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Review Article

Th1, Th2, Tc1 and Tc2 cells of patients with otolaryngological diseases

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Abstract

Cytokines are important regulatory mediators secreted by T cells and other immunoactive cells. Based on the cytokine synthesis patterns, CD4 T cells can often be classified into at least two populations with different immune regulatory functions. The Th1 cells, producing interleukin (IL)-2 and interferon (IFN)-γ, are often associated with cell-mediated immune responses such as delayed type hypersensitivity (DTH), whereas Th2 cells, secreting IL-4, IL-5 and IL-13, usually provide B cell help and enhance allergic reactions. Naïve CD8 T cells, similar to CD4 T cells, can differentiate into at least two subsets of cytolytic effector cells with distinct cytokine patterns. The Tc1 cells secrete a Th1-like cytokine pattern, including IL-2 and IFN-γ. The Tc2 cells produce Th2 cytokines, including IL-4, IL-5 and Il-10. There is increasing evidence that Th1/Th2 and Tc1/Tc2 cytokine imbalance has been of pathogenetic importance in various diseases, such as allergic and autoimmune diseases. The present review article focuses on the evidence that the imbalance of Th1/Th2 and Tc1/Tc2 cytokines plays an important role in various otolaryngological diseases, such as Kimura's disease, Wegener's granulomatosism, acute perceptive hearing loss and Meniere's disease. It is concluded that the predominance of Th1 or Th2 and Tc1 or Tc2 cells may contribute to the mechanism in the pathogenesis of these otolaryngological diseases.

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Introduction

Recent studies reported that T helper (Th) cells subdivided into mutually exclusive subsets: (i) Th1 cells, which produce interleukin (IL)-2 and interferon (IFN)-γ; (ii) Th2 cells, producing especially IL-4, IL-5, IL-9, IL-10 and IL-13; and (iii) cells that exhibit an unrestricted cytokine profile (Th0).[1–4] The Th1 cells are involved primarily in cell-mediated immune responses, whereas Th2 cells fulfill an important role in humoral and allergic immune responses[4] (Fig. 1). Similarly, $CD8^+$ T cells have recently been subdivided into $CD8^+$ T cells secreting a Th1-like cytokine pattern, which are defined as Tc1 cells, compared with $CD8^+$ T cells that secrete a Th2-like pattern (Tc2 cells).[2–5] A quantitative and functional disturbance of Th1 or Th2 cells is probably important for the pathogenesis of various otolarygological diseases; however, studies investigating this point are rare. The present review focuses on the evidence that the imbalance of Th1/Th2 and Tc1/Tc2 cytokines plays an important role in various otolaryngological diseases, such as Kimura's disease, Wegener's granulomatosis, acute perceptive hearing loss and Meniere's disease.

Wegener's granulomatosis

Wegener's granulomatosis (WG) is characterized by the classic clinicopathological features of necrotizing granulomatous vasculitis involving the upper and lower respiratory tracts, glomerulonephritis and variable degrees of systemic small vessel vasculitis. Necrotizing granulomatous inflammation produces nasal mucosal ulceration and saddle nose formation, tracheal inflammation etc. The causative agent leading to granuloma formation

