Hearing Research 338 (2016) 52–63

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review

Pathophysiology of the cochlear intrastrial fluid-blood barrier (review)

Xiaorui Shi

Oregon Hearing Research Center, Department of Otolaryngology/Head & Neck Surgery, Oregon Health & Science University, Portland, OR, USA

ARTICLE INFO

Article history:
Received 15 September 2015
Received in revised form
11 January 2016
Accepted 14 January 2016
Available online 20 January 2016

ABSTRACT

The blood-labyrinth barrier (BLB) in the stria vascularis is a highly specialized capillary network that controls exchanges between blood and the intrastitial space in the cochlea. The barrier shields the inner ear from blood-born toxic substances and selectively passes ions, fluids, and nutrients to the cochlea, playing an essential role in the maintenance of cochlear homeostasis. Anatomically, the BLB is comprised of endothelial cells (ECs) in the strial microvasculature, elaborated tight and adherens junctions, pericytes (PCs), basement membrane (BM), and perivascular resident macrophage-like melanocytes (PVM/Ms), which together form a complex "cochlear-vascular unit" in the stria vascularis. Physical interactions between the ECs, PCs, and PVM/Ms, as well as signaling between the cells, is critical for controlling vascular permeability and providing a proper environment for hearing function. Breakdown of normal interactions between components of the BLB is seen in a wide range of pathological conditions, including genetic defects and conditions engendered by inflammation, loud sound trauma, and ageing. In this review, we will discuss prevailing views of the structure and function of the strial cochlear-vascular unit (also referred to as the "intrastrial fluid-blood barrier"). We will also discuss the disrupted homeostasis seen in a variety of hearing disorders. Therapeutic targeting of the strial barrier may offer opportunities for improvement of hearing health and amelioration of auditory disorders.

This article is part of a Special Issue entitled <Annual Reviews 2016>.

Contents

E-mail address: shix@ohsu.edu.

http://dx.doi.org/10.1016/j.heares.2016.01.010
0378-5955/

1. Introduction

The inner ear is a remarkably stable homeostatic system controlled by a range of regulatory mechanisms, including control over ion, fluid, and nutrient transport (active and passive) by the blood-labyrinth barrier (BLB). Precise regulation of substrate transport into and out of the inner ear is essential for maintaining the stable composition of inner ear fluids for hearing (Juhn and Rybak, 1981, 2001). Normal function of the stria vascularis (referred to as the "intrastrial fluid-blood barrier") is critical for maintaining the ionic gradients and endocochlear potential (EP) required for sensory hair cell transduction (Hibino et al., 2010; Marcus et al., 1983; Quraishi and Raphael, 2008; Salt et al., 1987; Spicer and Schulte, 1996; Wangemann, 2002; Zhang et al., 2012). Dysfunction of the stria, including the intrastrial fluid-blood barrier, is considered to be one of the etiologies in a number of hearing disorders, including autoimmune inner ear disease, noise-induced hearing loss, age-related hearing loss, and genetically linked hearing diseases (Lin and Trune, 1997; Neng et al., 2015; Shi, 2009; Yang et al., 2011; Zhang et al., 2015). Despite the importance of the intrastrial fluid-blood barrier, the physiology of the barrier is largely unknown. Recent progress has been made in detailing the structural complexity of the barrier points to the important role accessory cells, such as pericytes (PCs), perivascular resident macrophage-like melanocytes (PVM/Ms), and basement membrane (BM), play in the intrastrial fluid-blood barrier. This review provides a topical overview of intrastrial fluid-blood barrier structure and function as well as a synopsis of the dysfunction seen in particular barrier components in different hearing disorders. The review also introduces current methods used for studying the pathophysiology of the intrastrial fluid-blood barrier.

