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Oncometabolic Tracks in the Heart

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Abstract

The term cancer and the heart is readily associated with the cardiotoxicity of antineoplastic agents, such as anthracyclines or receptor tyrosine kinase inhibitors. This *Viewpoint* offers a different perspective, drawing attention to the consequences of metabolic dysregulation in cancers for energy substrate metabolism and contractile function of the heart and to common cellular strategies present in cancers and in the failing heart.

Keywords

fetal heart; heart; heart failure; isocitrate dehydrogenase; metabolism; neoplasms; pyruvate kinase

On the basis of his observations in proliferating ascites tumor cells, Otto Warburg[1] proposed that cancer cells derive their energy from the glycolytic breakdown of glucose even in oxygen-rich conditions. Warburg postulated that this metabolic shift, or oncometabolism, arose from dysfunctional mitochondria, and the inability of cancer cells to carry out oxidative phosphorylation. The term oncometabolism refers to an ensemble of metabolic rearrangements that accompany oncogenesis and tumor progression. Recent advances in cancer cell metabolism research have amended Warburg's seminal findings by showing, for example, that mitochondrial metabolism in cancer cells is not defective. Today's system-oriented view is that the metabolism of cancer cells is reprogrammed to optimize the flux of glucose and amino acids into biosynthetic pathways supporting proliferation and cell division.[2,3]

Metabolic Rearrangements in Cancer and in Stressed Heart

In the context of cancer, metabolic rearrangements are required to enable tumor growth. Similar to cancer cells, cardiac metabolism is remodeled in response to stress, which allows fluxes of intermediary substrates to meet the challenges of energy demand and macromolecule synthesis. There are several lines of evidence for this hypothesis. First, the

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Disclosures

None.

failing human heart reverts to the metabolic gene program of the fetal heart,[4] which causes a shift from predominately utilization of fatty acids to glucose. Second, when stressed by pressure overload, the heart responds with an increase in glucose metabolism, as shown both ex vivo and in vivo.[5] In other words, the metabolic remodeling of the heart precedes its structural remodeling. In cancer cells, the loss or gain of enzyme activity can lead to metabolic remodeling. The losses of succinate dehydrogenase and fumarate hydratase[6] or the neomorphic activity of mutant isocitrate dehydrogenase[7] have all been implicated in influencing metabolism, cellular signaling, differentiation and tumorigenesis. Third, in heart muscle cells, as in cancer cells, there is extensive crosstalk between metabolism and signal transduction pathways, which regulate cell growth and differentiation.[3]

Oncometabolic D-2-Hydroxyglutarate and the Heart

Although the cardiotoxic effect of chemotherapeutic agents has been widely studied, the direct metabolic effect of the tumor biology has remained unrecognized. The role of metabolic enzymes and intermediary metabolites in the pathogenesis of both heart failure and cancer is controversial. The metabolic reprogramming in cancer cells often involves dysregulation of metabolic enzymes. Approximately 20% of acute myeloid leukemias bear mutations of the $NADP^+$-dependent isocitrate dehydrogenase 1 or 2. Mutations of the isocitrate dehydrogenase 1 and 2 lead to a neomorphic enzyme function, which causes production of the oncometabolite D-2-hydroxyglutarate. Excess of D-2-hydroxyglutarate inhibits α-ketoglutarate–dependent dioxygenases and is associated with systemic effects including dilated cardiomyopathy. We recently showed that D-2-hydroxyglutarate mediates cardiac dysfunction by inhibiting α-ketoglutarate dehydrogenase, which, in turn, leads to redirection of Krebs cycle intermediates and epigenetic modifications.[8] Our findings provide evidence that the heart in isocitrate dehydrogenase 1/2-mutant leukemia is at risk for contractile dysfunction because of the tumor biology. In other words, metabolic dysregulation in cancer cells causes metabolic reprogramming in the heart, which may put cancer patients and survivors at risk for developing heart diseases. Survivors of leukemia have a 5-fold higher risk for heart failure, making it a persistent and lifelong health problem.

The link between metabolic and structural remodeling in the heart is still relatively poorly understood. Advances in the cancer field offer to revisit common features to elucidate how heart cells remodel in response to stress. Although the biology of cancer cells is different from the biology of heart cells, there are shared mechanisms and processes in both cells to meet the challenges of macromolecular synthesis. In the heart, metabolism provides the energy for contraction[9] and cellular building blocks. In cancer cells, metabolism provides the energy for cell growth and cell division. In other words, metabolism is a defining feature of every living cell in the body, although the metabolic phenotype varies, even within the same organ or group of cells.[10]

Pyruvate Kinase M2—Footprints of the Warburg Effect in the Heart?

