Chapter 2 Signaling Mechanisms Regulating Vascular Endothelial Barrier Function

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ABSTRACT

During inflammatory conditions, such as sepsis, myocardial infarction and acute respiratory distress syndrome, endothelial cell-cell junctions start to disrupt because of the internalization of the junctional proteins such as vascular endothelial (VE) cadherin. This leads to the formation of minute inter-endothelial gaps, and the infiltration of protein-rich fluid and immune cells in the interstitial space. If remains unchecked, the persistent buildup of edema underlying the endothelial lining sets the stage for the serious life-threatening complications and ultimately leads to the multi-organ failure and death. Thus, to determine the molecular mechanisms underlying the opening and resolution phase of the gap formation, will provide an insight to better understand the pathology of the cardiovascular and pulmonary inflammatory disorders. In this chapter, we will discuss about how the signaling mechanisms activated by the known inflammatory molecules increase endothelial permeability.

Acronyms:

ALI: Acute Lung Injury ARDS: Acute Respiratory Distress Syndrome IEJs: Inter Endothelial Junctions AJs: Adherens Junctions

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LPS: Endotoxin Lipopolysaccharide **TEER:** Tansendothelial Electrical Resistance **PAR1:** Protease Activated Receptor 1 **MYLK:** Myosin Light Chain Kinase FAK: Focal Adhesion Kinase **RACK1:** Receptor for Activated C Kinase 1 **ROCK:** Rho kinase **PIP**,: phosphoinositol 4, 5-bisbiphosphate **IP**₃: Inositol 1, 4, 5 triphosphate **DAG:** Diacylglycerol STIM1: Stromal Interaction Molecule 1 **SOC:** Store Operated Ca²⁺ **SOCE:** Store Operated Ca²⁺ Entry ROCE: Receptor Operated Ca²⁺ Entry TRPC Channel: Transient **Receptor Potential Canonical Channel** SPHK1: Sphingosine Kinase 1 **S1P:** Sphingosine 1 Phosphate **CRAC Channel:** Ca²⁺ Release Activated Ca²⁺ Channel OAG: 1-Oleoyl-2-Acetyl-sn-Glycerol PECAM1: Platelet Endothelial Cell Adhesion Molecule-1

INTRODUCTION

Vascular endothelium forms the inner most lining of the blood vessels, regulates variety of biological processes such as angiogenesis, wound healing, cell growth and host defense mechanisms (Chavez, Smith, & Mehta, 2011; Gong et al., 2015; Komarova, Mehta, & Malik, 2007; Mehta, 2012; Mehta & Malik, 2006; Rajput et al., 2016; Sukriti, Tauseef, Yazbeck, & Mehta, 2014; Tauseef et al., 2016; Tauseef et al., 2012). Maintenance of uninterrupted endothelial barrier function is pre-requisite for the tissue fluid homeostasis, vessel tone and prevention of the activation of pathological coagulation cascade (Chavez et al., 2011; Komarova et al., 2007; Mehta, 2012; Mehta & Malik, 2006; Sukriti et al., 2014; Tauseef et al., 2016; Tauseef et al., 2012). However, endothelium is permeable to certain molecules ranging from the sizes 0.1 nm to 11.5 nm in diameters (Chavez et al., 2011; Komarova et al., 2007; Mehta & Malik, 2006; Sukriti et al., 2014). During physiological conditions, endothelium transport molecules such as ions and water molecules, using two different mechanisms (Chavez et al., 2011; Komarova et al., 2007; Mehta & Malik, 2006; Sukriti et al., 2014; Vandenbroucke, Mehta, Minshall, & Malik, 2008): i) Transcellular pathway (Chavez et al., 2011; Mehta & Malik, 2006; Sukriti et al., 2014) ii) Paracellular pathway (Chavez et al., 2011; Mehta & Malik, 2006; Sukriti et al., 2014). Molecules, which are greater than 3 mm radii, such as albumin, IgG, etc., are transported across the endothelium via transcellular transport mechanism (Komarova et al., 2007; Mehta & Malik, 2006; Sukriti et al., 2014; Vandenbroucke et al., 2008). This transport mechanism is also called vesicular transport or transcytosis (Mehta & Malik, 2006; Predescu, Predescu, & Malik, 2007). However, molecules, which are smaller than 3mm in sizes, for example, glucose molecules, water molecules and ions; transportation is mediated via paracellular mechanism through the inter endothelial junctions (IEJs) (Chavez et al., 2011; Komarova et al., 2007; Mehta & Malik, 2006; Sukriti et al., 2014; Vandenbroucke et al., 2008).

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