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Review

Role of innate immunity in the pathogenesis of otitis media

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SUMMARY

Otitis media (OM) is a public health problem in both developed and developing countries. It is the leading cause of hearing loss and represents a significant healthcare burden. In some cases, acute OM progresses to chronic suppurative OM (CSOM), characterized by effusion and discharge, despite antimicrobial therapy. The emergence of antibiotic resistance and potential ototoxicity of antibiotics has created an urgent need to design non-conventional therapeutic strategies against OM based on modern insights into its pathophysiology. In this article, we review the role of innate immunity as it pertains to OM and discuss recent advances in understanding the role of innate immune cells in protecting the middle ear. We also discuss the mechanisms utilized by pathogens to subvert innate immunity and thereby overcome defensive responses. A better knowledge about bacterial virulence and host resistance promises to reveal novel targets to design effective treatment strategies against OM. The identification and characterization of small natural compounds that can boost innate immunity may provide new avenues for the treatment of OM. There is also a need to design novel methods for targeted delivery of these compounds into the middle ear, allowing higher therapeutic doses and minimizing systemic side effects.

1. Introduction

Otitis media (OM) is one of the most frequent diseases afflicting humans and is prevalent in both developed and developing countries.[1] It represents a significant healthcare burden, with over 5 billion dollars spent every year in the world on this disease.[2] The term 'otitis media' covers a wide spectrum of disease, and is used to describe illnesses with predominantly middle ear symptoms. With its diverse clinical syndromes and affected host groups, OM remains one of the challenging diseases encountered in clinical practice.[3] It is the leading cause of hearing loss and is associated with significant morbidity.[4–7] Children are at greater risk and suffer most frequently from OM. This can cause serious deterioration in the quality of life.[8] Studies show that 80% of children will have experienced at least one episode of OM by their third birthday and 40% will have six or more recurrences by the age of 7 years.[9] OM is also the predominant reason for antibiotic prescription.[10] It is the primary indication for tympanostomy tube insertion, which is the most commonly performed operation on children.[11]

The pathogenesis of OM is thought to be multifactorial and includes Eustachian tube dysfunction, allergy, viral and bacterial invasion, reduced ciliary function of both the middle ear and Eustachian tube mucosa, smoke exposure, gastro-esophageal reflux, and autoimmune and many other etiologies not yet fully understood.[12] OM can lead to life-threatening extracranial and intracranial complications.[13] Every year 28,000 deaths are attributable to OM complications, mainly through meningitis and brain abscess.[14,15]

There are two main entities of OM: acute otitis media (AOM) and chronic suppurative otitis media (CSOM).[16] AOM is defined as the presence of inflammation in the middle ear accompanied by the rapid onset of signs and symptoms of an ear infection. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common causative agents of AOM.

Despite antibiotic therapy, AOM can progress to CSOM, characterized by the persistent infection and inflammation of the middle ear and mastoid air cells. This condition typically involves a perforation of the tympanic membrane, with intermittent or continuous otorrhea.[17] As chronic otomastoiditis and

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Eustachian tube dysfunction persist, the tympanic membrane is weakened, which increases the likelihood of an atelectatic ear or cholesteatoma formation. The presence of mucin prevents the transmission of sound waves from the middle ear to the inner ear, leading to conductive hearing loss. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common pathogens implicated in CSOM.[18–21]

Host resistance against pathogens depends on a complex interplay of innate and adaptive immune mechanisms. The innate immune system provides a first-line, non-specific defense mechanism, in contrast to the adaptive immune process, which is pathogen-specific and requires sensitization. Innate immunity also stimulates and modulates adaptive immune responses. The present review is focused on the role of the innate immune system in OM, specifically the role of middle ear epithelial cells, neutrophils, macrophages, fibroblasts, mast cells, and natural killer cells in protecting the middle ear against pathogens (Figure 1). The innate immune system detects microbial infection and uses pattern recognition receptors (PRRs) to recognize the molecular signature of pathogens, known as pathogen-associated molecular patterns (PAMPs).[22] PRRs include toll-like receptors (TLRs), cytoplasmic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG-I), and C-type lectin receptors (CLRs). The role of these PRRs in OM is also discussed.

2. Epithelial cells

The epithelial lining of the middle ear contains several key defense mechanisms including the presence of the mucociliary apparatus, trapping function of mucous glycoproteins and surfactants, ability to secrete innate defense molecules such as defensins, interferons, lactoferrin, and nitric oxide, and antibody production through the adaptive immune response. Middle ear epithelial cells also express PRRs like TLRs, which help in sensing pathogens through PAMPs.[22]

