

P006 Characterisation of CXCL12/heparan sulphate complex and functional importance

¹Rabia Sadir, ²Françoise Baleux, ³Anne Imberly and

¹Hugues Lortat-Jacob

¹IBS Grenoble, ²Institut Pasteur Paris, ³Cermav Grenoble, France

CXCL12 is a CXC chemokine which numerous biological effects are mediated by a specific G protein-coupled receptor, CXCR4. CXCL12 binds also to heparan sulphate (HS), a glycosaminoglycan present abundantly at cell surface and in the extracellular matrix. Site-directed mutagenesis and surface plasmon resonance-based binding assays were used to investigate the structural basis for CXCL12 binding to HS. We showed that K1, K24, K27 and R41 are aligned on the chemokine surface and involved in CXCL12/HS complex formation. Binding studies with selectively desulphated heparin and defined-length oligosaccharides permitted us to characterise the complex between CXCL12 and a polysaccharide fragment consisting of 13 monosaccharide units.

A number of cell surface enzymes inactivate CXCL12 by specific processing of the N-terminal domain of the chemokine, in particular, CD26/DPPIV. We report here that HS specifically prevents the processing of CXCL12 by DPPIV. A CXCL12 mutant that does not interact with HS is readily cleaved by DPPIV, demonstrating that an interaction between HS and CXCL12 is required for the protection to take place. Moreover we found that protection depends on the degree of polymerization of the HS sulphated S-domains. The mechanisms by which HS regulates CXCL12 may thus include, in addition to its ability to locally concentrate the chemokine at the cell surface, a control of selective protease cleavage events that directly affect the chemokine activity.