Journal Club No. 738

6th September, 2016

Amit Subedi

Mitochondrial redox balance and spheroids formation

Spheroids formation has been considered an essential feature of tumorigenic cancer cells. Tumor xenograft requires cells to grow in new environment which lacks proper surface for cells attachment unlike in monolayer cells culture where cells readily attaches on culture plate. Thus, cells lacking spheroids-forming or anchorage-independent ability are considered unable to form xenograft tumor. Although cancer cell lines are derived from tumor, all of them cannot form spheroids and such cell lines are not used in xenograft tumor. What limits the spheroids forming ability of cells? This question has remained intriguing puzzle. Connecting findings from previous study (in 2009) and recent study (in 2016) indicates that ability to maintain mitochondrial redox balance may determine spheroids forming ability of cancer cells.

Introduction:

Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment

Schafer Z. et. al., 461, 109-113, Nature 2009

Abstract

Normal epithelial cells require matrix attachment for survival, and the ability of tumour cells to survive outside their natural extracellular matrix (ECM) niches is dependent on acquisition of anchorage independence. Although apoptosis is the most rapid mechanism for eliminating cells lacking appropriate ECM attachment, recent reports suggest that non-apoptotic death processes prevent survival when apoptosis is inhibited in matrix-deprived cells. Here we demonstrate that detachment of mammary epithelial cells from ECM causes an ATP deficiency owing to the loss of glucose transport. Overexpression of ERBB2 rescues the ATP deficiency by restoring glucose uptake through stabilization of EGFR and phosphatidylinositol-3-OH kinase (PI(3)K) activation, and this rescue is dependent on glucose-stimulated flux through the antioxidant-generating pentose phosphate pathway. Notably, we found that the ATP deficiency could be rescued by antioxidant treatment without rescue of glucose uptake. This rescue was found to be dependent on stimulation of fatty acid oxidation, which is inhibited by detachment-induced reactive oxygen species (ROS). The significance of these findings was supported by evidence of an increase in ROS in matrix-deprived cells in the luminal space of mammary acini, and the discovery that antioxidants facilitate the survival of these cells and enhance anchorage-independent colony formation. These results show both the importance of matrix attachment in regulating metabolic activity and an unanticipated mechanism for cell survival in altered matrix environments by antioxidant restoration of ATP generation.

Reductive carboxylation supports redox homeostasis during anchorage-independent growth

Jiang L. et. al., 532, 255-258, Nature 2016

Abstract

Cells receive growth and survival stimuli through their attachment to an extracellular matrix (ECM). Overcoming the addiction to ECM-induced signals is required for anchorage-independent growth, a property of most malignant cells. Detachment from ECM is associated with enhanced production of reactive oxygen species (ROS) owing to altered glucose metabolism. Here we identify an unconventional pathway that supports redox homeostasis and growth during adaptation to anchorage independence. We observed that detachment from monolayer culture and growth as anchorage-independent tumour spheroids was accompanied by changes in both glucose and glutamine metabolism. Specifically, oxidation of both nutrients was suppressed in spheroids, whereas reductive formation of citrate from glutamine was enhanced. Reductive glutamine metabolism was highly dependent on cytosolic isocitrate dehydrogenase-1 (IDH1), because the activity was suppressed in cells homozygous null for IDH1 or treated with an IDH1 inhibitor. This activity occurred in absence of hypoxia, a well-known inducer of reductive metabolism. Rather, IDH1 mitigated mitochondrial ROS in spheroids, and suppressing IDH1 reduced spheroid growth through a mechanism requiring mitochondrial ROS. Isotope tracing revealed that in spheroids, isocitrate/citrate produced reductively in the cytosol could enter the mitochondria and participate in oxidative metabolism, including oxidation by IDH2. This generates NADPH in the mitochondria, enabling cells to mitigate mitochondrial ROS and maximize growth. Neither IDH1 nor IDH2 was necessary for monolayer growth, but deleting either one enhanced mitochondrial ROS and reduced spheroid size, as did deletion of the mitochondrial citrate transporter protein. Together, the data indicate that adaptation to anchorage independence requires a fundamental change in citrate metabolism, initiated by IDH1-dependent reductive carboxylation and culminating in suppression of mitochondrial ROS.