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Mini review

The IL-17A/IL-17RA axis in pulmonary defence and immunopathology

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ABSTRACT

The interleukin (IL)-17A/IL-17 receptor A (IL-17RA) axis is emerging as a key player in host defence. Several studies have demonstrated that IL-17A-mediated responses play a critical role in both acute and chronic inflammation induced by infectious agents, environmental stimuli and genetic diseases in the airways. In this regard, it is becoming evident that IL-17A/IL-17RA signalling may have a protective and beneficial impact on health, but that it can also result in detrimental outcomes. On one hand, the IL-17A/IL-17RA axis can contribute to the elimination of noxious stimuli and to the resolution of acute inflammatory processes; on the other hand, it can exacerbate immunopathological responses, contributing to the development and progression of chronic respiratory illnesses. In addition, cellular and molecular signatures underlying IL-17A/IL-17RA signalling have been increasingly identified, although further studies are needed to clarify such complex responses. Here, we discuss the latest discoveries on the role of the IL-17A/IL-17RA axis in driving host pulmonary defence and immunopathology.

1. Introduction

The cytokine IL-17A was first identified in 1993, and was initially called cytotoxic T lymphocyte-associated antigen 8 (CTLA-8) [1]. Today, the IL-17 cytokine family represents a wide class of pleiotropic inflammatory molecules that are structurally related. In the last two decades, researchers have particularly focused on the biological functions and regulation of IL-17A and IL-17F, although the functions of other IL-17 family members have recently become active areas of study. With respect to immunity, IL-17 cytokines modulate the outcomes of pathologic processes. For example, in the airways, IL-17-mediated immunity has been shown to modulate host defences, as well as the resolution phase of the inflammatory response. In addition, in the context of lung pathologies such as infectious processes, IL-17 cytokines have been shown to take active part in both acute and chronic phases of pulmonary inflammation. Among factors involved in IL-17-mediated responses, IL-17RA plays a pleiotropic role by interacting also with other IL-17 receptors (Fig. 1), thereby potentially activating pathways other than those triggered by IL-17A. This review aims to discuss the current knowledge on the role of the IL-17A/IL-17RA axis in lung and to note issues that still need to be clarified in this field.

2. The IL-17 cytokines family and their receptors

Six members have been identified in the IL-17 family, including IL-17A, IL-17F, IL-17E (also known as IL-25), IL-17C, IL-17B and IL-17D (Fig. 1), which all signal as homodimers [2]. In addition, the IL-17F/IL-17A heterodimer has also been identified [3]. IL-17A has the highest amino acid identity to IL-17F, while IL-17E is the most divergent IL-17 cytokine [2]. It has been proposed that the amino acid sequences of IL-17C, IL-17E and IL-17B differ substantially from those of IL-17A and IL-17F, suggesting potentially distinct sub-classes. Evidence supporting this hypothesis comes not only from the close chromosomal location of *Il17a* and *Il17f* genes in both humans and mice but also from biological evidence described in the literature. In particular, IL-17A and IL-17F promote neutrophil-mediated airway inflammation, whereas IL-17E (IL-25) is involved in type 2 responses by promoting Th2 cytokines [4]. Among the other IL-17 cytokines, IL-17C and IL-17D expression has been described in lung [5,6], although their functions are unclear; conversely, to our knowledge, there is no information on IL-17B presence in this tissue.

This cytokine family activates down-stream signalling through the IL-17 receptor (IL-17R) family, which includes five members

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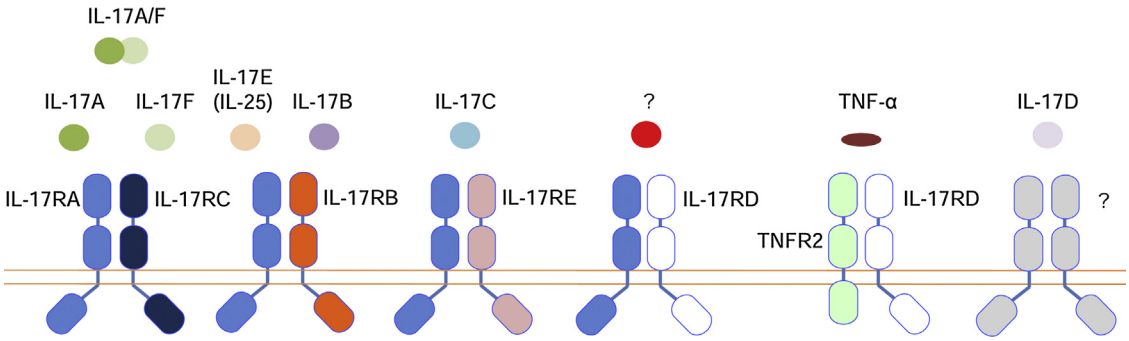

Fig. 1. Interleukin-17 cytokines and receptors. The IL-17 cytokine family includes six members, namely IL-17A, IL-17F, IL-17E (also known as IL-25), IL-17B, IL-17C and IL-17D, which signal as homodimers or heterodimers. IL-17 cytokines activate down-stream signalling through the IL-17 receptor (IL-17R) family, including homodimers or heterodimers formed by IL-17RA, IL-17RB, IL-17RC, IL-17RE or IL-17RD. In particular, IL-17A binds to the heterodimer IL-17RA/IL-17RC.

