Biology and Pathology

Cancer Biology

Oncology and Inflammation

Zaver M. Bhujwalla
Divison of Cancer Imaging Research, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Learning Objectives:

- Understanding the role of inflammation in the cancer phenotype
- Imaging phenotypic changes induced by inflammatory pathways in cancer
- Image-guided targeting of inflammatory pathways in cancer

Inflammation is a characteristic response of living vascularized tissue to injury and induces the formation of eicosanoids. Three phospholipases, phospholipase A_2 (PLA_2), phospholipase C (PLC) and PLD, participate in the formation of free arachidonate from membrane phospholipids in response to mechanical, chemical and physical stimuli. The arachidonic acid (AA) formed is converted to various eicosanoids by the action of lipoxygenases (LOX) and cyclooxygenases (COX) that impact on cell motility, invasion, vascular characteristics and metastatic dissemination. Most solid tumors, including breast cancers, exhibit inflammatory properties characterized by increased levels of prostaglandins and other proinflammatory molecules that are secreted by tumor cells, stromal cells, and specialized immune cells during inflammation. Such an upregulation of inflammatory characteristics is not surprising in view of the similarities between physiological conditions in injured tissue, such as hypoxia and low extracellular pH (pHe), and the physiological environment of solid tumors. COX-1 and COX-2 are cytoplasmic enzymes that convert PLA_2-mobilized AA into the lipid signal transduction molecules prostaglandins and thromboxanes. One major product of the COX-2-catalyzed reaction is prostaglandin E_2 (PGE_2), an inflammatory mediator participating in several biological processes, including development, pain, immunity and angiogenesis, and cancer. COX-2 function has been the target of pharmaceutical intervention in a multitude of widespread degenerating conditions, including autoimmune diseases, gastric inflammation, and several different cancers, such as gastric, lung, breast, and colon cancer. Its expression is induced by proinflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, and its promoter contains a cyclic AMP response element, a nuclear factor-κB binding site, and two nuclear factors for IL-6 target sequences. The activation of several genes that form the adaptive response of cells to hypoxia is mediated through the binding of HIF-1 to HRE that regulate the transcription of these genes. Under oxygenated conditions HIF-1 is rapidly degraded but under hypoxic conditions HIF-1 is stabilized. In addition to the oncogenic effects of PGE_2 in COX-2 expressing tumors, PGE_2 may also act through the HIF-1 axis with the multitude of effects such as drug resistance, increased invasion, increase of Chk, and the emergence of an aggressive phenotype even under well oxygenated conditions. Molecular and functional imaging provide a range of abilities to investigate the role of inflammation in cancer with a span that covers intact cells in culture to preclinical models to clinical translation. These opportunities will be discussed within the context of quantitative imaging data and data analysis. Examples will be provided of insights into oncology and inflammation obtained with multi-modal molecular and functional imaging and their potential for image-guided treatment strategies.