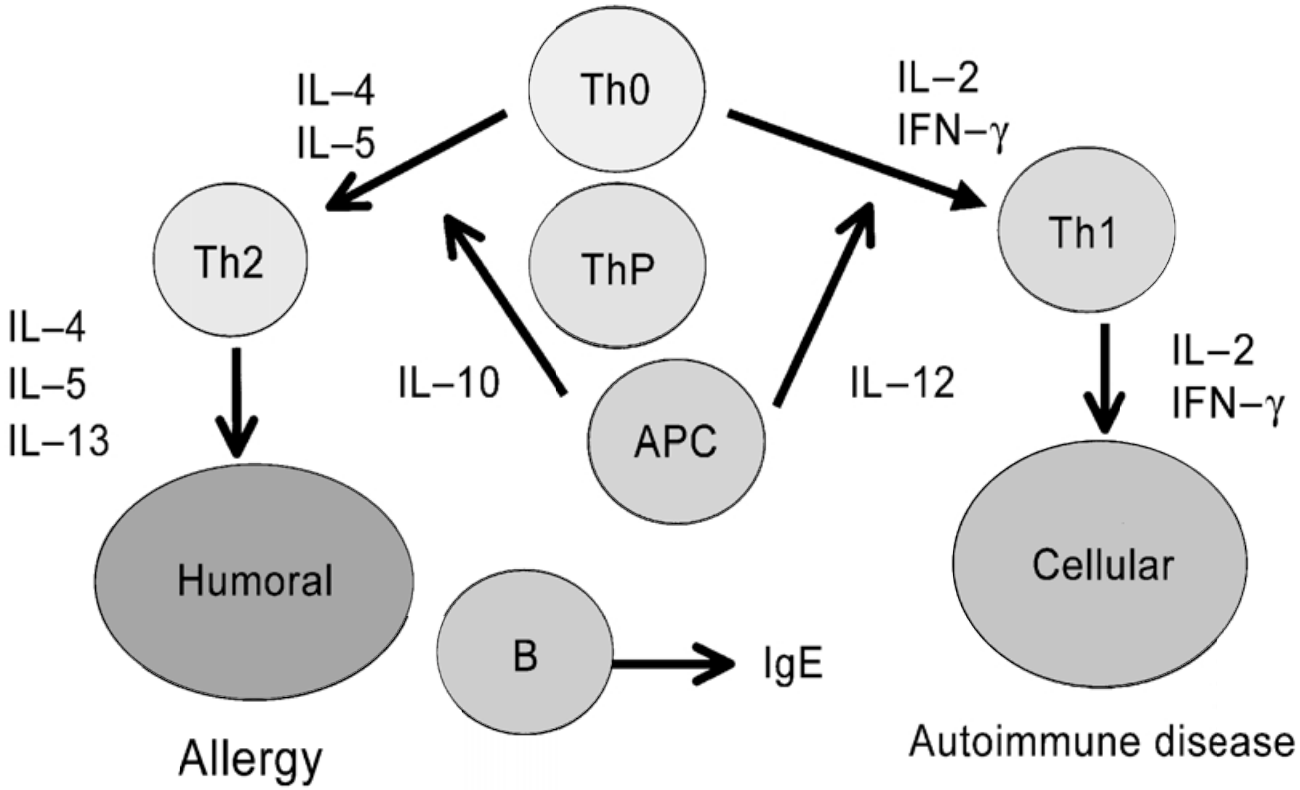

Fig. 1 T helper (Th) 1 and Th2 cells. ThP, Th precursors; IL, interleukin; APC, antigen-presenting cell; IFN-γ, Interferon-γ.

remains unknown, but the presence of granulomatous inflammation suggests T cell hyperactivity. In WG patients, there was a strong predominance of Tc1 cells and no significant difference was noted in the percentage of Th1, Th2 and Tc2 cells, which suggests that the predominance of Tc1 cells may contribute to the mechanism in the pathogenesis of WG.[6] Interferon-γ and IL-4 also induce the differentiation of naïve $CD8^+$ cells into type 1 and type 2, respectively, whereas IL-12 promotes the development of Tc1 cells.[7] After differentiation, effector T cells show a stable cytokine pattern and rarely, if ever, switch to the opposite phenotype or revert to their precursor state. However, some modifications have been described. The Th0 cells can shift towards Th1 or Th2 in response to cytokines and human Th2 clones can transiently express IFN-γ after IL-12 treatment.[7–9] The Th1 cells can produce IL-4 when stimulated in the presence of IL-4.[9] Interleukin-4 also inhibits the ability of differentiated Tc1 cells to synthesize IL-2 and down-regulates other functions, including cytokine synthesis, proliferation and long-term cytotoxicity.[10] In addition to their classic role in the killing of infected cells, CD8 T cells play a role in the regulation of the activation and differentiation of CD4 cells. This regulation could be mediated through secreted products (cytokines, chemokines) or by cell–cell interactions. The CD8 T cells can alter the balance of Th1/Th2 responses *in vivo* by influencing the development of IL-4- or IFN-γ-secreting CD4 cells.[11] In addition, CD8 T cells appear to play a role in the development of CD4 perforin-mediated cytotoxicity and have also been reported to suppress CD4 proliferative responses through the inhibition of costimulatory interactions.[12,13] The CD8 cells are also capable of influencing other components of the immune response, such as the recruitment of eosinophils into the lungs during respiratory syncytial virus infection or allergic asthma, the activation of macrophages and the regulation of antibody production by B cells.[14,15] In rheumatoid arthritis patients, there was a strong predominance of Th1 and Tc1 in synovial fluid, whereas no major difference in cytokine production was seen in peripheral blood.[16] In WG, the local secretion of high levels of IFN-γ and tumor necrosis factor may represent an important amplification loop leading to a tissue-destructive inflammatory response.[17,18] Interferon-γ may activate local macrophages and granulocytes to produce

pro-inflammatory cytokines and toxic metabolites, which cause damage to the tissue and maintain the inflammation.[6,19]

