Exploiting AML vulnerability: glutamine dependency

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In this issue of Blood, Jacque et al demonstrate that acute myeloid leukemia (AML) cells are selectively susceptible to disruption of glutamine metabolism through pharmacologic or genetic inhibition of the enzyme glutaminase C (GAC).1

The second law of thermodynamics states that the entropy, or simply chaos, of any system in the universe will always increase over time. Then, how are cancer cells, as new creatures, able to decrease entropy when synthesizing complex and “ordered” biochemical molecules? The answer is one word and is similar to the way that life started on this planet: metabolism. Rapidly dividing cancer cells, including AML cells, genetically reprogram their nutritional requirements to match an increased metabolic demand. The 2 main nutrient sources for growth and survival of cancer cells are glucose, a sugar, and glutamine, an amino acid.2 In humans, glutamine is the most abundant amino acid inside cells, as well as in plasma, with concentrations of ~20 and 0.6 to 0.9 mM, respectively.3 Glutamine supplies nitrogen for purine and pyrimidine synthesis, as well as for generation of nonessential amino acids for protein synthesis.4 Glutamine also stimulates the mammalian target of rapamycin complex 1 (mTORC1), and its deprivation inhibits mTORC1 and causes apoptosis of AML cells.5

Through a series of enzymatic reactions called glutaminolysis, glutamine, particularly in neoplastic cells, can feed mitochondria and contribute to the entire cancer cell metabolic machinery.6 After entering the cell through a special transporter, glutamine can be converted to glutamic acid by removal of its amide group. This important reaction is catalyzed by a family of enzymes called glutaminases.7 Subsequently, glutamic acid can be converted to α-ketoglutarate (αKG), either by transamination or by oxidation processes. In an elegant study, Jacque et al investigated the effect of perturbation of glutamine metabolism on mitochondrial function and its detrimental effect on AML cell survival. Glutamine depletion resulted in reduction of intracellular ATP and oxygen consumption rate and, eventually, induction of apoptosis in AML cells. A particular isoform of glutaminase, GAC, was shown to be overexpressed in primary AML cells isolated from patients, AML cell lines, and normal CD34+ hematopoietic cells. Genetic knockdown or pharmacologic inhibition of GAC negatively influenced mitochondrial respiration, cellular proliferation, and survival of AML cells but not normal CD34+ hematopoietic cells. AML cells undergoing these harmful events could be partially or
fully rescued by αKG, confirming the mechanism of cellular injury by glutaminase blockade. The investigators also demonstrated the antileukemic effect of glutaminase inhibition in an in vivo mouse model. Finally, by taking advantage of the fact that cytotoxicity of glutaminolysis inhibition is contingent upon mitochondrial depolarization and caspase-dependent apoptosis, the investigators showed a synergistic antileukemic activity between a glutaminase inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor.

What is the clinical importance of these findings for patients with AML and how soon can they be translated into a therapeutic regimen? First, for patients with AML who are reading the original article or this commentary, it is important to know that these findings absolutely do not suggest that they should avoid a protein- and glutamine-containing diet. Second, based on research findings on glutamine addiction of AML cells, there are ongoing clinical trials exploring the therapeutic potential of interruption of glutamine metabolism in AML (#NCT01810705, #NCT02071927, and #NCT02283190).

Third, the last 5 decades of hard work and trial after trial have sadly proved to clinicians, scientists, and patients that targeting a single aspect of the cellular apparatus in AML may not provide a significant clinical benefit. It stands to reason that one successful strategy for AML treatment might be to combine US Food and Drug Administration–approved and experimental agents that target specific aspects of glutamine metabolism and together may kill AML cells selectively and efficaciously. Such chemotherapeutic agents may include available inhibitors of glutaminase, mTOR, autophagy, and BCL-2, as well as asparaginase products. Let us not forget that further mechanistic studies such as the one reported by Jacque et al are necessary to enhance the diversity of drug candidates that can be logically added to the current list.

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REFERENCES


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THROMBOSIS AND HEMOSTASIS

Comment on Nickel et al, page 1379

New players in Trousseau syndrome

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In this issue of Blood, Nickel et al show that long-chain polyphosphates (polyP) on the surface of secreted microvesicles (MV) from prostate cancer cells activate coagulation factor XII (FXII), leading to thrombosis.1

Cancer accounts for 20% to 30% of all cases of venous thromboembolism (VTE). The incidence of VTE in cancer is increasing, and it portends poorer survival than the absence of thrombosis. Since the association between cancer and thrombosis was first recognized in the early 19th century, numerous studies have addressed possible underlying pathophysiologic mechanisms. Candidate prothrombotic pathways have included proadhesive and procoagulant tumor cell–derived mucins, cysteine proteases with direct factor X activating activity, and tissue factor (TF), a transmembrane glycoprotein and the primary physiologic initiator of coagulation.2

More recently, research in this field has focused on MVs (or microparticles) released from tumor cells in the form of ectosomes and exosomes. Ectosomes are derived from the cell membrane and vary in size from 100 to 1000 nm. Exosomes, with a diameter in the 30 to 100 nm range, are released when cytoplasmic multivesicular bodies fuse with the plasma membrane. At least some MVs are endowed with prothrombotic cargo molecules derived from their cell of origin. The presence of these entities in the circulation potentially explains how thrombotic events occur at sites remote from the primary tumor or metastases. For example, TF has been identified in plasma samples on the surface of MVs derived from several tumor types, as well as from host cells such as monocytes. Despite compelling evidence that MV–associated TF can initiate thrombosis in mouse models of cancer,1 human studies evaluating whether the measurement of MV–associated TF is a clinically useful biomarker of thrombotic risk in cancer have produced mixed results.3

The past decade has witnessed a resurgent interest in the contact activation pathway of coagulation, composed of the zymogen FXII, high molecular weight kininogen, and prekallikrein. In vitro, deficiency of any of these proteins is associated with prolongation of the activated partial thromboplastin time, due to the inability to generate FXIIa, one of two known activators of factor XI (FXI) (see figure). Patients with a deficiency of any of the contact factors do not have a bleeding propensity and, unlike FXI–deficient subjects, are not known to be at lower risk of thrombosis. However, genetic or pharmacologic inhibition of FXIIa is protective against thrombosis in mouse models of arterial and venous

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