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Metabolic priming for AML

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Cancer survivors have a brush with death that does not leave them untainted. The rigors of their fight predispose them to a second round only often with a more lethal foe in the form of secondary acute myeloid leukemia (AML). The risk of these events is high after particular types of cancer therapy. It is also high in people with “pre-malignant” myelodysplastic and myeloproliferative disorders (MDS and MPD) and therefore patient groups can be assessed for evidence of the fight to follow.

Approximately fifteen percent of all AML develops secondary to cancer chemotherapy with alkylating agents or topoisomerase inhibitors. [1] Alkylating agents function by adding alkyl groups to DNA, and causing interstrand cross-links. In the ideal situation this would result in cell death but it can also lead to incorrect chromosome segregation in cells that escape apoptosis, and frequent loss of portions of chromosome 5q and 7q. [2] DNA topoisomerase inhibitors result in DNA cleavage and chromosome breakage leading to apoptosis. However, in cells where this process does not go as planned, translocations often involving the mixed lineage leukemia gene can lead to secondary AML. [3]

Historically secondary AML was thought to be essentially untreatable. However, it is now clear that secondary AML comprises a heterogeneous group of disorders and prognosis and choice of treatment depends upon the cytogenetic and molecular changes found in the particular case under consideration. [4] The study of those at risk for secondary AML provides a unique opportunity to capture the molecular events driving clonal dominance that eventuates in leukemia.

By combining clinical data with gene sequencing of patient samples, it has been possible to assess genetic changes in the predisposition setting. For example, Walter *et al* compared whole genome sequence data from seven patients with de novo MDS and the secondary AML that emerged. They found that virtually all samples had clonal outgrowths and they identified 11 recurrently mutated genes in secondary AML including 9 that were also mutated in the precedent MDS. [5] Assessing a much larger group (439 samples) Bejar *et al* sequenced 18 genes for point mutations and identified the particular mutations associated with ultimate prognosis.[6] In a third study, Li *et al* selected a patient group with a high frequency of therapy related MDS and AML and described a 38 gene signature which

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indicated advanced risk of these disorders (99.3 percent positive predictive value). [1] Together, these studies are shaping our understanding of not just the specific genes associated with risk of secondary malignancy, but also the cellular processes involved. In the two studies where the genes evaluated were not pre-selected, there was a remarkable heterogeneity and identification of poorly annotated genes. Transcriptional regulators were predictably also found. Rather impressively, however is the implication of metabolism in at least one study. Metabolic derangement is well known in cancer, but less clearly associated with cancer predisposition.

The link of cancer metabolic alteration to cancer was first made by Otto Warburg in the early twentieth century when he provided the provocative observation that cancer cells preferentially consume glucose and metabolize it to lactate even in the presence of oxygen. [7] –This was thought to be an example of how deranged cancer cells were. Aerobic glycolysis was viewed as a corruption of the more highly efficient ATP-generating oxidative phosphorylation associated with normal cells. More modern interpretations, however, argue that the cancer cell is using a modification of metabolic pathways adaptively, shifting in favor of the production of macromolecules needed to meet the biomass demands of rapidly dividing cells [8]. This interpretation of Warburg's observation has accumulated a substantial amount of experimental data to indicate that it is indeed the case.

Several studies provide evidence that at least some leukemias utilize the Warburg effect. PKM2 and HIF1- α , both inducers of the Warburg effect, have both been implicated in AML pathogenesis. [9, 10]. IDH1 and IDH 2 mutations in AML are associated with production of an oncometabolite 2HG and promotion of aerobic glycolysis through induction of HIF1- α stability. [11] [12]. The 2HG produced by mutated IDH1 or IDH2 inhibits the activity of a DNA 5-methylcytosine hydroxylase, TET2, and may thereby also connect metabolism with epigenetic control of gene expression [13]

Left unanswered, however, is whether the metabolic events observed are always reactive to conditions imposed by transformation or can also be central to it. [14] That is, does cancer force a change in the way nutritive substrates are utilized out of the necessity proliferation imposes; something akin to changes in budgeting when there are more mouths to feed. Or is the metabolic shift a primary event, fostering the subsequent development of malignancy? The study by Li et al does suggest the latter as metabolic alterations were in the predictive gene set. However, other data argue that metabolic changes do little to engender cancer risk. In the case of *IDH2*, for example, germline mutations (*IDH2 R140*) in humans that are identical to those found in some human cancers do appear to provide a predilection to cancer in those individuals [15]. It is likely therefore that metabolic alterations are minor risk modifiers acting in concert with other changes. The way they might do that is exemplified by the case of IDH mutations where the mutated phenotype alters the activity of a chromatin modifier (TET2). That may change gene expression such that the state of differentiation is affected and cooperates with a distinct lesion altering cell growth, for example. Alternatively, the metabolic change may provide the macromolecular substrates needed for new cell generation, enabling a growth provoking mutation to circumnavigate the full reprogramming of cell metabolism that might otherwise prove limiting. A third, and entirely

unanticipated scenario recently emerged based on a study of the metabolic interaction between malignant cells and their microenvironment.

The relationship of parenchymal cells to their mesenchymal microenvironment in adult tissues is now accepted to be regulatory in part based on what has been learned of normal hematopoietic stem and progenitor cells and their niche. The niche concept had a controversial start when proposed in 1978 by Raymond Schofield [16]. At that time, the concept was in competition with an accepted wisdom that inherent randomness determined whether stem cells would differentiate, divide or self-renew; whether stem cell behavior was cell autonomous. Similarly, the notion that cancer is a cell autonomous disease has long and perhaps reasonably, been the predominant model driving pathophysiologic evaluations of cancer. But cancer cells clearly exist in the context of tissue and may be viewed as a tissue, not a cell, gone rogue. [17]

A recent study by Zhang et al in *Nature Cell Biology* indicated that cancer cell metabolism interacted with metabolic features of the bone marrow microenvironment in a fundamental way. In the setting of chronic lymphocytic leukemia (CLL), bone marrow stroma conversion of cystine to cysteine was crucial for the survival of leukemia cells. The cancer cells required control of reactive oxygen species (ROS) levels by stromal cell provision of cysteine that the tumor cells could use in the production of the reducing agent, glutathione. The authors regarded this finding as one of the reasons why CLL cells may not survive in ex vivo culture; they just don't have the necessary anti-apoptotic input from stromal cells. A dependence on the tumor cell microenvironment has been proposed before as a basis for why it is so hard to grow primary cancer cells in vitro or in vivo after transplant. However, this study directly implicates the metabolic milieu as part of the dependence. The match between the metabolic activity of therapy-damaged hematopoietic cells and perturbed microenvironmental cells may be needed to achieve the necessary ecosystem for cancer emergence. Going forward, inclusion of studies on the microenvironmental cells of those at high risk for secondary leukemia would be interest, particularly in evaluating whether there are changes in genes that create a symbiotic metabolic environment with the altered needs of a malignant cell. Identification of such parameters may offer therapeutic targets to render the microenvironment less hospitable for the deranged cancer cell. Any progress in helping cancer survivors in their fight against their second and more deadly foe would be worthy of our attention.

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