Acute sensorineural hearing loss and Meniere's disease

Meniere's disease is characterized by vertigo, hearing loss and tinnitus with episodic attacks of fluctuating severity. Hallpike and Cairns clearly described endolymphatic hydrops as the basic histopathological lesion associated with Meniere's disease.[20] In 1979, McCabe described bilateral rapidly progressive sensorineural hearing loss (SNHL) as the first convincing autoimmune hearing loss.[21] Since then, many immunological studies of SNHL have been undertaken in order to clarify its pathogenesis. However, several conflicting results have been reported and, as a result, the actual inner-ear target antigen remains unclear.[22–25] Gloddek *et al*. also reported an animal model that was developed by systemic challenge with swine inner-ear protein antigens.[26] These authors have established an autoreactive inner-ear-specific T helper cell line that is capable of passive transfer of the disease without antigen immunization. Infiltration of T helper cells in the inner ear tissue was observed in the transferred rats with hearing loss. Ikezono *et al*.[27] have speculated that the infiltrating cells in a labyrinth may produce various inflammatory mediators, such as cytokines, chemokines and eicosanoids. These mediators can flow longitudinally into the endolymphatic sac in maintaining homeostasis of the inner ear.[27,28] Furthermore, by studying the human temporal bone, similar findings of focal infiltration of lymphocytes and plasma cells in the tympanic lamellae have been observed.[29] These findings are both experimental and clinical evidence for the understanding of acute low-tone sensorineural hearing loss (ALHL) and Meniere's disease as cellular-mediated immune diseases of the inner ear. The immune response appears to develop endolymphatic hydrops associated with fluctuating hearing loss and play an important role in some types of acute sensorineural hearing loss (ASHL). In patients with ASHL, there was a strong predominance of Th1 cells and no significant difference was noted in the percentage of Th2, Tc1 and Tc2 cells.[31] Patients with Meniere's disease showed significantly increased natural killer cell activity, but not Th1, Th2, Tc1 and Tc2 dominance.[31] These patients had no obvious systemic or local disease except in the inner ear. Therefore, an abnormality of the Th1/Th2 balance in ASHL and increased natural killer cell activity in Meniere's disease are thought to be related to the inner ear disorder.[30,31] These results are consistent with the possibility that the etiology of ASHL and Meniere's disease involves an immune response.

Kimura's disease

Kimura's disease is a chronic granulomatous disease of unknown etiology. It is characterized by a single or multiple indolent tumor occurring in the subcutaneous soft tissue, especially the parotid gland and subumandibular glands, swollen lymph nodes in the neck, marked peripheral blood eosinophilia, high serum levels of IgE and lymph follicle proliferation with eosinophil infiltration.[32–34] These findings may allow us to speculate that Th2 cells play an important role in the pathogenesis of Kimura's disease. In patients with Kimura's disease, there was a strong predominance of Th2 and Tc1 cells and no statistically significant difference was noted in the percentage of Th1 and Tc2 cells.[35] These results indicate that the predominance of Th2 and Tc1 cells may contribute to the mechanism in the pathogenesis of Kimura's disease. The Th2 cells fulfilll an important role in humoral and allergic immune responses through the production, in particular, of IL-4, IL-5, IL-9, IL-10 and IL-13. The Th2 cells can be readily found in the late-phase response in the lung and after intradermal injection of antigen into the skin.[36,37] Some of the cytokines secreted by these cells have direct pro-inflammatory effects. Both IL-4 and IL-5 promote the recruitment and survival of esosinophils and mast cells and augment IgE production from B cells. Contrary to our expectation, there was a strong predominance of Tc1 cells in patients with Kimura's disease.[35] The Tc1 cells may contribute to suppress the induction of Th2 responses and IgE production during the induction phase through the production of INF-γ[38,39] (Table 1). Recently, Ishimitsu *et al*. reported that Th2-mediated allergic responses were suppressed

Table 1 Comparison of $CD4^+$ and $CD8^+$ T cell subset effector functions

	Th1	Th2	Tc1	Tc2
IgE	↓	↑	↓	↓
Cytotoxic	↑		↑↑	↑↑
Apoptosis	Low		High	
Survival	Good		Poor	
Anergy	Resistant		Susceptible	

by the induction of Tc1 responses.[39] Our findings[35] support the idea that Tc1 cells may augment the Th2 responses during the effector phase in Kimura's disease.

Conclusions

An imbalance of Th1/Th2 and Tc1/Tc2 cells was observed in various otolaryngological diseases, such as Kimura's disease, WG and acute perceptive hearing loss. It is concluded that the predominance of Th1 or Th2 and Tc1 or Tc2 cells may contribute to the mechanism in the pathogenesis of these otolaryngological diseases.

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