Scientists define a new mechanism leading to tumor hypoxia

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An article published recently in *Tumor Microenvironment and Therapy* - an open access journal by Versita, defines a novel mechanism of tumor hypoxia induced by the longitudinal gradient of residual oxygen along tumor vessels as they transverse the tumor.

Growing evidence from experimental studies and clinical trials suggests a fundamental role of hypoxia in solid tumors. The mechanisms leading to hypoxia include the rapid rate of tumor growth, poor tumor perfusion or transiently disrupted tumor blood flow. Now, scientists from the University of Pennsylvania, led by Professor Cameron J. Koch, have discovered a previously uncharacterized mechanism that contributes to - and may influence - the temporal and spatial distribution of tumor hypoxia.

Hypoxic cancer cells represent the most aggressive type of a tumor. In case of malignant tumors they tend to be resistant to radio therapy, and low oxygen concentration can actually enhance metastasis. Thus, hypoxia - labeled accordingly as a poor prognostic factor - is emerging as an important, high-priority target for cancer therapy.

So far, there have been two recognized forms of tumor hypoxia: Diffusion limited hypoxia occurs as a result of distance from vessels; it is a stable factor and it occurs at a scale of hundreds of microns. Perfusion limited hypoxia, in contrast, results from perturbations in tumor blood flow, which can be both transient and recurring, but it also generally occurs on a smaller scale. The current report demonstrates that

in addition to these two mechanisms, there is a stable gradient of oxygen that can occur over multi-millimeter distances along the length of a tumor vessel leading to hypoxia at the more distal portions of the vessel. This finding leads to a more complete understanding of the factors that have an influence on tumor oxygenation - adding a third mechanism that contributes to tumor hypoxia and would be expected to scale with tumor size.

The researchers used a 9L glioma model with defined and ordered vascular flow originating from the rat epigastric artery and vein pair to study hypoxia distribution using both immuno-histochemical and MRI methodologies. They further developed a gamma-H2AX labeling technique for defining hypoxia impact on DNA damage. Macroscopic regions of hypoxia occurred in every fourth of examined tumors. The researchers found large (mm) regions of moderate (0.3%) hypoxia that were not easily explained by the existing concepts of diffusion or perfusion-limited hypoxia. Due to its stability and the fact that it occurs over a large scale, this mechanism for the distribution of oxygen and other nutrients and drugs has substantial implications for hypoxia imaging, hypoxic cell targeting and for therapy effectiveness.

Hypoxia has historically been seen as occurring as the result of events at a microscopic scale. Diffusion-limited hypoxia, described in the 1950s by Thomlinson and Gray is stable and occurs as a gradient at distances of 100-200uM from vessels. Transient or perfusion limited hypoxia was described more recently and added to the complexity of detecting and targeting hypoxic cells, as well as having biological implications for tumor cell resistance to therapy. The current report superimposes a larger scale, presumably stable hypoxic gradient over these two mechanisms and could impact the interpretation of studies on hypoxia biology, approaches to hypoxia detection and targeting.

Hypoxia is a negative prognostic indicator for radiotherapy,

chemotherapy and surgery and also predicts for an aggressive and metastatic phenotype. Understanding its causes can aid in detection and intervention of cancer.

More information: Full article available at: www.degruyter.com/view/j/tumor … /tumor-2012-0001.xml

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