S6. PLASMINOGEN ACTIVATION AND CANCER: BASIC MECHANISMS AND PERSPECTIVES

Keld Danø[a], Niels Behrendt[a], Gunilla Høyer-Hansen[a], Morten Johnsen[b], Leif R. Lund[a], Michael Ploug[a], Boye Schnack Nielsen[a], John Rømer[a]. [a]*Finsen Laboratory, Rigshospitalet, Copenhagen, Denmark;* [b]*Institute of Molecular Biology, University of Copenhagen, Copenhagen, Denmark.*

During cancer invasion, breakdown of the extracellular matrix is accomplished by the concerted action of several proteases, including the serine protease plasmin and a number of matrix metalloproteases (MMPs). The activity of each of these proteases is regulated by an array of activators, inhibitors and cellular receptors. Thus, the generation of plasmin involves the pro-enzyme plasminogen, the urokinase type plasminogen activator uPA and its pro-enzyme pro-uPA, the uPA inhibitor PAI-1, the cell surface uPA receptor uPAR, and the plasmin inhibitor α_2-antiplasmin. The plasminogen activation system appears to be active in virtually all types of cancer, while various MMPs appear to be active more selectively in different types of cancer.

Generation of extracellular proteolysis in cancer involves a complex interplay between cancer cells and non-malignant stromal cells which has far-reaching consequences for our understanding of both carcinogenesis and establishment of metastases. For some types of cancer, the cellular interplay mimics that observed in the tissue of origin during non-neoplastic tissue remodelling processes. We propose that cancer invasion is considered as uncontrolled tissue remodelling.

Inhibition of extracellular proteases is an attractive approach to cancer therapy. Because the proteases have many functions in the normal organism, efficient inhibition will have toxic side effects. In cancer invasion, like in normal tissue remodelling processes, there appears to be a functional overlap between different extracellular proteases. This redundancy means that combinations of protease inhibitors must be used. Such combination therapy, however, is also likely to increase toxicity. Therefore for each type of cancer, a combination of protease inhibitors that is optimised with respect to both maximal therapeutic effect and minimal toxic side effects needs to be identified.

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S7. THE UROKINASE RECEPTOR, CELL MIGRATION, PROLIFERATION AND CANCER

Francesco Blasi. *Department of Molecular Biology and Functional Genomics, Università Vita-Salute San Raffaele, Via Olgettina 58, 20132, Milano, Italy; Unit of Transcriptional Regulation, IFOM, FIRC Institute of Molecular Oncology, via Adamello 16, 20169, Milano, Italy.*

uPAR is a GPI-anchored protein that signals by interacting with extracellular matrix proteins, transmembrane tyrosine kinase receptors, integrins and G-protein coupled receptors. uPAR regulates adhesion by either direct RGD-independent binding to vitronectin (VN), or by forming complexes with integrins. In this case uPAR appears to have higher affinity for alpha5 > alpha3 > alpham. uPAR can both activate and inactivate integrins and induce signaling via integrins or via other receptors. A seven trans-membrane G-protein coupled receptor, FPRL1, directly interacts with a uPA-cleaved form of uPAR (which cannot bind integrins) and transmits a chemokine-like signal inducing chemotaxis. In addition, uPAR can also interact with the EGF-receptor and induce either cell proliferation (via the ERK pathway) or cell migration. The choice between these two effects of uPAR may be dependent on different conformations of uPAR and hence on different types of interactions in different cells.

An important novel feature of uPAR is its involvement in the mobilization of hematopoietic stem cells. Indeed, uPAR Ko mice do not mobilize HSC, but this property can be rescued by administering a soluble form of uPAR or one of its fragments, D2D3. We have set up the tools and methodology for measuring the formation and the level of circulating D2D3 in human biological fluids since HSC mobilization is an important aspect of leukemia and lymphoma therapy. Indeed, the availability of a specific D2D3 assay allows the determination of the level of this fragments in all types of cancer and hence the correlation with the stage of the tumor.

Overexpression is one of the mechanisms transforming protooncogenes into oncogenes. In human tumors uPAR is almost invariably overexpressed. UPAR overexpression controls cell proliferation by constitutively activating integrins and growth factor receptor pathways. However, recent data on cells carrying no oncogenes mutation (embryonic mouse fibroblasts, MEF) have shown that the absence of uPAR causes an increase in cell proliferation rate and delays culture-induced senescence. On the other hand, overexpression of uPAR in MEFs causes senescence. In this type of activity, key regulatory proteins of the p53/Rb pathways are involved.

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S8. INVOLVEMENT OF p38-SAPK AND ENDOPLASMIC RETICULUM-STRESS SIGNALING PATHWAYS IN THE INDUCTION OF CANCER DORMANCY AND DRUG RESISTANCE

Julio A. Aguirre-Ghiso, Aparna C. Ranganathan, Lin Zhang, Alejandro P. Adam, Sharon J. Sequeira, Zoya Demidenko, Bibiana V. Iglesias, Shishir Ohja. *Department of Biomedical Sciences, School of Public Health and Center for Excellence in Cancer Genomics, University at Albany, State University of New York, Rensselaer, NY, USA.*

Most patients with inoperable primary cancer, with or without overt metastases, or patients with undetected disseminated disease undergoing surgery for their primary cancer, are not cured by adjuvant chemotherapy. It is thought that residual tumor cells in patients with disseminated disease might exit proliferation and activate a survival and G_0/G_1 arrest that allows them to become dormant. The mechanisms that trigger and maintain dormancy are not well understood and the assumption that the lack of proliferation of dormant cells is the only reason for their resistance to chemotherapy remains to be proven. The elucidation of the molecular basis of dormancy is of fundamental interest. We have shown that a rapidly tumorigenic and spontaneously metastasizing human carcinoma (T-HEp3) that is