Name: Paulius Mocevicius

Dr.med.

Role of interaction between endothelial adhesion molecules ICAM-1/RAGE and β2-integrins Mac-1/LFA-1 in leukocyte recruitment in experimental pancreatic cancer

Promotionsfach: Chirurgie

Doctorvater: Priv.-Doz. Dr. med. E. Ryschich

Pancreatic carcinoma remains an extremely aggressive malignancy with a very poor prognosis and a median survival of 4-6 months. More than 12,000 new cancer cases occur every year in Germany. Pancreatic carcinoma frequently induces an immune response, which results in leukocyte infiltration of tumor tissue and has been proposed for development of new therapeutical strategies to fight this malignant disease. Recruitment of activated leukocytes from peripheral blood into the tumor tissue is an important step of the immune reaction, which is controlled by specific adhesion molecules. Although reduction of leukocyte-endothelial adhesion has been proposed to influence the anti-tumoral immune response, the role of adhesion molecules in leukocyte recruitment in tumor tissue was poorly investigated. Almost all previous studies were focused on the investigation of leukocyte adhesion to tumor endothelium, whereas mechanisms of leukocyte extravasation and interstitial migration in the tumor are not known. The progress in some technologies such as time-lapse intravital microscopy and transgenic animal models allowed us to investigate the behaviour of different immune cells in pancreatic adenocarcinoma in vivo. The present study is the first investigation of the role of adhesion molecules in dynamic leukocyte recruitment in pancreatic cancer in vivo. Visualisation of leukocytes was performed using EGFP transgenic mice. The role of adhesion molecules was studied using LFA-1-/-, ICAM-1-/-, Mac-1-/- and RAGE-/- knockout mice. The dynamic immune response in orthotropic pancreatic tumor was studied using laser scanning confocal intravital time-lapse microscopy. Immunohistochemistry was used to identify subpopulations of tumor infiltrating leukocytes. We found that tumor tissue was infiltrated with numerous active lymphoid and myeloid leukocytes. Interestingly, leukocyte adhesion to endothelium and extravasation rates in tumor blood vessels was very low. Comparison between wild-type, ICAM-1-/-, Mac-1-/-, LFA-1-/- and RAGE-/- mice showed that there were no significant differences of blood vessel density, leukocyte adhesion, extravasation, as well as infiltration with Gr-1+ and CD68+ leukocytes. Surprisingly, CD3+ and CD4+ leukocyte infiltration in LFA-1-/- mice was significantly lower than in wild-type tumors, whereas CD8+ T cells were almost absent in tumors grown in LFA-1-/- mice. There was no difference of T cells infiltration of tumor tissue between wild-type, ICAM-1-/- and RAGE-/- mice. Analysis of interstitial leukocyte migration demonstrated that intratumoral leukocytes used haptokinetic type of migration, however, no significant differences of leukocyte migration between any strains of knockout mice were found. We concluded that leukocyte recruitment in pancreatic cancer is a low-speed process which may reflect low progress in inflammation in contrast to high-speed leukocyte recruitment during the acute inflammatory reaction. Despite of low-speed leukocyte recruitment, final results showed sufficient leukocyte infiltration of tumor tissue. Within “classical” adhesion molecules, only LFA-1 seems to control tumor infiltration with T cells, whereas other adhesion molecules (ICAM-1, Mac-1 and RAGE) do not participate in tumor angiogenesis, leukocyte recruitment and intratumoral migration of leukocytes in pancreatic cancer.