion and enhanced antigen-mediated mast cell degranulation (Figures 3 and 4) is similar to that found in the serum of stainless steel welders (Angerer and Lehner 1990). Although serum concentrations of Ni²⁺ in the general population are lower (10⁻³–10⁻⁸ M), there is evidence that environmental exposure from air pollution could increase the internal dose of Ni²⁺ (Andersen and Svenes 1999; Nixon et al. 1989; Smith-Sivertsen et al. 1997). Unlike the |

### Table 1: Effect of Metal and Transition Metal Ions on IL-4 Secretion in C57 Mast Cells

| Metal Ion | Concentration (M) | IL-4 (pg/mL/10⁶ cells) |
|-----------|-------------------|-----------------------|
| Ni²⁺      | 10⁻⁷              | < 200                 |
| Al³⁺      | 10⁻⁷              | > 200                 |
| Sr²⁺      | 10⁻⁷              | < 200                 |
| Cd²⁺      | 10⁻⁷              | > 200                 |
| Pb²⁺      | 10⁻⁷              | < 200                 |

*Statistically significant at p < 0.05 compared with control.

**Figure 5.** Effect of metal and transition metal ions on antigen-mediated IL-4 secretion in mast cells. C57 mast cells were sensitized with IgE and incubated 4 hr with antigen (DNP-HSA) or antigen combined with (A) AlCl₃, (B) CdCl₂, (C) NiSO₄, (D) SrCl₂, or (E) Pb(NO₃)₂. The amount of IL-4 secreted into supernatant was determined by ELISA. Each point represents the mean ± SEM from five independent experiments, each performed in duplicate.
environmental setting, experimental settings, and environmental sources. The interaction between metal ions and immune responses is crucial for understanding the role of metal ions in allergic disease. 

Experimental setting, environmental factors, and metal ion-mediated immunomodulation must be considered as part of the pathogenic process underlying an asthma attack (Busse and Lemanske 2001). We observed that several metal ions enhanced antigen-mediated mast cell activation (Figures 3 and 5), which resulted in the release of mediators in amounts exceeding the maximum amount observed with antigen alone. This observation is consistent with the hypothesis that bioavailable metals and transition metals from PM in ambient air increase the level of antigen-mediated mast cell activation and could worsen asthma symptoms. It would be important to consider the exposure of asthma patients to both allergen and metal compounds. Such exposure is supported by data demonstrating the presence of multiple allergens being adsorbed on the surface of inhalable particles (Ormstad 2000). Thus, the enhancement of antigen-mediated mast cell activation with low concentrations of metals and transition metals should be considered one of the mechanisms explaining specific susceptibility of asthmatic patients to air pollution.

Immune response is modulated by environmental factors that can enhance or suppress responses of immune cells to antigen. Several metal and transition metal ions mediate immunomodulation in experimental animals (Bigazzi 1999; Kiely et al. 1997; Lamberts et al. 2000). The presence of metallic compounds in PM from ambient air raises questions about the possible impact of air pollution on the immune system. To address these concerns, the cellular and molecular mechanisms of metal ion-mediated immunomodulation must be better understood. Metal and transition metal ion-mediated mast cell activation resulting in release of multiple proinflammatory and immunomodulatory mediators could be part of such immunomodulatory processes.

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Angerer J, Lehnert G. 1990. Occupational chronic exposure to mixture of Ni2+, Al3+, Cd2+, and Sr2+ induced experimental setting, environmental factors that enhance or suppress responses of immune cells to antigen. Several metal and transition metal ions mediate immunomodulation in experimental animals (Bigazzi 1999; Kiely et al. 1997; Lamberts et al. 2000). The presence of metallic compounds in PM from ambient air raises questions about the possible impact of air pollution on the immune system. To address these concerns, the cellular and molecular mechanisms of metal ion-mediated immunomodulation must be better understood. Metal and transition metal ion-mediated mast cell activation resulting in release of multiple proinflammatory and immunomodulatory mediators could be part of such immunomodulatory processes.