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Fire and water: Tumor cell adaptation to metabolic conditions

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ABSTRACT

Lorenz Poellinger was a leader in understanding the effects of altered microenvironmental conditions in tumor biology and in normal physiology. His work examining the effects of hypoxia and the HIF transcription factors has expanded our understanding of the role of the microenvironment in affecting the behaviour of both normal and malignant cells. Furthermore, his work provides a model for understanding the adaptive responses to other metabolic stress conditions. By investigating the molecular mechanisms responsible for the adaptive responses to metabolic stress in normal physiological situations, across pathological conditions, and in different model organisms, his work shows the power of combining data from different model systems and physiological contexts. In cancers, it has become clear that in order to evolve to become an aggressive malignant disease, tumor cells must acquire the capacity to tolerate a host of abnormal and stressful metabolic conditions. This metabolic stress can be thought of as a fire that tumor cells must douse with enough water to survive, and may offer opportunities to exploit smoldering vulnerabilities in order to eradicate malignant cells.

1. Lorenz Poellinger

Lorenz Poellinger made great contributions to our understanding of the role of hypoxia and the HIF transcription factors in producing adaptive responses to low oxygen conditions, and regulating cell fate in both normal physiology and in pathological conditions. These contributions ranged across the fields of tumor biology, exercise physiology [1], wound healing [2], stem cell biology [3], cardiology [4], immunology [5], and toxicology [6]. For example, his investigation of the role of hypoxia and the hypoxia inducible factor (HIF) transcription factor in the development of the mammalian cornea illustrated the developmental importance of hypoxia in a unique physiological context [7]. This work carried over to influence our understanding of tumor angiogenesis and the role of oxygen concentration during the development of other organ systems. Another of his insights was that the hypoxia response and the HIF transcription factors integrate with other signaling pathways to sense and control metabolism and differentiation [8]. In fact, one of his last papers described the effect of a metabolic feedback loop in which S-2-hydroxyglutarate regulates the fate of CD8 T-lymphocytes [5]. His work provides a model that illustrates the importance and power of developing a deep understanding of the function of genes, metabolites, and pathways across different tissues, conditions, and organisms.

The HIF transcription factors and the hypoxic response stand at the centre of many of the pathways that are altered during tumorigenesis, and a deeper understanding of their function in specific contexts will undoubtedly lead to improvements in human health. However, given our current understanding of tumor metabolism, it is clear that oxygen is only one metabolite out of many that is altered in tumor cells and the tumor microenvironment. The work of Lorenz Poellinger provides a road-map for investigating the role of not only oxygen metabolism in tumors, but also other metabolic perturbations that are present in specific malignant conditions. In this review we will attempt to illustrate some of the ways in which the work and ideas of Lorenz Poellinger have influenced the field of tumor metabolism, beyond the hypoxic response.

2. Introduction

Due to oncogenic driver mutations, altered metabolic requirements, and an abnormal local microenvironment, tumor cells experience a host of abnormal and often stressful alterations to intracellular and extracellular metabolite concentrations [9]. These potentially toxic metabolic conditions are akin to a fire that can result in the elimination of cells by apoptosis, immune surveillance, or necrotic death. However, during tumor development, these fires are countered by adaptive responses that allow tumor cells to douse these flames with enough water to survive. Many of these responses are not unique to tumor cells, as cells in normal tissues must also adapt to changing metabolic needs and external conditions. Hence, there are lessons to be learned by studying the response to abnormal metabolic conditions in both tumor tissues, their tissues of origin, and other pathological conditions.

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As a part of the normal physiological response to metabolic stress and microenvironmental perturbations, normal cells and tissues temporarily engage adaptive responses to altered metabolite levels in order to reestablish homeostasis. However, during tumor development, these adaptive responses do not result in a return to tissue homeostasis, and therefore persist, allowing the fires of altered metabolism to continue to smolder as malignant cells evolve. The hypoxic stress caused by low oxygen conditions is one example of this type of stress, but other metabolic conditions may operate in a similar way. This fine balance between the fire of abnormal metabolite levels, and the water of cellular adaptation in tumor cells may provide opportunities for therapeutic intervention.

3. Reactive oxygen species and antioxidant defence

In addition to the hypoxia that develops during the course of tumor progression, one of the most universal metabolic conditions encountered by tumor cells is an increased level of oxidative stress. This situation arises due to the increased production of a class of highly reactive, oxygen containing molecules classified as reactive oxygen species (ROS). These molecules include superoxide, hydrogen peroxide, the hydroxyl radical, and other secondary reactive species. These metabolites are produced in all cells and tissues as a byproduct of normal metabolic activity, but in tumor cells, elevated metabolic requirements combined with increased growth signaling and oncogenic alterations to metabolic pathways increase their production [10]. Furthermore, the abnormal tumor microenvironment, which features acidic pH, hypoxia, and altered nutrient concentrations can contribute to increased ROS production in tumor cells.

