Mast cell migratory response to TNF-α, IL-6 and IL-4

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Abstract

Mast cells accumulate at local tissues in different pathophysiological conditions, including both acute and chronic inflammation. It is well established that mast cell recruitment is mediated by different humoral factors, that act as mast cell chemoattractants. The aim of our study was to examine the ability of three cytokines, i.e. TNF-α, IL-6 and IL-4, to mediate rat peritoneal mast cell migration. We have found that IL-4 and IL-6 did not act as rat mast cell chemoattractants, whereas TNF-α significantly influenced rat mast cell migratory response. This cytokine at concentrations from 10^{-6} ng/ml to 5 x 10^{-4} ng/ml caused a statistically significant increase in mast cell migration with a maximal response at concentration 5 x 10^{-5} ng/ml. Higher concentrations of TNF-α, ranging from 0.01 ng/ml to 100 ng/ml, induced significant inhibition of mast cell migration. Checkerboard analysis indicated that migration of mast cells towards TNF-α was mainly chemotaxis and in part ensured from chemokinesis. Thus we have stated that TNF-α is a potent factor which influences rat mature mast cell migration in tissues.

Key words: *mast cells, mast cell migration, tumor necrosis factor, interleukin 4, interleukin 6*

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Introduction

Mast cells are normally distributed throughout connective tissues and are particularly numerous beneath the epithelial surface of the skin, in the respiratory system, in the gastrointestinal and genitourinary tracts, and adjacent to blood and lymphatic vessels [1]. These cells live in tissues for several months and their number in normal conditions is relatively constant. However, mast cell number increases at local tissues in different pathophysiological conditions, including both acute and chronic inflammation. Accumulation of mast cells has been observed in the course of asthma, hay fever and allergic rhinitis [2-6], during inflammatory bowel disease, fibrosis, rheumatoid arthritis and interstitial cystitis [7-10]. An increase in mast cell number occurs in neoplasia, angiogenesis and host defense against parasites and microbes, as well [11-16].

It is well established that differentiation and maturation of mast cells last over several weeks [1, 17]. Therefore, migration of mature mast cells within tissues might be a key mechanism accountable for rapid local accumulation of these cells. For a long time, mature mast cells have been considered as stationary cells with no ability to migrate. However, current data indicate that many humoral factors mediate mast cell migration within tissues. Nowadays, it is certain that those are stem cell factor (SCF) [18, 19], transforming growth factor beta (TGF-β) [20, 21] and nerve growth factor (NGF) [22], that out of cytokines function as chemoattractants for different mast cell populations. It is also indisputable that some chemokines such as RANTES [23, 24] and IL-8 [25] cause chemotaxis of mast cells. Finally, it should be pointed out that other factors such as anaphylatoxins C3a and C5a [26], histamine [27], and acute phase proteins like C-reactive protein (CRP) [28] and serum amyloid A (SAA) [29] have been also found to induce mast cell migration.

Tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and IL-4 are synthesized by different cell populations. These cytokines take part in development and regulation of many physiological and pathological processes, including acute and chronic inflammation [30]. TNF-α, IL-6 and IL-4 also direct many immunological reactions, especially

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those depending on the Th1 or Th2 lymphocyte subpopulations [30-32]. Considering the significance of TNF-α, IL-6 and IL-4 in the course of a variety of pathophysiological processes, and at the same time keeping in mind that mast cells take part in many of them, we have decided to evaluate the influence of these three cytokines on mast cell migration.