The molecular circuits that control the physiology of the heart are almost always more complex than they appear at first glance. Picking out a single molecule and turning it into a drug or drug target may be an ambitious goal. However, there are metabolic patterns

inherent to both rapidly dividing cells and the stressed heart. A case in point is pyruvate kinase M2. In mammalian cells, there are 2 pyruvate kinase (PK) genes (*PKLR* and *PK-M2*) and 4 PK isozymes (PKL, PKR, PK-M1, and PK-M2). Of those, the isoform PK-M1 is found in the brain and muscle, whereas PK-M2 is found in rapidly dividing cells. PK-M2's highly active tetramer favors formation of pyruvate (and ATP), whereas a less active dimer of PK-M2 causes upstream intermediates of the glycolytic pathway to accumulate, increasing substrate availability for the nonoxi-dative pentose phosphate pathway and the hexosamine bio-synthetic pathway. It is not surprising that in cancer cells, *PK-M2* gene expression is required for the manifestation of the Warburg effect and for tumor growth.[11]

We have shown that PK-M2 is also expressed in hearts of mice treated with the receptor tyrosine kinase inhibitor sunitinib and, perhaps even more importantly, in the hearts of patients with advanced heart failure.[12] Although the failing human heart reverts to the fetal gene program and shows features of fetal cardiac metabolism,[4] the ability of PK-M2 to cycle rapidly between a tetramer and a dimer should be advantageous for the failing heart. In its tetramer form, PK-M2 acts as a pyruvate kinase, providing pyruvate as substrate for oxidation or lactate/alanine production. The low catalytic activity of the homodimer slows the generation of pyruvate and redirects glucose-derived carbons into biosynthetic pathways. It is clear that regulation and function of PK-M2 go beyond cancer and include the heart.

Another activator of PK-M2 is the mechanistic target of rapamycin (mTOR). mTOR plays an important role in regulating cell growth, survival, and metabolism as part of the receptor tyrosine kinase/PI3K/AKT/mTOR signaling pathway and forms two complexes (mTORC1 and mTORC2).[13] The role of mTORC1 and mTORC2 in the pathogenesis of heart failure is still controversial. Both inactivation and increased activation of mTORC1 were found to induce contractile dysfunction and heart failure in rodent hearts.[14,15] Conversely, treatment with rapamycin improves contractile function and attenuates hypertrophy and fibrosis in hearts of mice subjected to pressure overload by aortic constriction.[16] Evidence about the role of mTORC2 in the heart is more consistent and shows that mTORC2 is necessary for normal contractile function[17] and the adaptive response to pressure overload.[18,19]

mTORC1 integrates a broad spectrum of signals and is a key regulator of metabolism, which prompted us to examine the mechanisms and consequences of activation of mTORC1 in the heart. Both, with insulin or high workload, the accumulation of glucose-6-phosphate (G6P) is necessary for activation of mTORC1 in the isolated working heart.[5] With increased workload, the accumulation of G6P is a consequence of a mismatch between the rates of glucose uptake and glucose oxidation.[5] In the presence of noncarbohydrate substrates to support contractile function, the effects of G6P on mTORC1 activation are mimicked by D-2-deoxyglucose, a glucose analog that is phosphorylated to D-2-deoxyglucose-6-phosphate, trapped in the cell, and not further metabolized.[5]

Furthermore, in failing human heart muscle, levels of G6P are increased, which are correlated with an activation of mTORC1. Mechanical unloading of these hearts resulted in a decrease of G6P levels and mTORC1 activity.[5] On the basis of these findings, we propose that glycolytic intermediates, for example, G6P, act as metabolic signals, which precede and induce structural remodeling in the heart.

Conclusions

The complexity of cardiac metabolism is formidable. New knowledge derived from cancer cell metabolism has exposed two new oncometabolic pathways in the heart. The first is the redirection of cardiac metabolism by a circulating oncomeabolite, and the second is the metabolic rewiring of the stressed heart, just like it occurs in proliferating cells. However, because heart muscle cells do not readily divide, the footprints of cancer cell metabolism may reflect a paradigm for self-renewal of the cardiomyocyte from within. As always, there is more to be known and even more to be understood.

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