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Bioenergetics of Cancer Cells—A Brief Orientation to This Minireview Series

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For almost seven decades it has been recognized that one of the most common and profound phenotypes of many cancer cells is their abnormal bioenergetics.[1] They frequently exhibit the capacity to utilize glucose at much higher rates than their cells of origin. This phenotype is characteristic of animal and human cancers including those derived from brain, breast, colon, liver, lung, and stomach.[1,2] Here, a close correlation exists among degree of differentiation, growth rate, and glucose catabolism with poorly differentiated cancer cells exhibiting the highest growth and catalytic rates.[3–5] In fact, the survival times of patients with brain tumors has been predicted on the basis of their glycolytic rate, with those harboring tumors with high rates surviving for much shorter time periods.[6] The molecular basis of the high glycolytic phenotype had long been suspected to involve some type of mitochondrial-glycolytic interaction,[1,2,5] and to have its origin within the genetic makeup of cancer cells.[4] However, it has only been in recent years that a picture has begun to emerge which relates genetic, glycolytic, and mitochondrial events in cancer cells to their common biochemical signature, i.e., a capacity for high glycolysis. One view developed by the author and his colleagues[7] involving an overexpressed, mitochondrially bound form of hexokinase is presented on the cover. However, as one reads through the series of review articles in this volume, it will become clear that the cover photograph, although complex in itself, remains an oversimplification of those events contributing to the highly glycolytic phenotype.

The first review article in this series by Bannash and coworkers[8] focuses on the early bioenergetic events in cancer cells and the importance of certain hormones like insulin. This is followed by the second review by Eigenbrodt and colleagues[9] which provides the reader with the current state of our knowledge about the role of phosphometabolites in cell proliferation, energy metabolism, and tumor therapy. Notably, this review provides over 200 references and is a "must" for anyone who wishes to learn more about this topic. The third review, by Golshani-Hebroni and Bessman,[10] brings an old hypothesis about the relationship of insulin to the mitochondrial binding of hexokinase up to date, and relates it to cell proliferation. The back to back articles (four and five of this series) by Mathupala *et al.*,[7] and by Dang *et al.*,[11] emphasize the importance of gene regulation in cancer cells to the increased expression of the first and last enzymes involved in tumor glycolysis (i.e., hexokinase and lactic dehydrogenase). Significantly, studies summarized in these two reviews are among the first to take an understanding of the high glycolytic phenotype of many cancer cells to the gene level. Notably, the Type II hexokinase gene is amplified as shown by Rempel *et al.*,[12] and its promoter is activated by glucose, insulin, hypoxic conditions, and a mutated form of the tumor suppressor p53,[13,14] while the lactic dehydrogenase promoter is believed to be responsive also to hypoxic conditions, and to the cMyc oncogenic transcription factor. Finally, the intriguing review by Brand[15] (six of this series) emphasizes a new role for the high glycolytic phenotype in protecting proliferating cells against oxidative stress.

Reviews seven though nine of this volume focus specifically on the properties of mitochondria in cancer cells. The article by Cuezva and colleagues[16] emphasizes that highly glycolytic tumors have a low mitochondrial content despite a paradoxical increase in oxidative phosphorylation mRNA transcripts, and the article by PaPa and colleagues[17] notes that biopsies from human hepatocellular carcinomas have a decreased rate of ATP synthesis and a decreased content of the catalytic β subunit of the ATP synthase complex. Finally, the article by Singh and col-

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leagues[18] emphasizes the importance of mitochondrial ATP production in cell cycle control.

The final two articles (ten and eleven) of this series focus on two somewhat different areas of cancer cell bioenergetics. The article by Grinstein and colleagues[19] summarizes many studies on the role of intracellular pH. The authors conclude that cytosolic pH is unlikely to play a role in signaling either cell growth or cell death. The article by Baggetto[20] provides new information about the multidrug resistant protein (MDR 1 or P-glycoprotein), an ATPase which exports anticancer drugs from tumor cells, and emphasizes the role that membrane cholesterol may play in the MDR phenotype.

Collectively, this series of reviews from eleven different laboratories should give the reader an excellent overview of the current status of work on the bioenergetics of cancer cells, and suggest new avenues of research focussed on arresting tumor cell growth. Over the past three decades the field of cancer research has deviated almost completely from its once central focus of understanding the most common biochemical signature of cancer cells, i.e., the highly glycolytic phenotype. Although much has now been learned about other areas, particularly at the gene level, the time is ripe to apply this new knowledge to understanding the aberrant energy metabolism of numerous types of cancer.

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