Chapter 14

Mitochondrial Respiratory Dysfunction and the Extrachromosomal Origin of Cancer

The credibility of any theory to explain a complicated phenomenon is dependent on the extent to which it can explain all or most observations associated with the phenomenon (1, 2). As I mentioned in previous chapters, there are serious inconsistencies with the somatic mutation theory of cancer. These inconsistencies have undermined the credibility of this theory to explain the origin of the disease. The gene theory has now reached a critical point of disbelief. The current acceptance of the gene theory as an explanation of cancer must be based more on ideology than on reason (1, 3).

Unlike Darwin, who incorporated most observations on the origin of species into his theory of natural selection, Warburg failed to explain how his theory of mitochondrial injury could explain metastasis or why some cancer cells might appear to respire. These omissions contributed in part for the failure of Warburg's theory to become the dominant explanation for the origin of cancer. However, no data have disproved Warburg's central hypothesis that damaged or insufficient respiration is the origin of cancer. As I discussed in Chapters 7 and 8, amino acid fermentation and anaerobic respiration in tumor mitochondria can give the appearance that aerobic respiration is normal when, in fact, it is not.

In Chapter 13, I have discussed how mitochondrial dysfunction can account for the phenomenon of metastasis in macrophage fusion hybrids and, in Chapters 7 and 8, how amino acid fermentation might simulate OxPhos. This evidence more strongly supports cancer as a metabolic disease than as a genetic disease. That the mitochondrion, rather than the nucleus, dictates the origin of tumorigenesis is now

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incontrovertible. The Warburg effect (aerobic glycolysis) is seen in most cancers. It is becoming clear how respiratory insufficiency arising from mitochondrial damage underlies the Warburg effect and all other phenomena associated with the disease. The evidence supporting cancer as a disease of mitochondrial respiratory insufficiency is overwhelming. As mitochondria constitute a classic extrachromosomal epigenetic system, cancer can be considered an epigenetic metabolic disease.

CONNECTING THE LINKS

The path from normal cell physiology to malignant behavior, where all major cancer hallmarks are expressed, is depicted in Figure 14.1, and is based on the evidence reviewed in previous chapters. The diagram has been modified slightly from our original diagram that was first published in *Nutrition & Metabolism* (4). Any unspecific condition that damages a cell's respiratory capacity, but is not

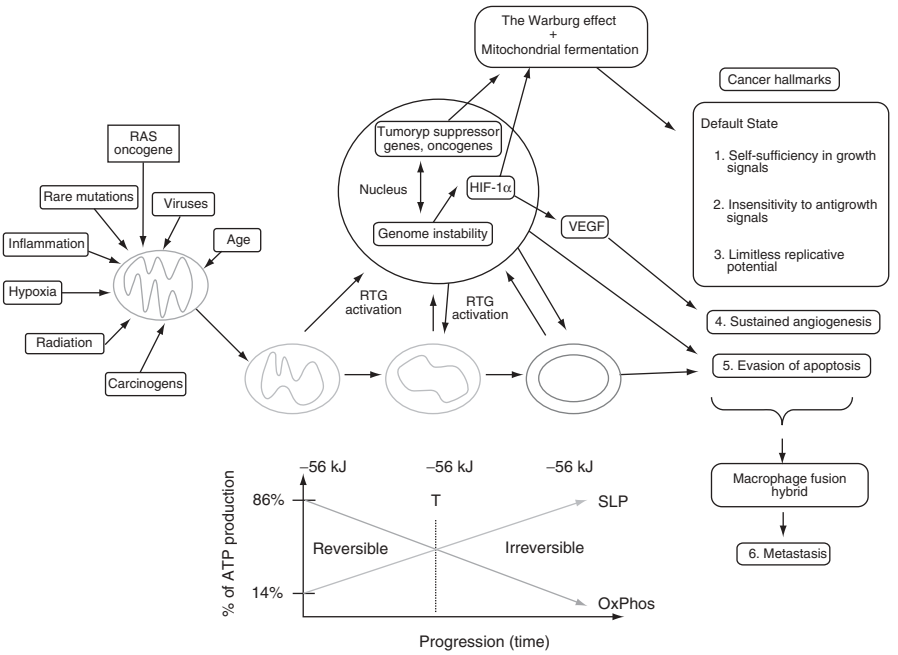

Figure 14.1 Mitochondrial respiratory dysfunction as the origin of cancer. Cancer can arise from any number of nonspecific events that damage the respiratory capacity of cells over time. The path to carcinogenesis will occur only in those cells that are capable of enhancing energy production through SLP (fermentation). Despite the shift from respiration to fermentation the $\Delta G'$ of ATP hydrolysis remains fairly constant at approximately −56 kJ. Oncogene upregulation and tumor-suppressor gene inactivation are necessary to maintain viability of incipient cancer cells when respiration becomes damaged. Metastasis arises from respiratory damage in cells of myeloid/macrophage origin. This scenario links all major cancer hallmarks to respiratory dysfunction. *Source*: Reprinted with modifications from Ref. 4. See color insert.

severe enough to kill the cell, can potentially initiate the path to a malignant cancer. Reduced respiratory capacity could arise from damage to any mitochondrial protein, lipid, or mtDNA. Some of the many unspecific conditions that can damage a cell's respiratory capacity thus initiating carcinogenesis include inflammation, carcinogens, radiation (ionizing or ultraviolet), intermittent hypoxia, rare germline mutations, viral infections, and age.