2. Major components and structure of the cochlear intrastrial fluid-blood barrier

The intrastrial fluid-blood barrier is a specialized capillary network characterized by a relative absence of endothelial cell (EC) fenestration (Juhn, 1988). Vascular ECs connected to each other by tight junctions (TJs) and an underlying BM form a diffusion barrier that prevents most blood-borne substances from entering the stria vascularis (Sakagami et al., 1999, 1987). Recent studies, however, have shown the intrastrial fluid-blood barrier to be more complex than the conventional view, as the barrier is shown to include a large number of PCs (Shi, 2009; Shi et al., 2008; Takeuchi et al., 2001) and PVM/Ms (Shi, 2010) in addition to ECs and the BM, as shown in Fig. 1. Through close anatomical and chemical interactions, these cells monitor the state of ion, fluid, and nutrient flow into the stria vascularis from the circulation and trigger responses to changes in demand.

A population of around 1220 to 1300 PCs is found in the intrastrial fluid-blood barrier of the normal adult C57/6J mouse cochlea (Neng et al., 2015), as shown in Fig. 2A. Extensively branched strial PCs tightly embrace the abluminal strial capillary wall and embed in the BM (Fig. 2B). PCs are known to display a heterogeneous range of morphology, phenotype, and function in

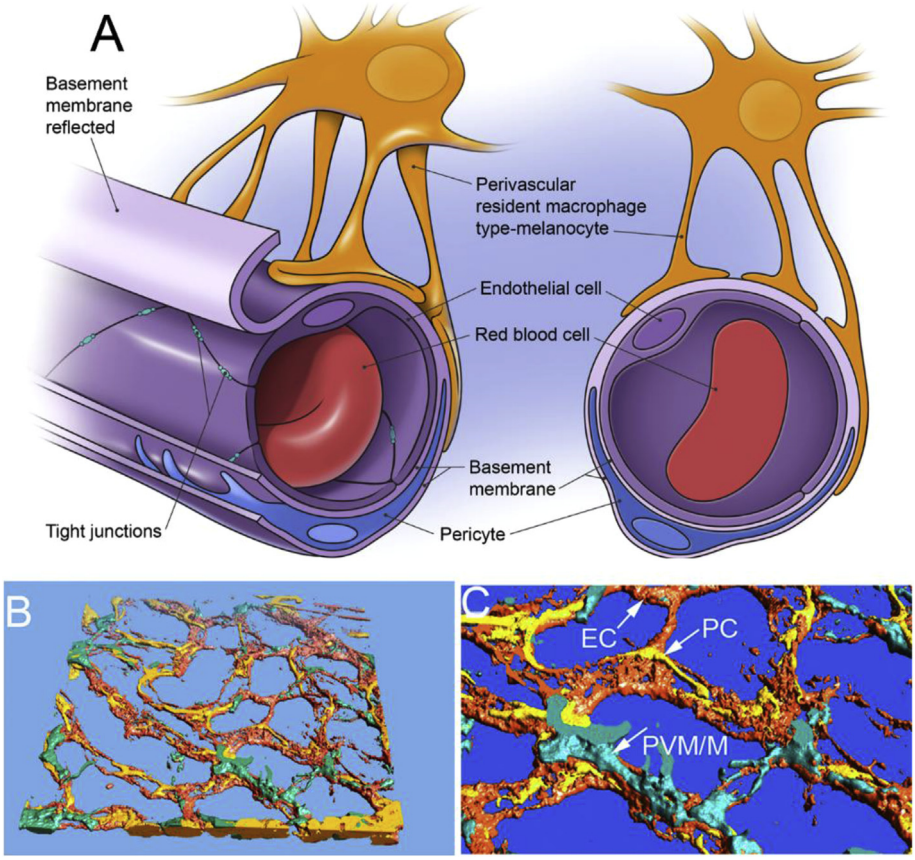

Fig. 1. (**A**) The illustration of a cochlear micro-vessel in cross-section shows the major components of the intrastrial fluid-blood barrier. The vessel lumen comprises ECs connected by TJs. ECs are ensheathed by a dense basement membrane shared with PCs. PVM/M end-feet cover a large portion of the capillary surface. (**B**) & (**C**) The reconstructed confocal image of the intrastrial fluid-blood barrier highlights the morphological complexity of interactions between ECs, PCs, and PVM/Ms. The PVM/Ms are immunolabeled for F4/80, PCs for desmin, and ECs with fluorescent Dil.