CHAPTER 5

ENDOTHELIAL AND EPITHELIAL BARRIERS IN GRAFT-VERSUS-HOST DISEASE

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Abstract: Endothelial and epithelial cells form selectively permeable barriers that separate tissue compartments. These cells coordinate movement between the lumen and tissue via the transcellular and paracellular pathways. The primary determinant of paracellular permeability is the tight junction, which forms an apical belt-like structure around endothelial and epithelial cells. This chapter discusses endothelial and epithelial barriers in graft-versus-host disease after allogeneic bone marrow transplantation, with a focus on the tight junction and its role in regulating paracellular permeability. Recent studies suggest that in graft-versus-host disease, pathological increases in paracellular permeability, or barrier dysfunction, are initiated by pretransplant conditioning and sustained by alloreactive cells and the proinflammatory milieu. The intestinal epithelium is a significant focus, as it is a target organ of graft-versus-host disease, and the mechanisms of barrier regulation in intestinal epithelium have been well characterized. Finally, we propose a model that incorporates endothelial and epithelial barrier dysfunction in graft-versus-host disease and discuss modulating barrier properties as a therapeutic approach.

INTRODUCTION

A key function of endothelia and epithelia is to form selectively permeable barriers that separate distinct tissue compartments. Transport across these barriers is accomplished by coordinating the specific, but saturable, transcellular pathway with the nonspecific, nonsaturable paracellular pathway. The paracellular space must be at least partially sealed in order to maintain the concentration gradient established by active transcellular transport. Such trans-epithelial and -endothelial gradients also direct passive paracellular transport. The tight junction, a component of the apical junctional...
complex, is the primary determinant of paracellular permeability, and can be regulated in response to physiological and pathological stimuli.

**Tight Junction Structure and Barrier Function**

A large number of transmembrane and cytosolic proteins, most notably the claudin family, the tight junction-associated MARVEL protein (TAMP) family, which includes occludin, and the zonula occludens proteins ZO-1, ZO-2 and ZO-3, form the tight junction, which creates a belt-like structure at contact sites between adjacent epithelial or endothelial cells.\(^1\)\(^2\) The interaction between tight junction transmembrane proteins at these sites creates a selectively permeable seal. While endothelial and epithelial cells express similar tight junction proteins, the structure is more complex and highly developed in epithelium,\(^1\) where tight junctions are clearly separated from the more basal adherens junction. In contrast, it can be difficult to differentiate the endothelial tight junction and adherens junctions, and these structures are collectively referred to as the interendothelial junction.\(^3\)

Transepithelial, or transendothelial, electrical resistance measures the properties of the seal that limits movement of ions across the paracellular pathway under most experimental conditions,\(^4\) and is generally higher in epithelia than endothelia.\(^5\)\(^-\)\(^9\) Although most endothelia are leaky, some do form tight seals, particularly at specialized sites. For example, endothelia that form the blood-brain barrier have extremely well developed tight junction structures and are some of the least permeable in the body,\(^10\) contrasting sharply with tight junctions within postcapillary venules. This difference in endothelial paracellular permeability depending on site illustrates the reduced permeability that is generally associated with a greater need to prevent mixing of separate compartments. While the vascular space is typically sterile, many epithelia are in direct contact with the external environment, including the airspaces and gut lumen. This requires a tighter paracellular barrier to prevent contamination of the tissues and subsequent inflammatory responses. In contrast, the leaky endothelial barrier supports free exchange of nutrients and waste products. In addition, although inflammatory cells can cross epithelia, primarily in the setting of disease, immune cells regularly traffic across vascular and lymphatic endothelium. This is particularly true in postcapillary venules, which readily allow immune cell extravasation.\(^9\)

Just as there are barrier differences between endothelia at separate sites, barrier function also varies between epithelia.\(^11\) For example, barrier function increases progressively from proximal to distal along the renal tubule.\(^12\)\(^-\)\(^14\) This reflects the need to establish a steep electrochemical gradient in order to concentrate or dilute urine in the distal tubule and collecting duct. It follows that bladder epithelium forms one of the least leaky mucosal barriers in the body.\(^11\)\(^,\)\(^15\)\(^,\)\(^16\) Although small intestinal and colonic epithelia are much leakier than those of the distal nephron and bladder, a qualitatively similar pattern of decreasing paracellular permeability occurs along the length of the intestine and correlates with the need to extract water and ions from lumen. Further, there is a gradient of barrier function along the small intestinal crypt-villus axis.\(^17\) Villus tight junctions are structurally well developed and have been characterized as preventing paracellular flux of molecules with radii greater than \(-6\) Å.\(^18\) In contrast, crypt tight junctions accommodate molecules up to 50 Å radius.\(^18\) This correlates with greater numbers and complexity of tight junction strands in villus, relative to crypt, epithelium\(^19\) (Fig. 1). As with the proximal to distal permeability gradient of the intestines and renal tubule, this crypt to villus gradient also reflects function. The crypt is primarily secretory, and the permeable tight junctions at that site support the paracellular water flow that follows transcellular Cl\(^-\) secretion.