Material and methods

Mast cells isolation

Mast cells were collected from peritoneal cavities of female albino Wistar rats weighing ~250 g. Mast cells were obtained by peritoneal lavage with 50 ml Hank`s balanced salt solution (HBSS) supplemented with 0.015% sodium bicarbonate. After abdominal massage (90 s) the cell suspension was removed from the peritoneal cavity and centrifuged (1200 rpm, 5 min). Cell pellets were polled (typically from two to three rats) and washed twice in complete Dulbecco`s Modified Eagle`s Medium (cDMEM) including DMEM, 10% foetal calf serum (FCS), 2 mM glutamine and 10 μg/ml gentamicin. To prepare purified mast cells, the suspensions of peritoneal cells were resuspended in 72.5% isotonic Percoll and centrifuged at 1500 rpm for 15 min. The upper cell layer was discarded, pelleted mast cells were washed twice in cDMEM by centrifugation (1200 rpm, 5min). After being washed, mast cells were counted and resuspended in an appropriate volume of cDMEM to obtain mast cell concentration ... cells/ml. Mast cells were prepared with purity over 90%, as determined by metachromatic staining with toluidine blue.

Migration assay

Mast cell migration was quantified *in vitro* using Boyden chamber assay in a 48-well chemotaxis chamber (Neuroprobe). Cytokines were prepared in cDMEM at varying concentrations ranging from 10^{-6} ng/ml to 10^{3} ng/ml. 30 μl of cytokines or buffer alone was placed in the lower compartment of microchemotaxis chamber. The lower compartments were covered with a polycarbonate 8 μm porosity membrane and then 50 μl of the cell suspensions (1.5×10^{6} cells/ml) were pipetted into the upper compartments. The chemotaxis chamber was then incubated for 3 hours in a humidified incubator with 5% CO_2 at 37°C. After the incubation period, cells adherent to the upper surface of the filter were removed by scraping with a rubber blade. Migrating cells adherent to the lower surface of the membrane were fixed in 99.8% ethanol, stained for 10 minutes with hematoxylin, cleared in distilled water and then mounted on microscope slide. Mast cell migration was quantified by counting the number of cells that had traversed the membrane and were attached to the bottom surface of the filter. In each experiment, 10 fields per filter were measured at x 400 magnification (high power field HPF).

Checkerboard analysis

Checkerboard analysis of mast cell migration was performed to find out whether the migration observed was chemotactic or chemokinetic. Varying concentrations of TNF-α were added to the upper and lower wells of the chemotaxis apparatus. Chemotaxis assay was performed as described above. Chemotaxis occurs when there is a positive gradient of the chemoattractant. Chemokinetic mobility occurs when the chemoattractant is present in both the bottom and upper wells at the same concentrations (equivalent concentrations), or when the chemoattractant is present in the top wells of the chamber (reversed gradient).

Histamine release assay

For histamine release assay, purified mast cells were resuspended in medium containing 137 mM NaCl, 2.7 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES buffer and 5.6 mM glucose supplemented with 1 mg/ml bovine serum albumine (BSA) (pH 6.9). Mast cell suspensions were carefully divided into 90 μl aliquots and incubated for equilibration at 37°C for 5 min. Subsequently, 10 μl of a stimulating agent i.e. TNF-α, IL-4, IL-6 or RANTES at different concentrations from 1 ng/ml to 100 ng/ml or compound 48/80 at the concentration 5 μg/ml was added. In every experiment appropriate controls for the determination of spontaneous histamine release in the absence of stimulating agent were included. Incubation was carried out for 30 minutes. The reaction was stopped by adding 1.9 ml of cold medium. Next, the cell suspensions were centrifuged (1200 rpm, 5 min) and the supernatants were decanted into other tubes for histamine determination. A total of 2 ml of distilled water was added to each tube with cell pellet. The histamine content was determined in both cell pellets (residual histamine) and supernatants (released histamine) by spectrofluorometric method. Histamine release was expressed as a percentage of the total cellular content of this amine after correction for spontaneous release found in controls.

Reagents

HBSS, DMEM, sodium bicarbonate, FCS, gentamicin and glutamine were obtained from GIBCO. NaCl, KCl, $MgCl_2$, $CaCl_2$, glucose, N-2-hydroxyethylpiperazine-N`-ethanesulphonic acid (HEPES), OPT, BSA, compound 48/80 were obtained from Sigma. Percoll was purchased from Pharmacia Biotech AB and rrRANTES (rat recombinant RANTES), rrIL-4, rrIL-6 and rrTNF-α were obtained from R&D Systems.