Inflammation has long been recognized in the initiation and promotion of cancer. Inflammation produces ROS and elevates TGF-β, which damage mitochondria while disrupting tissue morphogenetic fields (Chapters 10 and 12). Besides producing mutations, *carcinogens* also produce ROS (Chapter 9). Carcinogens, in addition to causing mutations, disrupt OxPhos and cause permanent injury to mitochondria. It is this effect of the carcinogen on mitochondrial energy production rather than its mutagenic effect that primarily initiates cancer. It is unfortunate that the Ames tests focused only on the mutagenic effects of carcinogens rather than on the mitochondrial damaging effects of these compounds (5). *Radiation* not only causes mutations, but also injures mitochondria (Chapters 7 and 9). Radiation causes necrotic cell death and inflammation (6). It is the production of ROS and the injurious effect of radiation on OxPhos that causes cancer (7, 8). While radiation can certainly kill cancer cells, radiation can also initiate cancer through its effect on the mitochondrial energy production. Similar to inflammation, *hypoxia* produces high levels of ROS in the microenvironment, which will damage mitochondrial respiratory capacity thus facilitating cancer initiation and progression. Although we did not include *age* in our original discussion of cancer inducing agents (4), it is certainly a cancer risk factor. The accumulation of ROS with age damages mitochondrial respiratory energy production. If mitochondrial damage underlies the origin of cancer according to my central hypothesis, then it is predictable that cancer risk should increase with age. Finally, rare *germline mutations* increase cancer risk through a direct effect on mitochondrial function (Chapter 9). Hence, the plethora of nonspecific factors known to increase the risk of cancer can all be linked to the disease through their protracted and deleterious effects on mitochondrial function, which leads to respiratory insufficiency.

ADDRESSING THE ONCOGENIC PARADOX

Szent-Gyorgyi stated,

> *The malignant transformation of tissues involves a paradox which, to my knowledge, has not been pointed out before. This transformation is a very specific process, which must involve very specific changes in a very specific chemical machinery. Accordingly, one would expect that such transformation can be brought about only by a very specific process, as locks can be opened only by their own keys. Contrary to this, a malignant transformation can be brought about by an infinite number of unspecific influences, such as pieces of asbestos, high-energy radiation, irritation, chemicals, viruses, etc. It is getting more and more difficult to find something that is not carcinogenic. That a very specific process should be elicited in such an unspecific way is very unexpected* (9).

According to the evidence presented in my treatise, protracted damage to the respiratory capacity of cells that are capable of upregulating fermentation can explain, in large part, Szent-Gyorgyi's paradox.

Chronic injury to the structure and function of mitochondria, which impairs respiration, will activate the mitochondrial RTG response within the damaged cell (Chapter 10). The RTG response is an epigenetic system that upregulates those genes needed to derive energy through fermentation. Fermentation involves SLP through glycolysis in the cytoplasm and through amino acid fermentation in the mitochondria (Chapter 8). Uncorrected mitochondrial damage will require continuous compensatory energy through fermentation involving SLP in order to maintain the $\Delta G'_{ATP}$ of approximately −56 kJ/mol. This standard energy of ATP hydrolysis is essential for cell viability. This ATP hydrolysis remains mostly constant regardless of whether the ATP is synthesized through respiration or fermentation (Chapter 4).

Although fermentation energy can temporally compensate for disruptions to respiration in order to maintain cell viability, persistent energy production through fermentation can compromise cellular differentiation. Tumor cells require energy production through fermentation because their mitochondrial respiration is insufficient to maintain energy homeostasis. If their respiration was sufficient, fermentation would not persist. Confusion arises from amino acid fermentation, which can simulate properties of normal respiration. Cancer cells appear to respire while also fermenting glucose (aerobic glycolysis). Hence, tumor cells differ from normal cells because they generate significant amount of energy through fermentation (Chapter 8).

Tumor progression is linked to irreversible respiratory damage with fermentation becoming the permanent compensatory energy source for the tumor cells. The change in shape of mitochondrial cristae from convoluted- to smooth illustrates the transition from respiration to fermentation as shown in Figure 14.1. Persistent and cumulative mitochondrial damage underlies the initiation and progression of cancer. To illustrate this point further, I have also inserted a threshold on the progression (time) line in the figure. The threshold (T) passes through the intersection of the OxPhos and SLP lines. This concept is based on Warburg's findings that fermentation gradually displaces respiration after a long time period (8). It is only when fermentation compensates for the greater part of total cellular energy production that tumor progression becomes irreversible according to our model. Tumor progression can be reversed, however, as long as some functional mitochondrial respiration remains. Mitochondrial enhancement therapies can help restore impaired respiration (Chapters 17–19). The failure to restore respiratory energy coupled with a greater dependence on fermentation energy underlies all hallmarks of cancer, including the Warburg effect. In addition to the fermentation of glucose to lactate, which is needed to drive glycolysis, many cancer cells might also ferment glutamine in the mitochondria. It is the fermentation of glucose and glutamine that primarily drives tumor progression and makes tumor cells unresponsive to most conventional therapies.

