IL-27 signaling promotes Th1 responses during chronic pulmonary infection with Aspergillus fumigatus

Ashley Strickland*, Yanli Chen, Gongguan Liu, Meiqing Shi
Division of Immunology, Virginia-Maryland College of Veterinary Medicine, University of Maryland, College Park

ABSTRACT

Aspergillus fumigatus is the opportunistic fungal pathogen responsible for causing invasive aspergillosis as well as a number of hypersensitivity respiratory disorders. In order to evade these diseases, A. fumigatus must be successfully cleared from the lungs following inhalation. Fungal clearance is associated with Th1 and Th17 responses, while a Th2 response is associated with fungal persistence and the development of allergic disorders. In ground-breaking studies, repeating exposure to A. fumigatus results in the convolution of all three immune responses in the lungs. For these reasons, it is essential that the host immune system have a way to maintain a balance between these immune responses. IL-27 is a heterodimeric cytokine that has been shown to regulate T helper responses. During chronic infection with A. fumigatus, IL-27 promotes Th1 responses in the lung by promoting the expression of the Th1 cytokine IFN-\(\gamma\). The absence of IL-27 signaling results in significantly reduced numbers of dendritic cells and activated macrophages recruited to the lung. In addition, the diminished Th1 responses result in the inability of macrophages to activate to M1 status. As such, fungal growth and tissue invasion is enhanced in those mice lacking IL-27 signaling. Taken together, this study demonstrates an important role for IL-27 in promoting Th1 responses in the lung during chronic infection with A. fumigatus.

BACKGROUND

Aspergillus fumigatus is a saprophytic fungus found globally, and is the most common of its species to cause disease in humans. A. fumigatus produces small (2-5 µm) spores known as conidia that are airborne and distributed ubiquitously throughout the environment. On average, individuals inhale upwards of 200 conidia per day! Due to their size, conidia are able to avoid cough and mucosal clearance and enter deeper into the Airways. In healthy individuals, these conidia are rapidly cleared by phagocytes such as macrophages and neutrophils, but in the case of immunocompromised individuals, conidia can avoid clearance and permeate into the tissues. This can result in the development invasive aspergillosis, an aggressive fungal disease with an estimated global incidence of 250,000 cases annually, and an associated mortality rate ranging from 30-40%. In addition, repeated exposure to A. fumigatus can also result in other health problems developing hypersensitivity respiratory disorders such as allergic bronchopulmonary aspergillosis, farmer’s lung and Aspergillus-induced asthma. As such, A. fumigatus is rapidly becoming a major threat to public health and global security.

Protection against A. fumigatus is associated with development of Th1- and Th17 responses, although uncontrolled or prolonged Th17 activation can result in persistent inflammatory and tissue damage. A Th2 response on the other hand is associated with fungal persistence and the development of allergic disorder. Interestingly, repeated exposure to A. fumigatus results in the convolution of Th1, Th17 and Th2 responses in the lung! For these reasons it is essential that the host immune system establish a balance between these responses in order to successfully clear A. fumigatus. IL-27 is a regulatory cytokine composed of a p28 subunit and an Epstein-Barr virus induced Gene 3 (EBI3) subunit that has been shown to either promote or suppress T helper responses depending on the context of the infection! This heterodimeric cytokine is secreted by antigen presenting cells such as macrophages, monocytes and dendritic cells. The p28 subunit is recognized by IL-27R\(\alpha\) (IL-27R), while EBI3 is recognized by gp30. These receptors are commonly found on B cells, NK cells, and especially T cells. IL-27 was originally described as a pro-inflammatory cytokine, but later studies demonstrated its anti-inflammatory properties through the activation of STAT3, STAT1 and the Th3-promoting transcription factor T-bet. Later, IL-27 was reported to have anti-inflammatory properties, suppressing the development of Th2 and Th17 cells through the downregulation of the transcription factors GATA3 and ROR\(\gamma\)t respectively. In addition, IL-27 was reported to suppress the production of IL-12, which may explain its broad suppressive effects on T cells, as well as promote the production of the anti-inflammatory cytokine IL-10. For these reasons, this study sought to examine what, if any, role IL-27 plays in shaping immune responses during chronic infection with A. fumigatus.

PROJECT GOAL

To examine the role of IL-27 during chronic pulmonary infection with Aspergillus fumigatus.

HYPOTHESIS

One or more regulatory facts, such as IL-27, must be in place in order to balance immune responses in the lung chronic A. fumigatus infection in order to ensure successful fungal cell clearance.

IL-27 expression is increased following acute infection with A. fumigatus.

IL-27 is required to suppress A. fumigatus invasion into lung tissue

REFERENCES

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