Statistical analysis

Statistical parameters included mean value, standard error of the mean (SEM) and Student`s *t*-test for "small groups". Values of $P<0.05$ were considered as statistically significant.

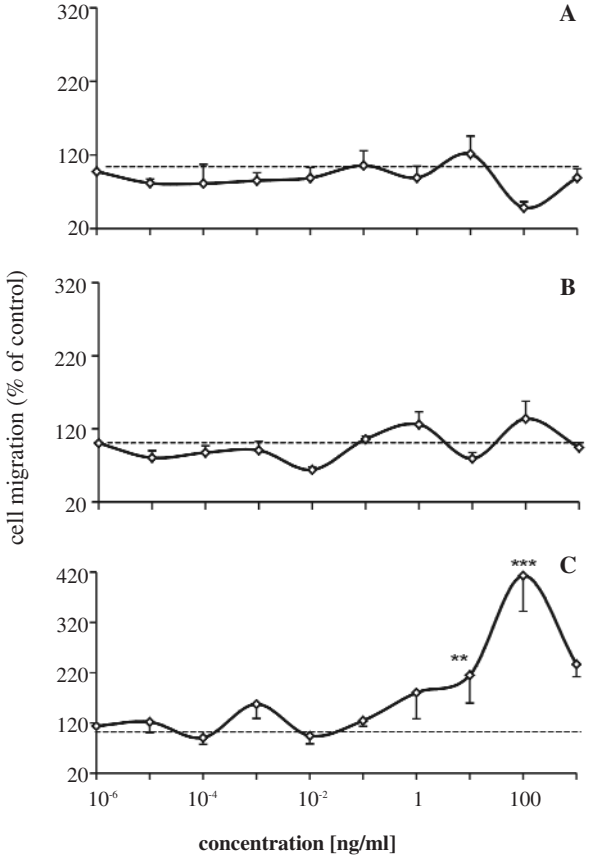

Fig. 1. Rat peritoneal mast cell migration in response to IL-4 [A], IL-6 [B] and RANTES [C]. Mast cells were incubated with different concentrations of cytokines or buffer alone (control mast cells) for 3 hours. In each experiment 10 high power fields were counted. Spontaneous migration of mast cells suspended in medium and with the same medium below the filter served as a control and was referred to as 100% migration. Each point represents the mean ± SEM of five experiments. **P<0.01, ***P<0.001

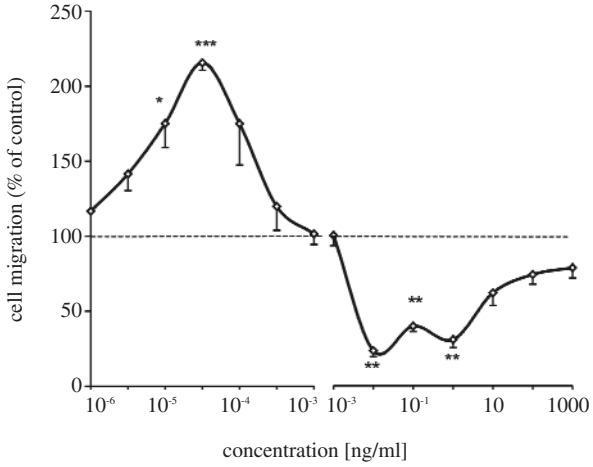

Fig. 2. Rat peritoneal mast cell migration in response to TNF-α. Mast cells were incubated with different concentrations of cytokine or buffer alone (control mast cells) for 3 hours. In each experiment 10 high power fields were counted. Spontaneous migration of mast cells suspended in medium and with the same medium below the filter served as a control and was referred to as 100% migration. Each point represents the mean ± SEM of five experiments. *P< 0.1, **P<0.01, ***P< 0.001

Results

We first evaluated the ability of IL-4 and IL-6 to induce migration of rat peritoneal mast cells. As shown in figures 1A and 1B, these cytokines were unable to induce migration of mast cells at none of the concentrations (from 10^{-6} ng/ml to 1000 ng/ml). For comparison, in the same experimental conditions rat mast cells migrated in response to RANTES, well-known mast cell chemotactic factor [23, 24], in a dose-dependent manner. The optimal concentration of RANTES for maximal migration of mast cells was 100 ng/ml (fig. 1C).