Most of the gene changes associated with tumor progression arise as direct or indirect consequences of insufficient respiration and elevated fermentation. Oncogene upregulation coupled with tumor-suppressor-gene downregulation becomes

necessary in order to increase those metabolic pathways needed for fermentation. If the oncogenes needed to drive cellular fermentation are not expressed then the cell will die from energy failure. Oncogene expression is essential to maintain cell viability following respiratory damage. This perspective addresses the NCI provocative question #22 (provocativequestions.nci.nih.gov). Succinate produced through mitochondrial glutamine fermentation could be responsible, in part, for stabilization of Hif-1α (Chapter 8). Hif-1α is required for maintaining elevated glucose uptake and glycolysis. Respiratory injury becomes the driver for the gene regulatory changes needed for increasing compensatory energy production through fermentation. Insufficient respiration drives oncogene expression, not the reverse.

As DNA repair mechanisms are dependent on the efficiency of respiratory energy production, the continued impairment of respiration will gradually undermine nuclear genome integrity leading to a mutator phenotype and the plethora of somatic mutations identified in tumor cells. Specifically, the integrity of the nuclear genome is dependent on normal cellular respiration. When cellular respiration becomes compromised genomic instability increases. Activation of oncogenes, inactivation of tumor-suppressor genes, and aneuploidy will be the natural consequences of protracted mitochondrial dysfunction (Chapter 9). These gene abnormalities will contribute to accumulative mitochondrial dysfunction while also enhancing those energy pathways needed to upregulate and sustain fermentation energy. The greater the dependency on fermentation and SLP over time, the greater will be the degree of malignancy.

As respiration is necessary for maintaining cellular differentiation, loss of respiration leads to dedifferentiation and a return to the default state of proliferation. Szent-Gyorgyi considered this cellular state as that which existed in the α-period in the history of life on the planet.

> To make life perennial, the living systems, in this period, had to proliferate as fast as conditions permitted. Energy for this proliferation had to be produced by fermentation so that the α-period could also be called the fermentative period of unbridled proliferation (9).

The first three cancer hallmarks are consequences of the cell's return to its mode of existence during the α-period (Chapter 2). This would naturally involve increased aerobic glycolysis and resistance to apoptosis. A large number of fermenting cells will also produce excess of lactate and succinate. This would naturally produce an acidic microenvironment. Angiogenesis is a natural response to wound healing and to the metabolic state in the tumor microenvironment. All of these cancer hallmarks arise as a consequence of insufficient respiration and tumor cell fermentation.

According to the recent commentary of Lazebnik, all hallmarks of cancer with the exception of invasion and metastasis can be found in benign tumors or nonmetastatic cancers (10). I have also mentioned in Chapter 13 that four of the five hallmarks of cancer are also found in the crown-gall tumors of plants. In contrast to animal cancers, crown-gall tumors do not invade or develop metastases. Hence,

it is the hallmark of invasion and metastasis that primarily makes cancer the deadly disease that it is.

Although EMT is currently viewed as a credible explanation for the cancer cell invasion and metastasis, this hypothesis does not link metastasis to defects in mitochondria, but rather to changes in developmental regulatory programs (11). As an alternative to the EMT explanation of metastasis, I have showed in Chapter 13 how macrophage fusion hybridization with neoplastic epithelial cells can logically account for all characteristics of the metastatic cascade. Many of the gene expression profiles observed in metastatic cancers are similar to those associated with the function of macrophages or other fusogenic cells of the immune system. Damaged respiration in these fusion hybrids can account for the invasive and metastatic properties found in cancer cells.

IS CANCER MANY DISEASES OR A SINGULAR DISEASE OF ENERGY METABOLISM?

If all cancer cells suffer from respiratory insufficiency, then respiratory insufficiency becomes the central hallmark of the disease. The current view of cancer as a hodgepodge of many diseases is fundamentally inaccurate in view of the central defect of the disease. Cancer appears as many diseases only if viewed from its histological appearance and from its genomic changes. I consider the histological appearance and gene expression profiles of cancer cells as "red herrings." When viewed in the light of energy metabolism, cancer is a singular disease of respiratory insufficiency.

The most convincing evidence supporting my view comes from the reduced growth response of all tumors when their ability to ferment glucose and glutamine becomes interrupted (Chapters 17–19). How long will it take before the cancer field comes to recognize that all cancer cells suffer from some degree of disabled respiration? It is my opinion that there will be no real progress in managing cancer until this fact becomes widely recognized and accepted.

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