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Review Article

Immune cells and non-immune cells with immune function in mammalian cochleae

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ABSTRACT

The cochlea has an immune environment dominated by macrophages under resting conditions. When stressed, circulating monocytes enter the cochlea. These immune mediators, along with cochlear resident cells, organize a complex defense response against pathological challenges. Since the cochlea has minimal exposure to pathogens, most inflammatory conditions in the cochlea are sterile. Although the immune response is initiated for the protection of the cochlea, off-target effects can cause collateral damage to cochlear cells. A better understanding of cochlear immune capacity and regulation would therefore lead to development of new therapeutic treatments. Over the past decade, there have been many advances in our understanding of cochlear immune capacity. In this review, we provide an update and overview of the cellular components of cochlear immune capacity with a focus on macrophages in mammalian cochleae. We describe the composition and distribution of immune cells in the cochlea and suggest that phenotypic and functional characteristics of macrophages have site-specific diversity. We also highlight the response of immune cells to acute and chronic stresses and comment on the potential function of immune cells in cochlear homeostasis and disease development. Finally, we briefly review potential roles for cochlear resident cells in immune activities of the cochlea.

Contents

Abbreviations: TLR, Toll-like receptor; RIG-I, Retinoic acid inducible gene-I; MDA5, Melanoma differentiation-associated gene 5; TGF-β, Transforming growth factor beta; MHC-II, major histocompatibility complex II; ICAM-1, Intercellular Adhesion Molecule 1; DIC, Differential interference contrast view; MIF, macrophage migration inhibitory factor

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The cochlea is the sensory organ responsible for hearing perception. Sensory cells in the cochlea are susceptible to various acute and chronic stresses such as acoustic overstimulation, ototoxicity and age-related degeneration. In response to these stresses, the cochlea launches an inflammatory response and this response is an integral component of the defense mechanism. Indeed, immune activities and inflammatory responses have been implicated in all major causes of acquired hearing loss (Fujioka et al., 2014; Goodall and Siddiq, 2015; Iwai et al., 2003, 2008; Malik et al., 2012; Oh et al., 2011; Tan et al., 2013; Toubi et al., 2004). Moreover, therapeutic intervention targeting inflammation has been shown to be effective for reducing the level of damage in many inner ear diseases that concur with inflammatory activities (Arpornchayanon et al., 2013; Arslan et al., 2011; Canlon et al., 2007; Rauch, 2004; Wakabayashi et al., 2010).

Immune cells are the primary players in immune responses. A scarcity of leukocyte activity in the cochlea was suggested by early investigations and this was attributed to the blood-labyrinth barrier that isolates the cochlea from the systemic immune system. However, recent studies provide evidence to the contrary. The cochlea in fact contains not only immune cells but also resident cells with immune capabilities. These cells reside within all of the major cochlear partitions important for cochlear function, and participate in the maintenance of cochlear homeostasis through immune surveillance of the cochlear microenvironment. Immune cells also regulate cochlear responses to disease formation following pathological insults. Their activities are believed to contribute to the progression and final outcome of cochlear pathogenesis. Here, we review properties of immunocompetent cells in the cochlea with a focus on macrophages that are the predominant immune cell in the cochlea. Over the past few years, several review articles have been published on cochlear immunity and immune cell responses to disease development (Fujioka et al., 2014; Goodall and Siddiq, 2015; Hirose et al., 2017; Kalinec et al., 2017; Wood and Zuo, 2017). Interested readers may refer to these references for additional information.

1. Leukocyte composition of the cochlea

Leukocytes are the first line of defense against invasive pathogens and endogenous damage-associated molecules. There are three types of leukocytes: lymphocytes, granulocytes and monocytes, each consisting of subgroups. Lymphocytes comprise T cells, B cells and natural killer cells. Granulocytes include neutrophils, eosinophils and basophils. Monocytes, once extravasated from the bloodstream into tissues, differentiate into macrophages and dendritic cells. The abundance of each type of leukocyte is tissue-specific: neutrophils are the most common leukocyte in the bloodstream and constitute roughly 50–70% of all leukocytes in humans (Bainton et al., 1971; Mayadas et al., 2014); the brain and eyes, which are protected by a tissue-blood barrier, are rich in monocytes and macrophages (Korin et al., 2017; Liyanage et al., 2016); tissues under constant exposure to microbial-derived molecules and intrinsic cytotoxic molecules host a more diverse population of resident immune cells including mast cells, natural killer cells and T cells (Mowat and Agace, 2014; Racanelli and Rehermann, 2006; Tay et al., 2014). This diversity reflects the difference in tissue immune microenvironments and is a biological basis for tissue-specific immune activity.

Leukocyte composition in the cochlea is not completely clear; several studies have shown that the macrophage is the most abundant immune cell population in the cochlea (Hirose et al., 2005; Okano et al., 2008), accounting for more than 80% of bone-marrow derived cells in the cochlea (Okano et al., 2008). Cochlear macrophages are identified by their expression of macrophage specific markers, including F4/80 (Frye et al., 2017; Okano et al., 2008; Tornabene et al., 2006; Yang et al., 2015), Iba1 (Hirose et al., 2005; Okano et al., 2008), CD68 (Hirose et al., 2005; Okano et al., 2008), and CD11b (Shi, 2010). This macrophage-dominated immune capacity in the cochlea differs from T cell-dominated immune capacity reported in the endolymphatic sac (Takahashi and Harris, 1988b).

The cochlea has a small population of lymphocytes that express T cell marker proteins under resting conditions and their number increases after immune challenge (Takahashi and Harris, 1988a). The cochlea also contains immune cells that bear features of dendritic cells, including expression of major histocompatibility complex II (MHC-II), an antigen presenting protein (Yang et al., 2015). However, under steady-state conditions, these cells do not express CD11c (Yang et al., 2015), an integrin that is enriched in classical dendritic cells. Thus, the identity of these cells requires further clarification.

Systematic analysis of immune cell populations in the cochlea is scarce. In a recent study, Matern and co-workers used fluorescence-activated cell sorting to characterize the composition of CD45-positive immune cells isolated from the cochleae of postnatal Gfi-^{Cre} mice (Matern et al., 2017). This study not only confirmed macrophages, which account for 81.3% of CD45-positive cells, as the most abundant immune cell population but also identified several groups of minority immune cells, including granulocytes (3.1%), T cells (0.8%), B cells (0.4%), and natural killer cells (3.4%). At present, it is not clear whether this composition in postnatal cochleae is applicable to mature cochleae. Because the murine cochlea undergoes active postnatal remodeling, its immune cell composition is likely to change during maturation. Therefore, the immune cell makeup in mature cochleae requires additional studies.

2. Distribution of macrophages in the cochlea

Immune cells are present in the cochlea starting from the early stages of development (Brown et al., 2017; Hinton et al., 2017; Hirose et al., 2017; Hu et al., 2017; Kaur et al., 2017; Kim et al., 2011), where they remain for life (Frye et al., 2017). While multiple leukocyte populations have been identified in the cochlea, only the distribution of macrophages has been studied in detail. Under steady-state conditions, macrophages are found in multiple cochlear regions and are particularly abundant in the spiral ligament and neural tissues (Hirose et al., 2005; Okano et al., 2008). Okano and co-workers reported that approximately 62% of cochlear macrophages reside in the neural tissue and about 36% are in the spiral ligament and spiral limbus (Okano et al., 2008). In general, macrophages are uniformly distributed along the apex-to-base

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