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Novel therapeutic approach to inhibit innate immune cell trafficking in inflammation using chemokines and their binding molecules

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Chemokines are involved in driving leukocyte migration into inflamed tissue. They achieve this by being presented to blood leukocytes by heparan sulphate proteoglycans (HSPGs) on the luminal surface of vascular endothelial cells. We have found that in the synovial endothelial cells of rheumatoid arthritis patients there is induction of a CXCL8 binding site on the HSPG syndecan-3. This suggests involvement of syndecan-3 in leukocyte trafficking into the synovium. Indeed we have shown that leukocyte accumulation and cartilage damage is reduced in syndecan-3 null mice with antigen-induced arthritis. Addition of soluble syndecan-3 in vitro binds chemokines CCL2 and CCL7, and redcues chemotactic responses of moncytes to these chemokines. Injection of soluble syndecan-3 reduces leukocyte accumulation and arthritis severity in antigen-induced arthritis. HSPGs interact with basic residues in chemokines. Therefore addition of competing peptides containing these residues should be inhibitory. Indeed we have found some chemokine peptides do inhibit chemokine-HSPG interaction. These peptides bind HS and inhibit chemokine-driven migration of neutrophils across brain microvascular endothelial cells *in vitro.* Furthermore these chemokine peptides reduce the swelling of joints of mice with antigen-induced arthritis. In conclusion targeting chemokine-HSPG interactions by adding competing soluble HSPGs (syndecans) and chemokine peptides have therapeutic effects and represents a novel therapeutic approach to inhibit innate immune cell trafficking.

Biography

Jim Middleton completed his PhD at Lancater University and Postdoc research at Cambridge and Bath before working as Senior Scientist in inflammation biology with Novartis (Vienna). He obtained an academic position in Keele University where he became Senior Lecturer, Reader and Professor of Immunology. Currently he is Professor and Reader of Immunology at the University of Bristol. He was a Visiting Professor at CNRS, Toulouse, and has acted as consultant for GSK and biotech industry. He is a Editorial Board Member for *Arthritis Research and Therapy* and has published in *Cell, J Exp Med, Nature Immunol,* and *J Immunol.*

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