2.1. Defensins

The middle ear epithelial cells primarily release beta defensins, which are cationic proteins with antimicrobial function against a wide range of viruses, bacteria, fungi, and protozoa.[23] Their major antimicrobial mechanism is thought to be through the formation of a pore into the microbial membrane. However, some defensins are known to stimulate pro-inflammatory cytokines/chemokines, to act as chemoattractants for neutrophils, mast cells, T cells, and dendritic cells, and to directly inhibit bacterial toxins.[23] The up-regulated expression of mouse β-defensins 2, 3, and 4 has been demonstrated in the tubotympanums in experimental OM, while no such up-regulation was seen in the middle ears of healthy controls.[24] Human β-defensin 2 (HBD2) is seen to be up-regulated in the middle ear response to bacteria and cytokines like non-typeable *Haemophilus influenzae* (NTHi) and interleukin (IL)-1α.[25,26] HBD2 expression occurs in response to NTHi binding to toll-like receptor 2 (TLR2) and subsequent activation of a toll/IL-1 receptor MyD88-IRAK1-TRAF6-MKK3/6-p38 mitogen activated protein (MAP) kinase signal transduction pathway.[25,26] Beta-defensin 2 production has been demonstrated to be greatest when the p38 MAP kinase pathway acts synergistically with the MyD88-independent Raf-MEK1/2-ERK MAP kinase pathway stimulated by IL-1α. [25,26] In addition, the β-defensin 2 production in epithelial cells is up-regulated with exposure to tumor necrosis factor alpha (TNF-α) and lipopolysaccharide (LPS).[27] The recombinant human β-defensin 3 (rhBD-3) plays a critical role in eliminating NTHi, and its function has been shown to be inhibited by biofilms.[28]

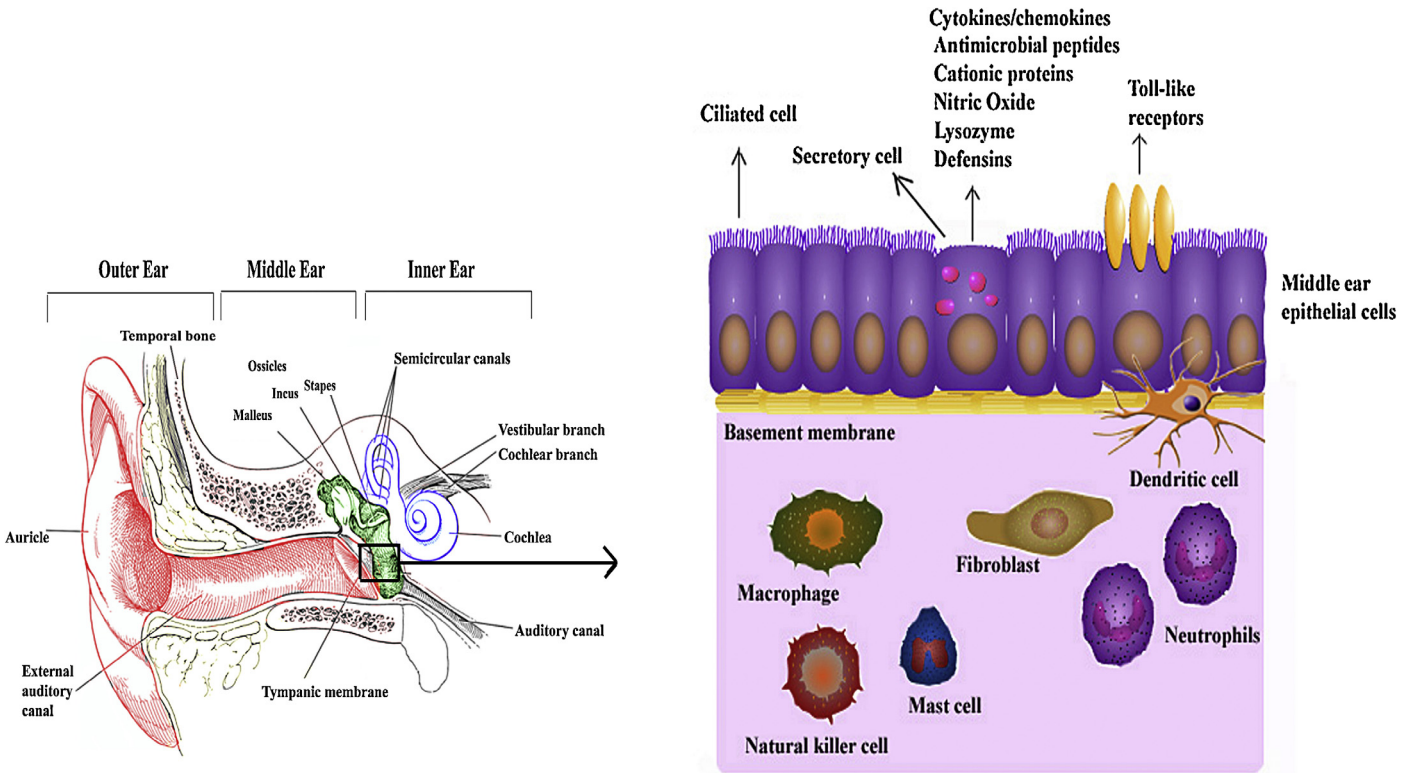

Figure 1. Middle ear innate immunity. The middle ear is lined by epithelial cells, which can provide protection by secreting antimicrobial molecules, or through toll-like receptors (TLRs). The middle ear also possesses innate immune cells such as neutrophils, macrophages, dendritic cells, mast cells, and natural killer cells providing defense against intruding pathogens.