

6460**Topic Category:** 4065-ASIP Leukocyte-endothelial cell interactions**First Author:** David Sullivan

Northwestern

Pathology 303 E. Chicago Ave., Ward 3-070 Chicago, IL 60611

United States

Phone: 7733512487

d-sullivan@northwestern.edu

First Author is a: Postdoctoral Fellow**First Author is a member of:** American Society for Investigative Pathology**First Author Degree:** PhD, DSc, or equivalent**Presentation Preference:** Oral**Sponsor:** William Muller**Sponsor Phone:** 3125035200

wamuller@northwestern.edu

Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society**Keywords:** 1. Diapedesis 2. IQGAP1 3. Inflammation

Endothelial Cell IQGAP1 is Required to Support Efficient Leukocyte Transmigration both In Vitro and In Vivo

David P Sullivan, Prarthana J Dalal, William A Muller. Pathology, Northwestern, Chicago, IL

Inflammation is the body's fundamental response to tissue insult and damage. When operating correctly, it allows the organism to fight infection, repair injuries, and return the body to homeostasis. When the response is incorrectly directed, whether insufficient, excessive, or against an improper target, it contributes to and even directly causes numerous human pathologies. One of the critical components of inflammation is the recruitment of leukocytes to the target site. This process is a carefully choreographed series of sequential steps that leads to the net efflux of leukocytes out of the blood stream and into tissue. In the culminating and putative committed stage, the leukocyte squeezes between adjacent endothelial cells in a process commonly referred to as transendothelial migration (TEM). TEM is a critical step that requires several intercellular interactions and thus represents an attractive therapeutic target for regulating aberrant inflammation. During TEM, endothelial cells direct the lateral border recycling compartment (LBRC), a sub-junctional membrane network, to the site of leukocyte migration to facilitate its passage. All manipulations that affect the function and delivery of the LBRC substantially reduce leukocyte efflux.

To better understand the molecular components and function of the LBRC, we recently conducted a screen for LBRC-interacting proteins and identified IQGAP1. IQGAP1 is a large multi-domain cytoplasmic protein that is reported to bind several signaling proteins in other systems. Knockdown of endothelial cell IQGAP1 disrupted the directed movement of the LBRC and substantially reduced leukocyte TEM. To determine which domains of IQGAP1 are required for its function in TEM, we expressed a series of truncated constructs and examined their ability to rescue the knockdown of endogenous IQGAP1. We found that the actin-binding domain of IQGAP1 is required for its localization to endothelial borders. Furthermore, both the actin-binding domain and the IQ-motifs are required for its function in TEM. We extended these studies in vivo by generating bone marrow chimeras, in which IQGAP1 knockout animals were reconstituted with wild-type leukocytes. These studies show that IQGAP1 in endothelium is required for efficient TEM in vivo in two different inflammatory models. Together these findings detail a novel function for IQGAP1 in TEM that involves both its actin-binding domain and IQ motifs which together coordinate the directed movement of the LBRC to the site of TEM.

Support or Funding Information

Funding Support: R01HL046849, R01HL064774