ROS are generated from a number of sources, including enzymatic redox reactions that consume molecular oxygen; leakage from the electron transport chain in the mitochondria; and via the activity of the NADPH oxidase system [10]. This ROS production occurs in several subcellular compartments, including the endoplasmic reticulum, peroxisomes, and the mitochondria, which is the main site of superoxide production. It is estimated that 2% of all oxygen consumed in the mitochondria undergoes a one electron reduction to produce superoxide rather than a complete two electron reduction to produce water. These reactive species have different chemical properties, and can go on to interact with proteins, lipids, nucleic acids, and other reactive metabolites. The chemical reactivity of these molecules presents a strong intracellular signal, which has been harnessed by cells in order to sense their own metabolic activity and redox state. Thus, at low levels, ROS act as signaling molecules that influence proliferation, differentiation and survival via classical transcriptional and post-transcriptional feedback loops. However, at high levels, ROS can act as a damaging and toxic class of metabolites, causing deleterious alterations to key cellular components, including DNA.

In order to keep the fires of elevated ROS under control, and maintain appropriate homeostasis, cellular antioxidant systems have evolved to limit excessive ROS production and to eliminate these reactive chemical species and the cellular components they have damaged. These systems include scavenger molecules that react with and eliminate ROS, and enzymatic systems that convert ROS to less reactive molecules or repair damaged macromolecules. Tumor cells rely heavily on these antioxidant systems in order to survive and proliferate in the face of inappropriate increases in ROS production.

In mammalian cells, the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is considered to be the master regulator of the antioxidant response. In many ways, its role in responding to oxidative stress is analogous to the role of the HIF transcription factors in responding to low oxygen conditions. Under conditions of oxidative stress, the NRF2 protein is stabilized, and acts to induce the transcription of a host of genes that provide the water to cool the fires of elevated ROS production.

There are data from a number of groups that implicate the antioxidant response as a critical survival feature during tumorigenesis. In breast cancer, mutations in BRCA1 have been identified as important influencers of this response. Under normal conditions, BRCA1 physically interacts with NRF2 and enhances its activity in order to integrate the DNA damage response with cellular redox state [11]. When BRCA1 is mutated, this integration with NRF2 is lost, and BRCA1 mutant tumor cells must adopt alternate strategies to cope with their increased levels of oxidative stress. Furthermore, it has been found that NRF2 integrates the oxidative stress response with estrogen signaling [12]. Just as the HIF transcription factors integrate signals from local oxygen concentration with other environmental cues. Thus, although BRCA1 mutant tumor cells are able to survive and form an aggressive malignant disease, there may be latent vulnerabilities based on their inability to fully engage an appropriate response to oxidative stress [11].

Similarly, data from genetically engineered mouse models show that the balance between oxidative stress and specific antioxidant systems can have different effects at different stages of tumorigenesis [13]. The glutathione system provides reducing power to eliminate ROS and repair oxidized proteins. In mice lacking a key enzyme (GCLM) responsible for the production of this key antioxidant, tumorigenesis is impaired, suggesting that the initial stages of malignant transformation require sufficient antioxidant capacity in order to maintain cell survival. However, during later stages of malignant progression, reliance on the glutathione system is not as critical, as other adaptive responses including the thioredoxin system are able to compensate.

The roles of NRF2 in determining the fate of tumor cells during the initial phases of transformation, as well as the later stages of malignant progression and response to therapy are still under investigation. However, there are many lessons to be learned from the work of Lorenz Poellinger's description of the response to hypoxic stress that is integrated by the HIF transcription factors. In the case of the response to elevated oxidative stress, a key question remains. Which downstream genes are responsible for maintaining cellular viability in specific tissues during the process of malignant transformation and tumor progression? The work of the Poellinger lab has shown the power of taking a broader view and learning from the roles of genes not only in cancer but in other pathological and physiological conditions. In the case of the oxidative stress response, there are strong links between genes involved in the development of neurodegenerative disease, especially Parkinson's' disease, including the genes DJ-1 and PINK1.

4. Adaptive responses mediated by DJ-1 and PINK1

DJ-1 is an oncogene that is found overexpressed in many types of cancer, acting as a signaling molecule downstream of oxidative stress conditions. It is a redox sensitive chaperone capable of binding to specific subsets of proteins when it becomes oxidized. Thus, it can act as a redox switch, and has been implicated in a wide range of physiological processes including fertilization, inflammation, and tumorigenesis.

A number of independent screens have identified DJ-1 as a mediator of resistance to oxidative stress not only in tumor cells but in a number of other physiological contexts. It has also been identified as a mediator of chemotherapeutic resistance to a variety of agents, especially those linked to induction of ROS. Upon activation by oxidative stress, DJ-1 functions to antagonise PTEN activity and thus increase signaling through the critical PI3K/Akt axis, promoting cell proliferation and survival. It has also been shown to translocate to the mitochondria and act directly by binding proteins that regulate mitochondrial function. Finally, DJ-1 interacts directly with the KEAP1/NRF2 complex in order to promote NRF2 stability and increase antioxidant capacity.

The downstream functions of DJ-1 are cell type and environment