
Rapid Communication

Meeting report: 4th Amsterdam Zoo Meeting: "Cell Adhesion and Migration in Inflammation and Cancer"

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The 4th Zoo Meeting was held in Amsterdam, Netherlands, October 4-7, 2006. This meeting is named for the location of the conference, which is adjacent to the zoo. For this meeting, approximately 100 investigators from all over the world gathered to discuss their most recent and exciting data on cell adhesion and migration in inflammation and cancer. Presentations were given as talks or posters. Here we summarize some of the key findings that were discussed at the meeting.

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The recruitment of neutrophils from the blood into inflamed sites is mediated by the interactions between selectins and their ligands. Although previous studies showed that P-selectin glycoprotein ligand-1 (PSGL-1) and CD44 mediate E-selectin-dependent rolling of neutrophils *in vivo*, the identities of other physiological E-selectin ligands were uncertain¹). Andrés Hidalgo (New York, USA) identified E-selectin ligand-1 (ESL-1) as a physiological E-selectin ligand using a lentiviral-based short hairpin RNA knockdown strategy, and addressed the role of PSGL-1, CD44, and ESL-1 in E-selectin-mediated neutrophil rolling by intravital microscopy²). Hidalgo presented that ESL-1 and PSGL-1 mediated all neutrophil tethering on the venules of TNF α -treated cremaster muscle and that ESL-1 and CD44 controlled the neutrophil rolling velocities. He also demonstrated

that CD44, but not ESL-1 and PSGL-1, mediated E-selectin-induced clustering of L-selectin observed on slow-rolling neutrophils. These observations indicate that PSGL-1, ESL-1 and CD44 exhibit remarkably distinct functions as E-selectin ligands by acting sequentially in E-selectin-dependent neutrophil tethering, rolling and activation *in vivo*²).

Beat Imhof (Geneva, Switzerland) presented recent data on the role of junctional adhesion molecule-C (JAM-C) in angiogenesis and in tight junction- and integrin-mediated cell adhesion. JAM-C is involved in the formation and maintenance of tight junctions in endothelial and epithelial cells. Treatment with the anti-JAM-C mAb H33 reduced tumor growth, angiogenesis, tumor vascularization, and the infiltration of macrophages into tumors, indicating that JAM-C is involved in the remodeling of

endothelial junctions³⁾. Imhof showed that the introduction of JAM-C into a carcinoma cell line, KLN205, which lacks endogenous JAM-C expression, improved the tight junction barrier, whereas an S281A mutation of JAM-C, in which serine is replaced by alanine at position 281 in the cytoplasmic domain of JAM-C, abolished tight junction formation⁴⁾. Furthermore, the expression of the JAM-C S281A mutant increased cell adhesion to fibronectin by inducing $\beta 3$ integrin activation. Thus, JAM-C participates not only in cell adhesion and tight junction formation but also in integrin activation, and thereby is potentially a valuable target for anti-tumor and anti-inflammatory therapies.

Audrey Gérard (Amsterdam, Netherlands) presented some exiting data about T-cell polarization and chemotaxis regulated by the partitioning-defective (Par) polarity complex⁵⁾. Cell polarization is closely related to T-cell functions such as chemokine-induced T-cell migration. Although T-cell polarization is known to be triggered by the small GTPase Rap1, Rap1's downstream signaling pathways are poorly understood. Gérard demonstrated unequivocally that Rap1 and chemokines induced T cell polarization by activating the Par polarity complex, consisting of Par3, Par6, and PKC ζ . Coimmunoprecipitation experiments showed that T lymphoma invasion and metastasis 1 (Tiam1), an activator of the Rho GTPase Rac, which regulates the reorganization of the actin cytoskeleton, interacted with Rap1 and the Par polarity complex. In addition, Rap1, the Par polarity complex, and Tiam1 were colocalized to the leading edge of polarized T cells. In Tiam-1-deficient T cells, chemokine-induced polarization and chemotaxis were impaired. These results indicate that the Par polarity complex and Tiam1 are required for Rap1- and chemokine-induced T-cell polarization and that they regulate Rac-mediated actin remodeling in T-cell polarization.

The mechanism by which mucosal antigen-presenting cells (APCs) achieve their precise discrimination between harmless antigens and dangerous pathogens is probably essential for the maintenance of mucosal immune homeostasis. There were several interesting presentations on immunological tolerance at the mucosal surface. Reinhold Forster (Hannover, Germany) addressed the role of lung dendritic cells (DCs) in the induction of tolerance against harmless inhaled Ags⁶⁾ and discussed the importance of CCR7 in tolerance induction⁷⁾. Forster presented the novel and exciting observation that CCR7-dependent trafficking of CD103⁺ lung DCs to the bronchial lymph nodes (brLNs) was critical for the induction of tolerance to harmless inhaled Ags. He demonstrated that CD103⁺ lung DCs in CCR7 knockout mice failed to migrate from the periphery to the draining LNs, whereas soluble Ag was drained swiftly to the brLNs and

taken up by resident brLN DCs in both wild-type and CCR7-deficient mice. While Ag-transporting CD103⁺ lung DCs induced the proliferation of anergic T cells in the brLNs, they could not tolerize T cells in the absence of CCR7. The chronic inhalation of Ags protected wild-type but not CCR7-deficient mice from developing allergic airway diseases, owing to the impaired induction of airway tolerance in the CCR7-deficient mice. Thus, CCR7 is clearly important in establishing peripheral tolerance.

Adam Lacy-Hulbert (Cambridge, USA) presented recent data on the role of the αv integrins, which modulate cell adhesion, migration, phagocytosis, and angiogenesis, *in vivo*. Because studies on the functions of αv integrins have been hampered by the lethality of αv knockout mice, he generated αv integrins-tie2 CRE mice to delete the αv integrins in endothelial and hematopoietic cells. The αv integrins-tie2 CRE mice appeared normal at birth, but developed spontaneous intestinal inflammation accompanied by the production of high titers of anti-DNA auto-antibodies; most died from intestinal obstruction. These findings indicate a novel role for the αv integrins in establishing immunological tolerance in the gut, although the mode of action is currently unclear.

In summary, the 4th Amsterdam Zoo meeting provided a valuable forum for discussing recent data on adhesion molecules and chemokines, the crosstalk among these molecules, and the trafficking of immune cells in inflammation and cancer. These studies will greatly contribute to the development of new immunotherapeutics for cancer and inflammation in the near future.

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