Tumor microenvironment as a target for selective immunotherapy

Luca Vannucci[1], Oleksandr Chernyavskiy[2], Jiří Křížan[1], Lenka Rajsiglová[1], Monika Burocziová[1], Renata Štěpánková[1], Jiří Janáček[2], Pavel Rossmann[1], Klára Klimešová[1], Veronika Poláková[3], Jana Slyšková[3], Ludmila Vodičková[3], Miroslav Levý[4], Lide Arana[5]

[1]Dept. of Immunology and Gnotobiology, Institute of Microbiology, v.v.i., [2]Dept. of Biomathematics, Institute of Physiology, v.v.i., [3]Dept. of Molecular Biology of Cancer, Institute of Experimental Medicine, v.v.i., Academy of Sciences of the Czech Republic, [4]Dept. of Surgery, Thomayer's Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic, [5]Dept. of Biochemistry and Molecular Biology, University of the Basque Country, Bilbao, Spain

A model for studying cancer and inflammation relationships is furnished by the bowel, both in healthy and disease conditions. Observations in GF rats has suggested suggest that in these animals the different antigenic challenge, absence of the "physiologic inflammation" elicited by the presence of commensal microflora in the gut (threshold of immune regulation), together with the different metabolism of the intestinal content, may influence both structure of the bowel and systemic immunity. The different stromal architecture may create different niches for colonocyte and immune cell maturation influencing local and systemic immunity. Thanking the new technical progresses in confocal imaging, we went to evaluate both in the living animal, fresh samples and fixed samples the variations induced on the tissue architecture by induced cancer as well as induced inflammation, following the evolution of these processes. Interestingly, since the inflammation was re-discovered as an important multifaceted process accompanying cancer evolution, we firstly found alterations of cancer stromal organization similar to alterations induced in the colon inflammatory models (colitis induced by dextan-sulfate) *in vivo*. Moreover, the comparison with germ-free animals suggested an important role of pro-inflammatory products in shaping the tissue stromal structure. Animals induced to colon inflammation (DSS) and subsequently challenged with a carcinogen (AOM) developed tumors with important anticipation than in the treated with DSS-only or AOM-only. Germ-free animals developed tumors at a lower extent than animals with intestinal bacteria. We found correlations within the immunological conditions, oncogene products levels and morphological changes, with possible important role of TGF-beta. K-ras, TGF-beta and VEGF expression differently associated to inflammation and cancer in different colon segments. Therefore, it is possible that molecules produced by and delivered within the microenvironment may be elicited and may drive the evolution of a pathological state. This makes the tumor microenvironment (as other pathological microenvironments) and its structures suitable for new therapeutic approaches directed to target *in situ* the components orchestrating the illness development. Nanotechnologies can permit a very wide application for trying to control and/or interfere with pathogenic mechanisms involving the dynamic interplay between cells and stroma in the microenvironment. Preliminary results in a mouse melanoma model resulted very promising, showing cytoplasmic accumulation of specifically designed physiological nanoparticles inside the tumor cells. Acknowledgements of funding by: GAAV IAA500200917 (CZ); AIRC No. MFAG10545 (IT), Fondazione Anna Villa e Felice Rusconi, Varese (IT); IRC MBU No. AV0Z50200510 (CZ).