Breast cancer research; from cellular studies to patient’s diagnosis applying magnetic resonance imaging and spectroscopy

Overview

The goals of our research are based on integrating the characterization of molecular events responsible for breast cancer growth and regression, such as hormonal manipulation, with the final function and physiologic aspects of this regulation.

In recent years our scientific activities in breast cancer research focused on:
1. Hormonal regulation of angiogenesis in breast cancer.
2. Mechanism of chemotherapy induced apoptosis.
3. The role of phospholipid metabolism in malignant transformation.

In addition, experimental tools were developed and improved, predominantly Magnetic Resonance (MR) imaging and spectroscopy. These methodologies enabled us to study the metabolism and physiology of breast cancer cell cultures, spheroids and tumors in animal models, and more recently also in patients. Although the MR technique is unique in its non invasive/non destructive application, it has many limitations and needs to be complemented by molecular and cellular investigations in order to resolve biological questions at the mechanistic level.

In the course of our research we also developed a new breast cancer diagnostic method of practical application termed the 3TP (3 time points) contrast enhanced method. This method is based on mapping at high resolution the distribution of the density of the cells and of the density and permeability of the microcapillaries using color coding as demonstrated in Figure 1. This non empiric, model based method is now being tested in clinical trials. The results obtained so far demonstrate excellent sensitivity in detecting breast tumors and very high specificity in differentiating between breast cancer and benign breast diseases.

Current Research Activities

We are investigating the role of estrogen and antiestrogens in regulating the expression of the different isoforms of vascular endothelial growth factor (VEGF): VEGF isoforms of 121, 145, 165, 189, and 206 amino acids produced by alternative splicing of VEGF mRNA.

Studies of the hormonal regulation of breast cancer are now being extended to retinoic acid as well. We are investigating differentiation of breast cancer cells by retinoic acid, specifically, the effects of differentiation on glucose metabolism and the expression and function of the glucose transporters.

Another metabolic process typical to human breast cancer is associated with the presence of high levels of phosphocholine. We continue our efforts to relate this finding to malignant transformation by investigating the differential routing of choline through its various metabolic pathways.

In parallel to the tumor biology research we are developing MRI methods to monitor neovascularization and the formation of different types of capillaries with variable permeability properties. In addition to improving the Gd-based contrast enhanced MRI methods we are introducing the use of new blood pool agents and also the use of D₂O and high resolution deuterium MRI.

The ability of magnetic resonance to monitor diffusion under steady state conditions is exploited in order to characterize breast cancer without the need to add external contrast agents. Figure 2 demonstrates an image of the extracellular volume fraction (EVF) of human breast cancer implanted in nude mice, derived by processing diffusion MRI data. This method yields also maps of the intracellular and extracellular diffusion coefficient. The T2 image on the right demonstrates the regions of necrosis (white) and viable tissue (gray). This unique method can now be adapted to patients using clinical scanners.
Our efforts in developing MRI/MRS are extended to other organs including kidney, pancreas and brain and to nuclei such as carbon-13 and sodium.

References


