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Loss of HS1 inhibits neutrophil extravasation during inflammation via disturbed PKA signaling

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Neutrophil extravasation is a critical step in innate immunity in response to tissue injury or invading pathogens. Inflammatory signals activate β2-integrins and facilitate neutrophil adhesion on to the endothelial apical surface and intraluminal crawling to the site of diapedesis. Hematopoietic cell-specific lyn substrate (HS1), the cortactin homologue in hematopoietic cells, regulates actin dynamics at the immune synapse and in neutrophils during migration. However, it is not yet known if HS1 plays a role in the regulation of the neutrophil extravasation cascade. Investigating HS1-deficient mice by intravital microscopy of the inflamed cremaster, we found an increased rolling velocity and a strong inhibition of neutrophil adhesion and transmigration. Additionally, HS1-deficient neutrophils showed disturbed polarization in response to both tumor necrosis factor-α and keratinocyte-derived chemokine (KC). These effects were not due to disturbed expression of adhesion molecules but could rather be explained by disturbed Rap1 activation causing reduced neutrophil adhesion in response to KC treatment. Interestingly, this process was dependent on PKA activation since PKA inhibition blocked KC-induced Rap1 activation. The importance of PKA for HS1-mediated support of extravasation was corroborated by the finding that PKA activation increased whereas inhibition reduced transmigration of WT neutrophils but not of HS1-KO neutrophils. However, HS1 is not a direct substrate of PKA but it co-immunoprecipitates with phosphorylated VASP. This interaction is also inhibited after PKA inhibition and may thus provide an important scaffold for Rap1 activation. Our results establish HS1 and PKA as critical signal mediators that coordinate the molecular machinery required for Rap1 activation and efficient neutrophil transmigration.

Biography

Michael Schnoor studied Chemistry and Biochemistry at the University of Münster, Germany and received his PhD in 2004. He then joined the lab of Dr. Parkos at Emory University, Atlanta, GA as Post-doc before moving to the Max-Planck-Institute of Molecular Biomedicine in Germany to investigate the importance of the actin-binding proteins cortactin and HS1 in leukocyte recruitment during inflammation. In November 2011, he accepted an appointment as PI at the Department for Molecular Biomedicine, Cinvestav, Mexico-City where he continues to investigate molecular mechanisms regulating vascular permeability and leukocyte extravasation. In 2012, he received the Pathologist-in-Training Merit Award from the American Society of Investigative Pathology.

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