EDITORIAL

INTERLEUKIN-9 AND MAST CELLS

S. TETÈ[1], M. NICOLETTI[2], A. SAGGINI[3], G. MACCAURO[4], M. ROSATI[5], F. CONTI[5], E. CIANCHETTI[6], D. TRIPODI[1], E. TONIATO[7], M. FULCHERI[8], V. SALINI[9], A. CARAFFA[10], P. ANTINOLFI[10], S. FRYDAS[11], F. PANDOLFI[12], P. CONTI[7], G. POTALIVO[13] and T.C. THEOHARIDES[14]

[1]Dental School, University of Chieti-Pescara, Italy; [2]Department of Biomedical Sciences, University of Chieti, Italy; [3]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [4]Department of Orthopedics, Catholic University of Rome, Rome, Italy; [5]Gynecology Division, Pescara Hospital, Pescara, Italy; [6]Ortona Hospital, University of Chieti-Pescara, Italy; [7]Immunology Division, Medical School, University of Chieti-Pescara, Italy; [8]Psychology Department, University of Chieti; [9]Orthopeadics Division, University of Chieti-Pescara, Italy; [10]Orthopeadics Division, University of Perugia, Perugia Italy; [11]Parasitology Department, Veterinary School, Thessaloniki, Greece; [12]Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy; [13]Nicola's Foundation, Arezzo, Italy; [14]Department of Pharmacology and Experimental Therapeutics, Biochemistry and Internal Medicine Tufts University School of Medicine, Tufts-New England Medical Center, Boston, MA, USA

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Mast cells are granulated hematopoietic cells derived from stem cells that reside in nearly all tissues and are involved in protection of a host from bacterial infection with a protective and pathogenic activity. Mast cells are important for both innate and adaptive immunity in tissues which are in close contact with the environment. These cells express proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor which are necessary for innate immunity. Mast cells also produce interleukin-9 and enhance mast cell expression of several cytokines including IL-1beta, IL-5, IL-6, IL-9 and IL-13. In addition, IL-9 can induce mast cell production of TGF-beta which can have proinflammatory downstream effects. IL-9 can function as either a positive or a negative regulator of immune responses and can have a detrimental role in allergy and autoimmunity. Furthermore, IL-9 contributes to disease by promoting mast cell expansion and production of IL-13 which in turn contributes to airway hyperresponsiveness. Here, in this editorial we review the interrelationship between IL-9 and mast cells.

Mast cells were first described in 1879, but their origin remained controversial for almost a century. At least two easily identifiable types of human mast cells have been reported: connective tissue mast cells that contain tryptase and chymase (TC mast cells), and mucosal mast cells that contain only tryptase (T mast cells) (1-3). These two cell types differ in the number and type of secretory granules they contain, as well as their responsiveness to stimuli (4-9). For instance, TC mast cells contain more heparin,

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Mailing address: Prof. S. Tetè,
Dipartimento di Scienze Orali,
Università "G. d'Annunzio" Chieti- Pescara",
Via dei Vestini, 31
Chieti, Italy
Tel./Fax: +39 0871 3554095
e-mail: tete@unich.it

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Table I. *Biological effects of IL-9 on multiple cell types.*

- **Growth factor (T cells)**
- **IgE production (B cells)**
- **Enhances Treg function**
- **Promotes Th17 differentiation**
- **Mast cell growth and survival**
- **Induces expression of Fc RI alpha**
- **Increases expression of IL-6, mast cell proteases**
- **Involved in cell metaplasia**
- **Enhances chemokine production in several cell types**
- **Supports erythroid colony formation**
- **Promotes maturation of hematopoietic stem/hematopoietic progenitors**
- **Activates production of IL-8, IL-13, and eotaxin**

whereas T mast cells contain more chondroitin sulphate; in addition, TC mast cells respond to neuropeptides, whereas T mast cells do not (10-14). Mast cells express primarily pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor-α (TNF-α), which are necessary for innate immunity (15-18). Both the expression and the synthesis of these cytokines, however, depend on: 1) the state of maturation of the mast cells; 2) the location of mast cells within compartments of the same or different tissues (19); and 3) the type of cytokine(s) present during mast cell activation (20-23). However, mast cells can also produce cytokines that are released from T helper 2 (Th2) cells (so-called Th2 cytokines), such as IL-4 and IL-13, which are present in increased levels in several diseases (24-28). Th9 phenotype cells develop *in vitro* in the presence of IL-4 and TGF-β and secrete high levels of IL-9 as well as IL-10, CCL17 and CCL22 (29-34).

Mast cells have also been reported to produce IL-9 (35-40). One of the main targets of IL-9 is the mast cell and, as mentioned earlier, initial studies described a role for IL-9 in promoting the expansion of mast cell populations (41-44). Subsequent research on mice that were deficient for both IL-9 and IL-9Rα showed that IL-9 is not required for the generation of mast cell precursors, as the basal numbers of mast cells in these mice were normal. However, mice that were deficient for IL-9 or IL-9Rα showed defective expansion and recruitment of mast cell populations in response to intestinal nematode infection or following the induction of experimental autoimmune encephalomyelitis (EAE) (45-50). IL-9 can induce mast cell production of TGFβ, which can have pro-inflammatory downstream effects on neurons in a murine stroke model and on epithelial cells during intestinal inflammation (51-54). Following antigen-specific crosslinking of surface IgE molecules on mast cells, IL-9 can enhance mast cell expression of several cytokines, including IL-1β, IL-5, IL-6, IL-9, IL-10 and IL-13 (55-59). Of these cytokines, IL-5 and IL-13 are of particular interest, as the previously described direct effects of IL-9 in promoting eosinophilia and mucus production in the lung and the gut instead seem to be indirect effects mediated through the induction of these cytokines by IL-9 (60-63).

