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Leukocytes recruitment in intra- and peritumoral blood vessels of experimental pancreatic cancer

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Almost all previous studies were focused on the investigation of leukocyte adhesion to tumor endothelium whereas mechanisms of leukocyte extravasation in pancreatic cancer, as well as interstitial migration and spatial distribution of leukocytes in pancreatic cancer remained poorly investigated. New technologies, such as time-lapse intravital, laser confocal microscopy and transgenic animal models allow us to investigate *in vivo* the behaviour of different immune cells in pancreatic adenocarcinoma. The present study is the first investigation of dynamic recruitment of leukocytes in normal pancreatic, pancreatic cancer and host peritumoral blood vessels. The present study was aimed to investigate the leukocyte-endothelium interactions, recruitment and migration of adaptive and innate immune cells in pancreatic cancer, peritumoral host tissue and normal pancreas. An intraperitoneal pancreatic cancer model in transgenic animal was used. A Lys-EGFP-ki mice strain was used to study the innate immune response of neutrophils/monocytes in pancreatic cancer. To visualise lymphocytes, a CD2-EGFP⁺ mice strain was used. The dynamic immune response in tumor, peritumoral and normal pancreatic tissue was studied using fluorescent intravital time-lapse microscopy. Laser confocal microscopy and immunohistochemistry were used to investigate the static leukocyte infiltration. We found the diminished leukocyte-endothelium interactions in tumor in comparison with peritumoral and normal pancreatic blood vessels in Lys-EGFP-ki and CD2-EGFP⁺ mice. The local application of inflammatory substance (fMLP) had no effect on neutrophil-endothelium interactions and extravasation in tumor-own blood vessel, whereas these processes were increased significantly in peritumoral and normal pancreatic vessels. There were significant differences in migration velocity and penetration depth between neutrophils or monocytes and lymphocytes. Although immune cells migrated with high velocity in peri- and intratumoral tissue, they failed to infiltrate tumor and were distributed mostly peripherally. Our findings imply strongly that immune cells infiltrate experimental pancreatic adenocarcinoma mostly from the peritumoral blood vessels. Since tumor blood vessels provide little potential to recruit effector immune cells into tumor, further strategies can be aimed to enhance effector immune cells recruitment via the peritumoral or intratumoral blood vessels.