Next, we tested the migratory response of rat mast cells to the action of TNF-α. We have found that this cytokine influenced mast cell migration (fig. 2). Interestingly, mast cell migratory response exhibited itself in a bell-shaped biphasis profile. TNF-α at concentrations from 10^{-6} ng/ml to 5 x 10^{-4} ng/ml caused an increase in mast cell migration with a maximal response of 215% of control migration at 5 x 10^{-5} ng/ml. Higher concentrations of TNF-α, ranging from 0.01 ng/ml to 100 ng/ml induced significant inhibition of mast cell migration.

We conducted experiments to determine whether mast cell migratory response induced by TNF-α at concentrations ranging from 5 x 10^{-6} ng/ml to 10^{-4} ng/ml was due to directional (chemotaxis) or random (chemokinesis) activation. Mast cell migratory response was analysed by employing a checkerboard analysis. As shown in figure 3, the presence of cytokine in the lower compartment of Boyden chamber (positive gradient of TNF-α) resulted in gradient-dependent mast cell migration. However, a slight dose-dependent increase in migration of mast cells was also observed when TNF-α was only in the upper compartment of the chamber (negative gradient), or when equal concentrations of this cytokine were added in both the upper and lower chambers. Thus, we concluded that migration of rat mast cells towards TNF-α was based predominantly on chemotaxis and in part derived from chemokinesis.

In next experiments we have determined the ability of TNF-α, IL-6 and IL-4 to direct stimulation of rat mast cells to degranulation and histamine release. The cytokines were

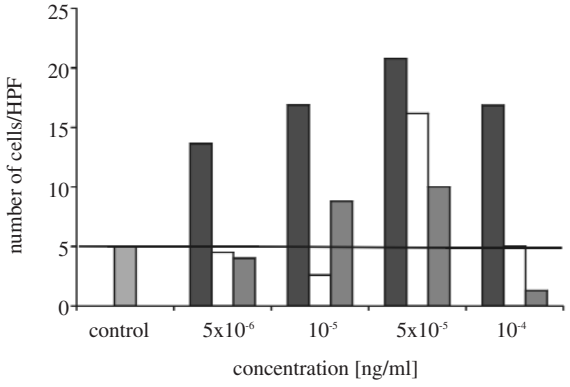

Fig. 3. Checkerboard analysis of rat peritoneal mast cell migration in response to TNF-α. Dark bars – the cytokine only in lower compartment (positive cytokine gradient), open bars – the cytokine only in upper compartment (negative cytokine gradient), striped bars – the cytokine both in upper and lower compartments in equal concentrations. In each experiment 10 high power fields were counted. The data are presented as a mean number of migrating cells per high power field (HPF)

used at a wide range of concentrations, from 10^{-5} ng/ml to 1000 ng/ml. We have stated that neither TNF-α nor IL-6 or IL-4, in any concentration used, directly activated mast cells to histamine release. For comparison, in the same experimental conditions rat mast cells were activated and released up to 64.0±2.8% of histamine to the challenge with compound 48/80 at concentration 5 μg/ml (data not shown).

