CHAPTER 8

THE BLOOD-BILIARY BARRIER, TIGHT JUNCTIONS AND HUMAN LIVER DISEASES

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Abstract: Tight junction (TJ) composes of an intriguing class of cell junction molecules, for which these molecules share similar organizations and structure features among different organs. Four types of transmembrane molecules namely occludins, claudins, junctional adhesion molecules and coxsackievirus and adenovirus receptors act as core units and each link directly and indirectly with a panel of peripheral molecules and underlying cytoskeletons to constitute the functional protein complexes at TJs. Individual TJ complex alone or in co-operation with other complexes via cross-talk mediated by peripheral molecules activate signaling pathways pertinent to various physiological and pathological processes in livers. In human livers, TJs are located at two regions in association with hepatocytes and cholangiocytes and perform major roles in controlling bile flow and metabolism. Apart from this physiological function, the other functions of TJs relating to liver diseases of hepatitis and liver cancer are gradually uncovered. The understanding of how TJs are involved in these clinical conditions hint for the development of new treatments at the molecular level.

INTRODUCTION

Cell junctions constitute a unique structural feature lining the cell-cell border. Because of this specific cellular localization, junctions were discovered initially to maintain cell-cell adhesion and interactions, contributing a main role in cell adhesion and communication. These functions are exemplified clearly in intestinal epithelium, such that adjacent epithelial cells adjoin each other via cell junctions and that in turn leads to the formation of epithelial cell sheet. The adherence of nearby epithelial cells also facilitates cell-to-cell communications. Establishment of selective permeable barrier is an additional function associated with the formation of intestinal epithelium, thereby
guarding the unwanted entry of micro-organisms and pathogens while at the same time facilitating the absorption of the luminal contents. However, it is not possible to describe all the properties associated with various junctions in different parts of the body and readers should refer to other chapters in this book for more details. Apart from the physiological functions of different junctions, research is also devoted to investigate the cellular mechanism related to cell junctions. In a broad sense, cell junctions are involved actively in several signaling pathways during physiological and pathological processes, such as growth, differentiation, disease progression and degeneration. Cell junction-related Wnt/β-catenin pathway is one such pathway that is often activated when cancers progress. Therefore, cell junctions are key players in a series of cellular processes. In view of the significance of cell junctions in this aspect, they remain targets for biomedical research in particular for those involving infectious diseases and cancers.

In eukaryotes, junctions exist in various locations in different organs and tissues, conferring structural integrity and maintaining functional property. Mammalian cell junctions are classified into various types based largely on the anatomical features and structural compositions. Five major junction types are found, which are known as tight junction (TJ), adherens junction, gap junction, desmosomes, and hemidesmosomes. These junctions situate precisely at their respective locations. Taking epithelium as the example, TJ is located at the most proximal position sealing the gap between neighboring epithelial cells, whereas adherens junctions, desmosomes and gap junctions are frequently found at the lateral faces of these cells. Hemidesmosomes are those junctions anchoring cells with the extracellular matrix. It is therefore obvious that different junctions serve intrinsic roles in adjoining, communicating, situating and positioning cells to assemble a functional system. Among the many types of junctions, TJ is exceptional to certain extent as TJs are sometimes named after an organ based on their specific locations. For instance, blood-brain barrier is found in brain and blood-testis barrier is located in the testis. Since liver is the theme of this chapter, TJs found in the liver will be further described and discussed.

ANATOMY AND PHYSIOLOGICAL FUNCTIONS OF TJs IN THE LIVER

Liver is one of the most complicated organs in the body, carrying out numerous metabolic activities-like glucose metabolism, detoxification, bile secretion, urea metabolism and others. Basically, it is composed of heterogeneous cell types, such as hepatocytes, cholangiocytes/bile duct cells, hepatic stellate cells, blood cells, and others. Among these, hepatocytes contribute most of the tissue mass in the mammalian livers. Similar to other epithelia and tissues, cells in the livers are also connected and communicated to each other via the establishment of different junctions. For the interest of this chapter, we focus only on TJs. TJs in the livers are found associating with two cell types, namely hepatocytes and cholangiocytes. Both of these cells are polarized epithelial cells with apical and basolateral surfaces that are enriched with various junctions to maintain hepatic anatomy and to sustain physiological functions of the livers. They perform similar functions as TJs in other epithelia by modulating or restricting the passage of small molecules and ions across the cell monolayers. In particular, TJ found lining the apical face of hepatocytes surrounding the bile canaliculi is referred specifically as blood-biliary barrier. From its name, this barrier functions mainly to enable collection of bile acids and bile salts inside the bile canaliculi away from blood circulation and prevent the backflow