Reinventing Cancer Cell Metabolism

In today’s media world, when journal publications seem at times to be outdated by the time they appear in print, oncologists are fascinated to find that experiments reported some 80 years ago could be the object of surprising new discoveries. And yet, that is precisely the setting for the CCR Focus published in this issue of Clinical Cancer Research. In 1931, Otto Warburg (top photo) was awarded the Nobel Prize in Physiology or Medicine for his discovery that, in essence, cancer cells under normal conditions metabolize glucose as though they lack oxygen, deriving much of their energy from a high rate of glycolysis. In a 1956 lecture, Warburg explained that normal livers and kidneys obtain 100 times more energy from mitochondrial respiration [oxidation of pyruvate in the tricarboxylic acid (TCA) cycle] than from glycolysis and lactate production in the cytoplasm, whereas cancer cells obtain energy equally from both sources (1). Warburg went further to state that cancer was caused by respiratory impairment, the Warburg hypothesis, which can be contrasted with the experimental observation known as the Warburg effect. We now understand that this "glycolytic preference" allows the cancer cell to generate all the components required for sustained cellular proliferation. All successful cancers engage this switch to glycolysis, and many of the mutations that drive proliferation and oncogenesis also alter metabolic regulation. With the leadership of Guest Editor Beverly Teicher, the experts contributing to this CCR Focus section discuss the profound metabolic changes that promote cancer cell survival. The articles examine the role of Myc and HIF-1 in metabolism; the metabolic switch at the level of pyruvate kinase M2; the discovery of IDH1 and 2 mutations, FH, and SDH mutations in the TCA cycle; and genomic approaches to metabolic modeling.

While the Warburg effect is not disputed, the hypothesis that cancers result from respiratory impairment has been argued—including debates with AACR’s Past President Sidney Weinhouse (refs. 2, 3; bottom photo). Two decades ago, most authors would have said that enhanced glycolysis is a consequence of the genetic dysregulation that underlies carcinogenesis. Subsequent discoveries of mutations in TCA cycle enzymes that interrupt oxidative metabolism suggest that Warburg may also have been right about the cause of cancer in some specific tumor types. That should give pause to those who think that the only papers in the literature that matter are those published in the most recent journal issues. As with every CCR Focus section, we strive to include articles that interest and inform the nonexpert but also challenge and encourage those already working in the field.

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References


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