Discussion

It is beyond any doubt that cytokines influence proliferation, differentiation and maturation of mast cells [17]. It is also well documented that cytokines in various ways affect mature tissue mast cell functions by modulating their activity, survival and apoptosis [1, 33]. Among the cytokines that regulate the biology of mast cells in tissues are TNF-α, IL-6 and IL-4. It has been proven that TNF-α modulates expression of intercellular ahesion molecule (ICAM-1) [34] and causes induction of MHC class II molecules on mast cell surface [35]. It also inhibits expression of integrins and downregulates mast cell adhesion [36]. This cytokine influences mast cell reactivity as well [37, 38]. IL-6 induces expression of integrins, stimulates mast cell adhesion to extracellular matrix [36], and influences mast cell reactivity [37]. IL-4 enhances expression of some adhesion molecules on mast cells [39], affects expression of FcεRI [40] and regulates the adhesion of these cells to extracellular matrix protein [41]. Moreover, IL-4 modulates mast cell reactivity [37, 42] and induces apoptosis of these cells [43].

In the present study we have analysed whether TNF-α, IL-6 and IL-4 can also affect migration of mature tissue mast cells. We have observed that *in vitro* IL-4 and IL-6, used at a wide range of concentrations, from 10^{-6} ng/ml to 10^{3} ng/ml, did not influence migration of rat mast cells isolated from peritoneal cavities. In the same experimantal conditions, RANTES caused migration of these cells, and the optimal concentration of RANTES for induction of maximal mast cell migration was 100 ng/ml, which is in accord with the observations made by other authors [23, 24]. Olsson et al. [44] have already documented that IL-6 does not cause migration of human mast cell line HMC-1, whereas IL-4 acts as mast cell chemoattractant. Taub et al. [45] have also observed migration of mouse bone marrow-derived mast cells towards IL-4. It is worth noticing, however, that these researches have been conducted on immature mast cells. Matsuura and Zetter [46] have found that IL-4 did not cause chemotactic response of mature mast cells isolated from murine peritonael cavities.

The results of our experiments have indicated that TNF-α greatly influenced rat mast cell migration, and the effect of this cytokine activity depends on its concentration. We have found that migration of mast cells was markedly stimulated by this cytokine, even at concentrations as low as from 5 x 10^{-6} ng/ml to 5 x 10^{-4} ng/ml, and showed a maximal response at the concentration of 5 x 10^{-5} ng/ml ($P<0.001$). Checkerboard analysis have indicated that this migration of rat mast cells towards TNF-α was based mainly on chemotaxis and in part is a result of chemokinesis. Higher concentrations of TNF-α ranging from 5 x 10^{-3} ng/ml to 100 ng/ml induced statistically significant inhibion of mast cell migration. Our data have indicated that chemotactic potency decribed here for TNF-α is also 100 to 1000-fold greater than for other well-known mast cell chemotaxins such as RANTES [23, 24] and SCF [18, 19]. Thus, it can be stated that TNF-α is one of the most effective mast cell chemotaxins identified and only TGF-β is a stronger chemoattractant factor, as it has a chemotactic effect at concentration 40 fM [20]. To our knowledge, only Olsson et al. [44] had previously tested the ability of TNF-α to induce mast cell chemotaxis. These authors have determined that this cytokine is a chemoattractant agent for human immature mast cells (HMC-1 line) with optimal migration at 10 ng/ml.

In inflammatory processes a vital role is undoubtedly played by both TNF-α and mast cells [47-49]. Our observations, that the effect of TNF-α on mast cell migration depends on the concentration of this cytokine, seem to be extremely interesting. These results suggest that in the early phases of the inflammatory process, when the concentration of TNF-α is low, this cytokine induces rapid influx of mast cells to the place of the ongoing process, which in turn leads to mast cell local accumulation. In the next phase of the process, when TNF-α concentration increases, this cytokine inhibits migration of mast cells thereby keeping these cells on the spot.

Mast cell migration largely depends on adhesion of these cells to extracellular matrix proteins [41, 50, 51]. A great role in this process is played by laminin [52, 53] and fibronectin [53-55]. In our in vitro experiments we have been using uncoated membranes. Studies on the influence of laminin and fibronectin on migration of rat mature mast cells induced by IL-6, IL-4 and particularly TNF-α are in progress in our laboratory.

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