Highly sensitive detection of early-stage pancreatic cancer by multimodal near-infrared molecular imaging in living mice.

Pancreatic cancer is a serious disease with poor patient outcome, often as a consequence of late diagnosis in advanced stages. This is in large part due to the lack of diagnostic tools for early detection. To address this deficiency, we have investigated novel molecular near-infrared fluorescent (NIRF) in vivo imaging techniques in clinically relevant mouse models of pancreatic cancer. Genome wide gene expression profiling was used to identify cathepsin cystein proteases and matrix metalloproteinases (MMP) as targets for NIRF imaging. Appropriate protease activatable probes were evaluated for detection of early-stage pancreatic cancer in mice with orthotopically implanted pancreatic cancer cell lines. Mice with pancreatitis served as controls. Whole body in vivo NIRF imaging using activatable cathepsin sensitive probes specifically detected pancreatic tumors as small as 1-2 mm diameter. Imaging of MMP activity demonstrated high specificity for MMP positive tumors. Intravital flexible confocal fluorescence lasermicroscopy of protease activity enabled specific detection of pancreatic tumors at the cellular level. Importantly, topical application of NIRF-probes markedly reduced background without altering signal intensity. Taken together, macroscopic and confocal lasermicroscopic molecular in vivo imaging of protease activity is highly
sensitive, specific and allows discrimination between normal pancreatic tissue, inflammation and pancreatic cancer. Translation of this approach to the clinic could significantly improve endoscopic and laparoscopic detection of early-stage pancreatic cancer.

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