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

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Abstract

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-Argâ 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.

Chemokines have two types of interactions that function cooperatively to control cell migration. Chemokine receptors on migrating cells integrate signals initiated upon chemokine binding to promote cell movement. Interactions with glycosaminoglycans (GAGs) localize chemokines on and near cell surfaces and the extracellular matrix to provide direction to the cell movement. The matrix of interacting chemokine–receptor partners has been known for some time, precise signaling and trafficking properties of many chemokine–receptor pairs have been characterized, and recent structural information has revealed atomic level detail on chemokine–receptor recognition and activation. However, precise knowledge of the interactions of chemokines with GAGs has lagged far behind such that a single paradigm of GAG presentation on surfaces is generally applied to all chemokines. This review summarizes accumulating evidence which suggests that there is a great deal of diversity and specificity in these interactions, that GAG interactions help fine-tune the function of chemokines, and that GAGs have other roles in chemokine biology beyond localization and surface presentation. This suggests that chemokine–GAG interactions add complexity to the already complex functions of the receptors and ligands.

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