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NEWS & VIEWS

Legends of Allergy and Immunology

Legends of allergy and immunology: Sergio Romagnani

I, Enrico Maggi, have known Sergio Romagnani in 1973 and from that date I tightly collaborated with him continuously for over 45 years. Paola Parronchi and Francesco Annunziato joined his group at early 1980s and 1990s, respectively.

Sergio started his work in 1964 after graduating in Medicine under the supervision of Professor Mario Ricci at Institute of Internal Medicine of University of Florence (Italy). In 1968, he attended the John Turk's lab at Saint John's Hospital of London transferring to Florence immunologic techniques still unknown in Italy. Through them he published the first studies on the immune purification of *Dermatophagoides pteronyssinus* allergens and lymphocyte response to allergenic components. He then developed a method for studying the in vitro production of IgE by B lymphocytes (1981) and the role of T cells on IgE synthesis (1985). His first international breakthrough was the discovery that human IgE production by B cells was due to the IL-4 produced by some T-cell clones, whereas interferon-γ, alternatively, produced by other clones, was inhibitory (1988).

In 1991, mainly through the collaboration of Gianfranco Del Prete, Paola Parronchi and myself,[1] he was the first to demonstrate type 1 (Th1) and type 2 (Th2) T lymphocytes in humans.[2] At that time, immunology was dominated by murine studies and, therefore, the major ambition for a human immunologist was to repeat in humans what already discovered in mice. However, in 1993, thanks to the work by Roberto Manetti,[3] he discovered that the human Th1 polarization was due to IL-12 produced by dendritic cells, then confirmed also in mice. Based on this study, Sergio hypothesized that the type of adaptive immunity was related to the type of innate immunity response, then becoming an established paradigm and the basis of the so-called "hygiene hypothesis" for allergy. Between 1992 and 1997, the Romagnani's group demonstrated the pathogenic role of Th1 cells in several autoimmune and chronic inflammatory disorders (autoimmune thyroiditis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, and *Helicobacter pylori*-induced autoimmune gastritis), whereas Th2 responses were responsible for vernal conjunctivitis, atopic dermatitis, allergic rhinitis, and bronchial asthma, thus introducing the so-called Th1/Th2 paradigm[4] (1997) (Figure 1). Then after, he moved to study the plasticity of polarized T effector subsets and the different activity of T regulatory cells from the early thymus and adult blood on such subsets. In the same period, he demonstrated CCR3 on human mast cells (1999) and identified a previously unknown chemokine receptor (CXCR-B), recognizing the until then orphan chemokine Platelet Factor-4.