IL-9 can function as both a positive and negative regulator of immune responses (Table I). In general, it seems that IL-9 has detrimental roles during allergy and autoimmunity (64-67). However, during parasitic infections, IL-9 can help to clear the pathogen, and during skin transplantation, IL-9 can promote the maintenance of a tolerant environment (68-69). During some allergic responses in the lung, which are traditionally thought of as being T_H2 cell-mediated, IL-9 contributes to disease by promoting mast cell expansion and production of IL-13, which in turn promotes the release of mucus that contributes to airway hyperresponsiveness (70-72). The initial influx of mast cells in this model is likely to be driven by IL-9 that is derived from NKT cells

(73-75). In addition, T_H9 cells also seem to contribute to disease in this model, as mice with PU.1-deficient T cells and a global IL-25 deficiency are protected from allergic airway inflammation (76-78).

Interleukin-9 (IL-9)

IL-9 cloned more than 20 years ago was originally identified as a T-cell growth factor and is a member of the common γ-chain-receptor cytokine family, with other members including IL-2, IL-4, IL-7, IL-15 and IL-21. (79). Moreover, IL-9 has been reported to be expressed by T helper 2 (T_h2), T_h9, and regulatory T (T_{Reg}) cell subsets and appears to increase the suppressive effect of Treg cells as well as enhance the proliferation and/or accumulation of Th17 cells (80-81). The Th17 cells have been also reported as a T-cell subset that has the ability to produce IL-9 both *in vitro* and *in vivo* (82). There is much evidencs to suggest that IL-9 production in Th17 cells is pathogenic in several immunological diseases. It is now clear that IL-9, along with IL-17 play a role in modulating immune responses in some types of infections.

IL-9 was first purified and characterized as a T cell and mast cell growth factor respectively termed P40, based on m.w., or mast cell growth-enhancing activity and has pleiotropic functions in the immune system (83). The major source of IL-9 is T lymphocytes; however, mast cells involved in the pathogenesis of inflammatory diseases are also a source of IL-9 in response to LPS, IL-1, histamine, and antigen-specific immunoglobulin E antigen. However, IL9 itself can help to facilitate mast cell growth and expansion.

In certain conditions regulatory T cells (Tregs) may also produce IL-9. It has been found that TGF-β and IL-4 enhance IL-9 production from activated T cells. IL-9 has biological effects on a number of distinct cell types such as: lymphocytes, mast cells, smooth muscle cells, epithelial cells and demonstrates proinflammatory activity in several models of inflammation. Therefore, IL-9 affects immune cells, as well as resident tissue cells that contribute to the development of inflammation.

Results from other reports demonstrated that IL-9 is involved in autoimmune inflammation. Interleukin (IL)-9 regulates the development of airway inflammation, mucus production, airway hyperresponsiveness, and airway fibrosis largely by increasing mast cell numbers and activity in the airways. Thus, targeting the IL-9 pathway may provide a new therapeutic modality for asthma, and allergic and inflammatory diseases.

Interleukin-9 (IL-9) has attracted renewed interest owing to the identification of its expression by multiple T helper (T(H)) cell subsets, including T(H)2 cells, T(H)9 cells, T(H)17 cells and regulatory T (T(Reg)) cells.

Interleukin-9 (IL-9) activates a heterodimeric receptor that consists of the IL-9 receptor α-chain (IL-9Rα) and the γ-chain and promotes the cross-phosphorylation of Janus kinase 1 (JAK1) and JAK3. This leads to the activation of signal transducer and activator of transcription 1 (STAT1), STAT3 and STAT5 and the upregulation of IL-9-inducible gene transcription (79). IL-9 was first linked to T helper 2 (T_H2) cells, which express IL-4, IL-5 and IL-13 during parasitic infections and provides a protective role in immunity to intestinal parasites (68). This is good evidence that IL-9 plays a role in regulating immunity to infectious diseases. Production of IL-9 occurs in an autocrine manner in response to IL-9-induced signals and as a consequence of the cross-linking of IgE molecules on the surface of mast cells. Histamine and IL-1β, can promote further IL-9 production. As IL-9 is a growth factor for mast cells, it is thought that these pathways promote the survival and expansion of mast cells during an active immune response. Results from other reports demonstrated that IL-9 is involved in autoimmune inflammation.

The purpose of this editorial is to summarize the interrelationship between IL-9 and mast cells in the pathogenesis of inflammatory diseases. Cytokine receptor antagonists, combined with natural substances that inhibit mast cells, such as plant-derived flavonoids (84, 85), provide new therapeutic options for diseases where inflammatory mast cells are involved.

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