Radiotherapy, Tumor Oxygen Dynamics, and the Likely Role of the Glycolytic Oscillator

Many preclinical studies show tumor hypoxia is very dynamic (‘acute’) with cells that experience acute hypoxia being largely the ones responsible for aggressive tumor signaling and causing increased radioresistance, yet the clinic does not typically distinguish between acute and chronic hypoxia. The time scale of these dynamics is approximately equal to the time scale of a typical fraction: minutes to tens of minutes. This talk will propose a hypothesis for the cause of at least some of acute hypoxia based on a well-established biophysical phenomenon: a limit cycle oscillation in cellular metabolism under hypoglycemic conditions called the ‘glycolytic oscillator.’ The time scale matches observations. This hypothesis addresses the sometimes cyclical nature of acute hypoxia that is hard to square with purely vascular causes from random vessels and random blood flows which are no doubt happening as well. We are also gathering evidence from in vitro studies (no vessels, only metabolism dynamics) that large dose of ionizing radiation can also shut down the electron transport chain and stabilize HIF-1a within the time scale of a typical fraction, but only for cancer cells, not normal cells. Prompt changes in metabolism can also further perturb the local oxygen levels during treatment in perhaps complicated ways. It is therefore hard to imagine significant clinical future breakthroughs towards adaptive hypofractionated radiotherapy which do not take into account acute hypoxia and its effects on radiotherapy treatment success. A call is made for the use of high time resolution functional imaging in cancer near and/or during treatment of metabolites and oxygen.