

Neutrophil exocytosis: An ally or an enemy to the lungs?

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Neutrophils are indispensable for defense against intruding microorganisms; however it is equally important that the influx of neutrophils is controlled to prevent neutrophil-mediated tissue damage. Exocytosis of neutrophil granules potentially contributes to tissue injury through release of toxic enzymes and enhanced plasma membrane expression of receptors and signaling molecules. We showed that a TAT cell penetrating peptide containing the amino terminus SNARE domain of SNAP-23 (TAT-SNAP-23) inhibits stimulated exocytosis of secretory vesicles, gelatinase and specific granules, but not azurophil granules. To examine the ability of TAT-SNAP-23 to inhibit neutrophil-mediated tissue injury *in vivo*, a rat model of immune-complex deposition acute lung injury (ALI) was used. The effect of inhibition of neutrophil exocytosis by intravenous administration of TAT-SNAP-23 on ALI was assessed by albumin leakage, neutrophil infiltration, lung histology, and proteomic analysis of bronchoalveolar lavage fluid (BALf). Administration of TAT-SNAP-23, but not TAT-Control, significantly reduced albumin leakage, total protein levels in the BALf, and intra-alveolar edema and hemorrhage. Evidence that TAT-SNAP-23 inhibits neutrophil exocytosis included a reduction in plasma membrane CD18 expression by BALf neutrophils and a decrease in neutrophil granule proteins in BALf. Similar degree of neutrophil accumulation in the lungs and BALf suggests that TAT-SNAP-23 did not alter vascular endothelial cell function. Proteomic analysis of BALf revealed that components of the complement and coagulation pathways were significantly reduced in BALf from TAT-SNAP-23-treated animals. Our results indicate that administration of a TAT-fusion protein that inhibits neutrophil exocytosis reduces *in vivo* ALI. Targeting neutrophil exocytosis is a potential therapeutic strategy to ameliorate ALI.

Biography

Silvia M. Uriarte has completed her Ph.D in microbiology and immunology in 2004 from the University of Buenos Aires, Argentina and did postdoctoral studies from University of Louisville, School of Medicine. She is an Assistant Professor at the University of Louisville, School of Medicine. She has published more than 20 papers in reputed journals and served as an ad-hoc reviewer for several scientific journals. She is the editor of the electronic newsletter of the Society for Leukocyte Biology and an active member of the publication committee of that society.

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