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Chemokine-glycosaminoglycan interactions and neutrophil recruitment: Simple and yet so complex

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Circulating neutrophils, rapidly recruited in response to microbial infection and injury, form the first line in host defense, and a dysregulation in this process has been implicated in several diseases including sepsis and COPD. In humans, seven chemokines, characterized by the conserved 'Glu-Leu-Arg' motif, mediate neutrophil recruitment. Neutrophil-activating chemokines (NACs) share similar structures, exist as monomers and dimers, activate the CXCR2 receptor on neutrophils, and interact with tissue glycosaminoglycans (GAGs). Considering NACs have similar CXCR2 activity, the question has been and remains, why do humans express so many NACs? In my talk, I will make the case that NACs are not redundant and that chemokine-specific *in vivo* function arises from distinct GAG interactions. Glycosaminoglycans (GAGs), such as heparan sulfate and heparin, are sulfated polysaccharides that are ubiquitously expressed by nearly all cell types. Our recent studies indicate GAG binding interactions of NACs are distinctly different, and that conserved and specific residues in the context of structure determine geometries that could not have been predicted from sequences alone. Animal model studies also indicate monomer-dimer equilibrium regulates in vivo neutrophil trafficking, recruitment profiles vary between chemokines and between tissues for a given chemokine. We conclude in vivo GAG interactions finetune and define the functional response of each chemokine for successful resolution of an inflammatory response but in a highly context dependent manner.

Biography

Krishna Rajarathnam has obtained his BS and MS degree in Chemistry in India, MS in Biochemistry from Michigan State, and PhD from UC Davis. He has completed his Post-doctoral research at the Univ. Alberta on chemokine structural biology. He has joined University of Texas Medical Branch (UTMB) as an Assistant Professor in 1998. He is currently a Professor in the departments of Biochemistry and Molecular Biology, Microbiology and Immunology, and the Sealy Center for Structural Biology and Solution Biophysics.

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