



Cover story

Super paramagnetic nanoparticles for the diagnostic imaging of pancreatic cancer



The adenocarcinoma of the pancreas is the fourth leading cause of cancer death in the United States. This type of cancer tends to express no symptoms until it is in a late stage and less than 20% pancreatic cancers are radiologically confined to the pancreas at the time of diagnosis. The overall five-year survival rate is under 10%. Aside from surgery, there are only a few therapeutic options at the moment. One of the major problems for diagnosis and therapy is that this type of cancer is hypoperfused, resulting in a low uptake of contrast agents and drug delivery systems. These characteristics are in contrast to the much rarer hyperperfused neuroendocrine tumors of the pancreas, which allows highly specific means of diagnosis as well as therapy leading to a five-year survival rate of more than 40%. The hypoperfused adenocarcinomas of the pancreas require improved diagnostic and therapeutic approaches.

Nanoparticles have been used as a diagnostic as well as a therapeutic tool for hypoperfused adenocarcinomas. In this issue, Professor Jörg Kreuter and his colleagues show that superparamagnetic particles can be directly visualized using generally available MR-scanners and are toxicologically well tolerated in animals [1]. Vascular endothelia in tumors are known to be relatively leakier as compared with normal blood vessels. This, in combination with an impairment of lymphatic drainage, can result in an accumulation of nanoparticles in the malignant tissue. Tumor specific ligands, such as tissue plasminogen activator derived peptides (tPA-ligands), can be covalently bound to these particles potentially increasing their specificity and interaction with target cells. This work is based on the objective of the EU-project SaveMe (<http://fp7-saveme.com>) to develop particles targeted for the adenocarcinoma of the pancreas. The Kreuter team incorporated iron oxide (maghemite, γ -Fe₂O₃) into nanoparticles by desolvation followed by crosslinking of recombinant human serum albumin (rHSA). Such particles can be visualized and quantified using T₂ MRI sequences and, after radiolabeling, nuclear techniques such as SPECT-CT and gamma-camera. A 30 amino acids long tPA-derivate with high *in vitro* affinity to galectin-1 receptors was covalently attached to the nanoparticle surface to increase the specific uptake of particles in pancreatic tumor tissue. Galectin-1 receptors are known to be upregulated in pancreatic carcinoma but not in healthy or inflamed pancreatic tissue. SPECT-CT, handheld gamma camera and conventional MRI showed no difference

in the accumulation of targeted and non-targeted nanoparticles in the hypoperfused tumor. However, 1.5T MRI relaxometry was able to show a significantly increased uptake of the targeted vs. the non-targeted contrast agent.

The particles used by the Kreuter team represent a promising approach in the direction of the detection and diagnosis of pancreatic cancer, a cancer that is extremely difficult to detect in its early stages and for this reason possess a very high mortality rate. This task is very demanding due to the hypoperfused nature of the pancreatic adenocarcinoma. The next step is to elaborate whether the increased uptake of particles in pancreatic carcinomas will be able to differentiate these from inflamed tissue, a task that is hardly possible with currently available diagnostic means. It is of major clinical importance since chronic inflammation is the most important risk factor for the development of pancreatic carcinomas. The study by the Kreuter team also provides valuable insights into the use of nanoparticles for diagnosis and potential therapy. As shown in the article, there was no quantitative difference in delivery of targeted and non-targeted nanoparticles in the hypoperfused tumor visible using conventional methods, but a significantly increased uptake with the tPA-derivate was indicated by 1.5T MRI relaxometry. The value of a specific ligand on the nanoparticle surface is in the enhanced cellular uptake. The drug delivery scientists need to continue their quest in increasing the delivery of diagnostic agents and drug delivery systems to the target site.

Reference

- [1] I. Rosenberger, A. Strauss, S. Dobiasch, C. Weis, S. Szanyi, L. Gil-Iceta, E. Alonso, M. González Esparza, V. Gómez-Vallejo, B. Szczupak, S. Plaza-García, S. Mirzaei, L.L. Israel, S. Bianchessi, E. Scanziani, J.-P. Lellouche, P. Knoll, J. Werner, K. Felix, L. Grenacher, T. Reese, J. Kreuter, M. Jiménez-González, Targeted diagnostic magnetic nanoparticles for medical imaging of pancreatic cancer, *J. Control. Release* 214 (2015) 76–84.

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