named IL-17RA, IL-17RB, IL-17RC, IL-17RE and IL-17RD (Fig. 1). It is widely accepted that homodimers or heterodimers are required for functional IL-17 signalling. In particular, IL-17RA and IL-17RC heterodimers are required to transduce IL-17A and IL-17F homodimer- and IL-17A/F heterodimer-mediated signals [3], whereas the IL-17RA and IL-17RB heterodimers are required for pathways activated by IL-17E (IL-25) or by IL-17B [2,7,8]. In addition, IL-17RE synergistically acts as a heterodimer with the IL-17RA subunit in recognition of IL-17C [5]. Finally, although the role of IL-17RD is still controversial [9], a recent study found that Tumour Necrosis Factor Receptor 2 (TNFR2) may heterodimerise with IL-17RD to mediate TNF-α signalling [10].

3. IL-17A-secreting immune cells in the lung

IL-17 cytokines and type 17 cells may determine the outcome of respiratory diseases, playing a critical role in the resolution of the infectious/inflammatory processes or in determining pathologic outcomes. IL-17A released from innate or adaptive immune cells may have a different role in response to pathogens, by modulating

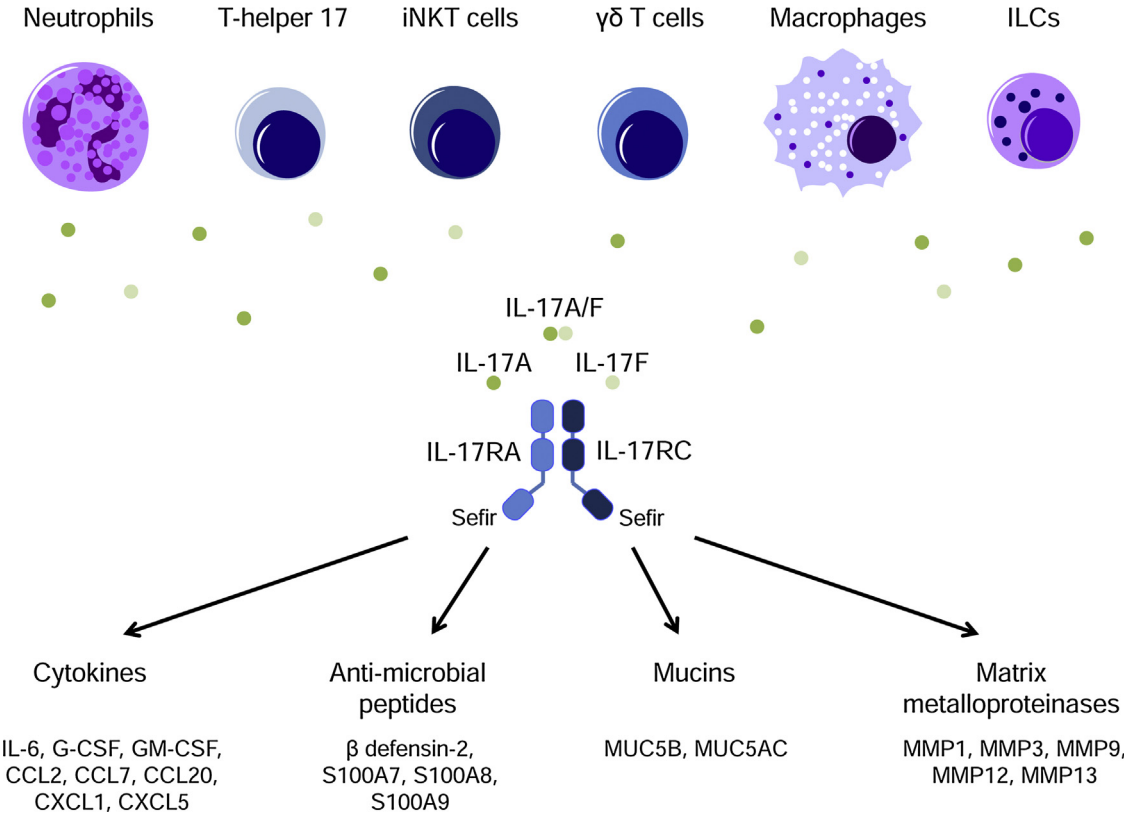

Fig. 2. The IL-17A/IL-17RA axis. This figure illustrates the IL-17A/IL-17RA-axis, from IL-17A secretion by immune cells, to the production of downstream mediators. IL-17A is produced by several innate and adaptive immune cells and binds to IL-17RA/IL-17RC, a receptor engaged also by IL-17F and IL-17A/IL-17F. Activation of down-stream signalling pathways leads to the production of cytokines (IL-6, G-CSF, GM-CSF), chemokines (CCL2, CCL7, CCL20, CXCL1, CXCL5), anti-microbial peptides (β defensin-2, S100A7, S100A8, S100A9), mucins (MUC5B and MUC5AC) and matrix metalloproteinases (MMP1, MMP3, MMP9, MMP12 and MMP13).

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