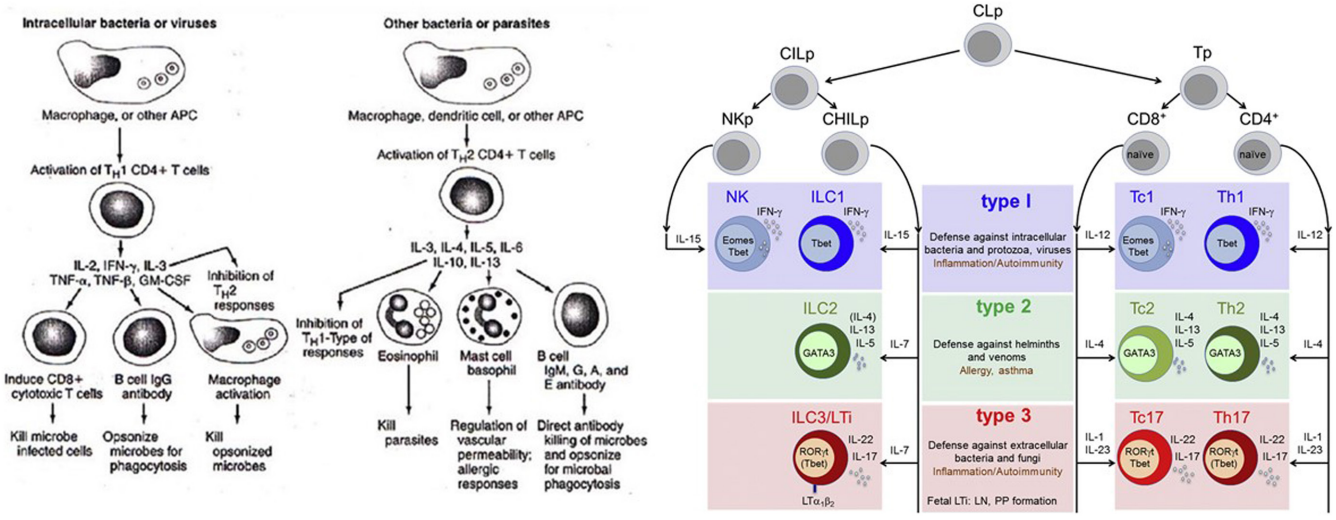

FIGURE 1 On the left: the inclusion of the Th1/Th2 paradigm (as adapted from Romagnani) in one of the major books of Medicine: Harrison's. Principles of Internal Medicine (15th edition, 2001, p. 1863). On the right: the more recent view by Sergio Romagnani on the existence of three major types of both innate and adaptive cell-mediated effector immunity, as detailed in Ref.[6]

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TABLE 1 Sergio Romagnani: major contributions

- IgE production by human B cells is due to IL-4 produced by T lymphocytes and is inhibited by interferon-γ (1988)
- Type 1 and type 2 T helper (Th1 and Th2) exist not only in mice but also in humans (1991)
- Th1 polarization of naïve T helper into Th1 cells is due to the activity of IL-12, which was the first demonstration that the type of adaptive immunity is due to the type of innate immunity (1993)
- Allergy is a Th2 cell-mediated hypersensitivity (1994) whereas Th1 cells are involved in the pathogenesis of some autoimmune and chronic inflammatory disorders, thus defining the Th1/Th2 paradigm in humans (1992–1997)
- CCR3 is expressed on human mast cells (1999) and the new chemokine receptor, named as CXCR3-B, is the receptor of platelet factor-4 (2003)
- Human Th17 cells are phenotypically and functionally characterized and their rarity is due to the shift into non-classic Th1 cells; they play a critical role in the pathogenesis of autoimmune and chronic inflammatory disorders (2007–2011)
- Human memory Th2 cells are plastic (subsequently shown also for Th17 cells and ILC2) and can be shifted into cells with a more protective cytokine profile (type 1 response); this first description introduced the concept that mechanisms of allergic inflammation could be modified by external interventions, thus paving the way to the use of biologic drugs with pathogenic targets (1992–2001)

Note: Sergio Romagnani is author of 468 peer-reviewed publications, with a number of citations equal to 42,285 and a h-index of 105 (from Google Scopus).

In 2007, mainly through collaboration with Francesco Annunziato e Lorenzo Cosmi,[5] Sergio was the first to define the main features of human Th17 cells and to identify their origin from a subset of thymic CD161+ T cells under the combined activity of IL-1β and IL-23 (Figure 1). More importantly, the mechanisms responsible for the rarity of these cells in the inflammatory sites were identified, the most important being the shifting of Th17 cells into Th1 cells under the activity of IL-12 and TNF-α. These cells, defined as "non-classic Th1 cells," were found to be the most important players in the pathogenesis of autoimmune and chronic inflammatory disorders (Table 1).

From 1995, he was Director of the Department of Internal Medicine and, after his retirement, (2010) Professor Emeritus of the University of Florence.

Because of his studies, Sergio received several awards and honors: Honorary Professor of the Universidad Major de San Marco (Lima, Peru) in 1999. President of EFIS and Scientific Program Coordinator of the EAACI in 2000, Member of the IUIS Council and Chairman of the Clinical Immunology Committee of the same Society in 2004, Honorary Member of the American Association of Immunologists and of the Societies of Allergology and Clinical Immunology from Germany, Austria, Argentina, Peru, and Chile. In 2005, he was honored from the President of the Italian Republic as Great Official of the Order of Merit for having increased the level of the Italian science throughout the world. In 2021, he received the "Gold Florin," the highest honor from the city of Florence.

FIGURE 2 Sergio Romagnani (on the center) with the three major co-workers of his carrier, Enrico Maggi (on the left) and Francesco Annunziato and Paola Parronchi (on the right).

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The authors have had the pleasure and honor of working in an environment characterized by very high scientific levels, intense and stimulating discussions, great energy and enthusiasm, all hallmarks of Romagnani's approach to research. They worked together at Medicine Faculty of the University of Florence also beyond his retirement (2010) (Figure 2). Sergio Romagnani taught us how translational research from basic to clinical immunology can best bear fruit in prepared minds. For these reasons, we believe that he must be considered a real legend and one of the most insightful scientists of Allergology and Immunology of the last decades.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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