Succinate Dehydrogenase in Cancer and Metabolism

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All biological tissues, including cancer, are made of microscopic living cells. Metabolism is the processes of assembling molecules together to generate functional cells and organisms. Cellular growth (in size) and division (in number) are metabolic- and energy-intensive processes. Cancer cells divide uncontrollably and therefore, are metabolically demanding. Yet, tumors are often found in microenvironments low in oxygen and molecular building blocks. Hence, to sustain high rates of growth and division the metabolism of cancer cells becomes rewired.

Research into cancer metabolism has increased dramatically in recent years. Technological advances in analytical chemistry, collectively known as "metabolomics", have facilitated the simultaneous measurements of many metabolic building blocks in cells and tissues. This enables researchers to engage analytical chemistry on a large scale to answer basic biological questions, such as, what energy sources and building blocks do cancer cells use, and can we cut the supply line of cancer cells to inhibit their growth?

There are two ways to produce energy in cells: The most efficient one is 'oxidative phosphorylation' which takes place in an intracellular organelle called mitochondrion (mitochondria in plural) where oxygen is utilized to break down (burn) other molecules to water and carbon dioxide. The second is 'glycolysis', a less efficient but oxygen-independent process that generates energy by a partial breakdown of sugar molecules. By the late 1990s, our understanding of cancer metabolism centered on the Warburg effect, an observation made by Otto Warburg in the early 20th century, that cancer cells preferentially rely on glycolysis. But in more recent years, it was appreciated that glucose is not only used as an energy source, but is also the carbon source for many of the building blocks needed to make fatty acids, nucleic acids and other molecules that growing and dividing cells need. Furthermore, it was appreciated that cancer cells also use non-traditional oxidizable substances, such as amino acids (the building blocks of protein), lipids, and even acetate (vinegar) for oxidative phosphorylation and for cell growth.

In an unexpected twist, one key observation that cemented the link of cancer to metabolism was a genetic, rather than a biochemical, discovery. In the early 2000s, several genetic studies of families with a tendency to develop some kind of relatively rare tumors, such as paraganglioma, pheochromocytoma and GIST, discovered that the affected patients carry a germline (heritable) mutation in one of the genes that encode for the metabolic protein complex 'succinate dehydrogenase' (SDH). These genetic alterations eventually lead to a dysfunctional SDH complex in the tumor cells.

SDH is a protein that is based in the mitochondria and is directly involved with oxidative phosphorylation. Hence, its loss causes a major energy and metabolic crisis. Despite this, some type of cells can 'benefit' from the loss of SDH and continue to grow uncontrollably and generate tumors. One accepted mechanistic explanation for this phenomenon is the accumulation of high amount of succinate in cells where SDH activity is lost. Succinate is a small molecule (compared to proteins) which typically is oxidized in the mitochondria by SDH during energy production. Its accumulation in SDH-inactive cells generates a molecular signal that interfere with other cellular processes such as the oxygen sensing machinery and the regulation of gene expression. Those derailed processes contribute to cancer development despite the severe energy crisis caused by SDH loss.

All these metabolic changes mean that cancer cells in general, and SDH-deficient cells in particular, are potentially dependent on some metabolic routes that are not essential for normal cells. Identifying and inhibiting such routes can be an effective therapeutic approach, with specific toxicity to cancer cells only. Any metabolic process is catalyzed by a unique 'enzyme' which is a protein that facilitate a biochemical reaction. In principal, from a drug development standpoint, inhibiting the activity of enzymes with synthetic small chemicals is possible. Hence, identifying metabolic enzymes as molecular drug targets that are uniquely-essential for the survival of SDH-deficient cells is a key first step in the development of new therapies for SDH-deficient tumors. Some of these druggable enzymatic targets are being actively pursued.