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New imaging approaches of metabolism in tumours

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Cancer cells have a remarkable ability to adapt and survive. Finding effective treatments against cancer depends upon identifying and attacking targets and pathways critically important for the cancer cell. Multi-modality and multi-parametric molecular and functional imaging are providing exciting new opportunities for imaging and targeting tumor metabolism. Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and MR spectroscopic imaging (MRSI) techniques have been used for several decades to characterize tumor vasculature, oxygenation, and necrosis, pH and metabolism. Recent advances in the development of molecular targeted contrast agents have expanded the traditional strengths of MRI and MRS of characterizing functional tumor parameters such as pH, vascularization, metabolism and cell death to include visualization of molecular pathways. Using combined MR and optical imaging of human breast and prostate cancer xenografts engineered to express green fluorescent protein (GFP) or red fluorescent protein (RFP) under hypoxia, we have obtained useful insights into the dynamics between the tumor ECM, vascularization, extracellular pH, interstitial fluid transport, and metabolism. MRI and MRSI were used to obtain co-localized maps of vascular volume, permeability, interstitial fluid transport, total choline and lactate/lipid, while optical imaging was used to obtain co-localized maps of hypoxia and ECM fiber distribution. These insights can be exploited to find effective treatment strategies. One common metabolic feature identified by MRS in most cancers is the elevation of total choline. This elevation of choline compounds presents a unique target to exploit for therapy; such targeting can be imaged noninvasively with MRS. We are developing molecular and molecular imaging based approaches to target choline metabolism, specifically choline kinase activity, which is the first step in choline phospholipid biosynthesis. New areas that are being developed in our program include targeting choline kinase using siRNA delivered using lentiviral vectors, and performing image-guided targeting of choline kinase using siRNA in combination with a prodrug enzyme cytosine deaminase using a multi-modal imaging platform. These advances demonstrate the array of roles that multi-modality imaging can play in understanding and targeting tumor metabolism.

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SYMPOSIUM

Immune system and cancer

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The molecular bases of the immunogenecity of cell death

No abstract received

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Tumor-promoting stroma impregnated by cancer cells is destroyed by specific T cells

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To be “relevant” with experimental systems, we need to ensure that the effects we observe are significant enough that they might at some point reach clinical importance. Thus, we ask whether eradication or long-term equilibrium can be achieved for clinical size solid tumors. Such cancers are at least 1 cm diameter when first diagnosed in patients. Since human and mouse cancer cells have similar cell sizes, roughly 109 cancer cells will be present in these tumors. Because the indisputable genetic instability of human or mouse cancer cells, the presence of therapy resistant variants is assured among this number of cancer cells and very few protocols and procedures except complete surgical excision can arrest or destroy solid tumor without relapse. We find that cancer cells constitutively impregnate their tumor-promoting stroma with materials, probably exosomes, continuously being released from the cancer cells. These materials include cancer-specific mutant proteins. T cells can specifically recognize and destroy non-malignant tumor stroma cross-presenting mutant proteins released from the cancer cells. Perforin, IFNγ and TNF released by the adoptively transferred T cells and the IFNγRs and TNFRs expression on BM-derived as well as non-BM-derived stromal cells are needed for the stromal destruction that causes the elimination of cancer cell variants responsible for the recurrences. Radiation or chemotherapy causes a transient increase in stromal loading with tumor antigen and therefore synergizes with the therapeutic effect of T cells. For tumor eradication, antigen-specific T cells must not only kill the stroma but also directly the majority of cancer cells. Tumor eradication is obviously preferable to tumor arrest. However, for many aggressively growing rapidly lethal cancers that may have down-regulated MHC expression, long-term arrest of growth with equilibrium between the host and cancer would be an acceptable goal. This has been achieved in an experimental setting where T cells can only target and destroy stroma loaded with antigen released from cancer cells into the tumor microenvironment.

1. Spiotto MT, Rowley DA, Schreiber H. Bystander elimination of antigen loss variants in established tumors. Nat Med. 10:294-8, 2004.
2. Zhang B, Bowerman NA, Salama JK, Schmidt H, Spiotto MT, Schietinger A, Yu P, Fu YX, Weichselbaum RR, Rowley DA, Kranz DM, Schreiber H. Induced sensitization of tumor stroma leads to eradication of established cancer by T cells. Exp Med. 204:49-55, 2007.
3. Zhang B, Karrison T, Rowley DA, Schreiber H. IFN-gamma- and TNF-dependent bystander eradication of antigen-loss variants in established mouse cancers. J Clin Invest.; [Epub ahead of print] Mar 3, 2008.
4. Zhang B, Zhang Y, Bowerman NA, Schietinger A, Fu YX, Kranz DM, Rowley DA, Schreiber H. Equilibrium between host and cancer caused by effector T cells killing tumor stroma. Cancer Res. 68(5):1563-71, 2008.
5. Schreiber H, Rowley DA. Cancer. Quo vadis, specificity? Science 319(5860):164-5, 2008.

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Tumor-educated macrophages as promoters of tumor progression

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The tumor microenviroment is populated abundantly with macrophages. In many cases the density of these cells is correlated with poor prognosis. Genetic ablation of macrophages in a mouse model of breast cancer caused by the mammary epithelial restricted expression of the Polyoma Middle T oncoprotein, delayed tumor progression and dramatically reduced metastasis. Restoration of macrophages specifically to the mammary tumors corrected these phenotypes in mutant mice while early recruitment enhanced tumor progression and doubled the rate of metastasis in wild type mice (1). These data together with those of others, indicate that macrophages play a trophic role in mammary tumors that enhances their malignancy.

Intravital imaging of fluorescently labeled cells together with a novel micro-capillary invasion assay, has shown an obligate paracrine interaction between macrophages and tumor cells that is required for tumor cell migration and invasion (2, 3). This interaction involves reciprocal signaling between macrophage synthesized EGF and tumor-produced CSF-1, growth factors whose receptors are expressed upon tumor cells and macrophages respectively (2). In addition macrophages enhance the intravasation of tumor cells into the circulation (3). Macrophage depletion also regulates the angiogenic switch that is associated with the transition to malignancy (4). Together these data show that a high density of macrophages confers a triple whammy in tumors, not only do they enhance tumor cell invasion and intravasation but they increase the number of target vessels through which the tumor cells escape into the vasculature (5, 6). These studies suggest that the tumor microenvironment educates different populations of macrophages to perform specific functions that promote malignancy and that these cells define the invasive microenvironment (3)(7).

1. Lin EY, Nguyen AV, Russell RG, Pollard JW 2001 Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. The Journal of experimental medicine 193:727-740.
2. Wyckoff J, Wang W, Lin EY, Wang Y, Pixley F, Stanley ER, Graf T, Pollard JW, Segall J, Condeelis J 2004 A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. Cancer research 64:7022-7029
3. Wyckoff JB, Wang Y, Lin EY, Li JF, Goswami S, Stanley ER, Segall JE, Pollard JW, Condeelis J 2007 Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. Cancer research 67:2649-2656
4. Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, Qian H, Xue XN, Pollard JW 2006 Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer research 66:11238-11246
5. Condeelis J, Pollard JW 2006 Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 124:263-266
6. Pollard JW 2004 Tumor educated macrophages promote tumor progression and metastasis. Nature Reviews Cancer 4:71 - 78
7. Pollard JW 2008 Macrophages define the invasive microenvironment in breast cancer. Journal of leukocyte biology In Press