Cancer as a Metabolic Disease

On the Origin, Management and Prevention of Cancer

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The ink on paper image in Figure 1.9 depicts the suffering of a woman receiving her scheduled chemotherapy. Pope recalled that the injection days were the worst days of his life. The woman pictured winces in pain as the poisonous drug is administered. In contrast to the treated patient, the mask and gloves protect the nurse from the toxic effects of the chemotherapy.

Figure 1.10 is also an ink on paper image that conveys Pope's memories of his sickness from chemotherapy treatment and the responses of his father (driving) and brother (in back seat) to Pope's suffering. Many cancer patients and their family members continue to experience these emotions. Indeed, these sufferings have become even worse with some of the newer drugs available (15, 22).
Chapter 2

Confusion Surrounds the Origin of Cancer

A major impediment in the effort to defeat cancer has been due, in large part, to the confusion surrounding the origin of the disease. "Make no mistake about it, the origin of cancer is far from settled." Contradictions and paradoxes continue to plague the field (1–5). Much of the confusion surrounding the origin of cancer arises from the absence of a unifying theory that can integrate the diverse observations on the nature of the disease. Without a clear idea on cancer origins, it becomes difficult to formulate a clear strategy for effective management and prevention. The failure to clearly define the origin of cancer is responsible in large part for the failure to significantly reduce the death rate from the disease.

Currently, most researchers consider cancer as a type of genetic disease where damage to a cell’s DNA underlies the transformation of a normal cell into a potentially lethal cancer cell. The finding of hundreds and thousands of gene changes in different cancers has led to the idea that cancer is not a single disease, but is a collection of many different diseases. Consideration of cancer as a “disease complex” rather than as a single disease has contributed to the notion that management of various forms of the disease will require individual or “personalized” drug therapies (6–8). This therapeutic strategy would certainly be logical if, in fact, most cancers were of genetic origin. What if most cancers are not of genetic origin? What if most of the gene changes identified in tumor tissue arise as secondary downstream epiphenomena of tumor progression? What if cancer were a disease of respiratory insufficiency?

The somatic mutation theory, which has guided cancer research and drug development for over half a century, is now under attack. Carlos Sonnenschein and Anna Soto along with others have identified major inconsistencies in the evidence supporting the genetic origin of cancer (2–4, 9–12). Despite these concerns, the cancer field slogs forward with massive genome-based projects to identify all gene defects that occur in various tumor types (13–16). Gabor Miklos provided a compelling

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Chapter 5

Respiratory Dysfunction in Cancer Cells

“As we study cancer bioenergetics more in depth, we gradually realize that comprehending the true meaning of Warburg effect implicates resolving a continuously growing puzzle, which spans several fields of scientific research and occupies the mind of thousands of investigators and students.”
— Leonardo M.R. Ferreira (1)

If Warburg’s theory were correct, then some degree of respiratory insufficiency should occur in the neoplastic cells of all tumors. Although this treatise will present substantial evidence in support of Warburg’s theory, it is not always easy to recognize mitochondrial dysfunction or respiratory insufficiency in cancer cells. Mitochondria are complex organelles responsible for cell respiration. What part of mitochondrial function is abnormal in neoplastic cells?

Warburg considered oxidative phosphorylation (OxPhos) injury or insufficiency to be the origin of cancer. OxPhos is the final stage of cellular respiration involving multiple coupled redox reactions where the energy contained in carbon–hydrogen bonds of food molecules is captured and conserved in the terminal phosphoanhydride bond of ATP. The process specifically involves the following: (i) the flow of electrons through a chain of membrane-bound carriers, (ii) the coupling of the downhill electron flow to an uphill transport of protons across a proton-impermeable membrane, thus conserving the free energy of fuel oxidation as a transmembrane electrochemical potential, and (iii) the synthesis of ATP from ADP+Pi through a membrane-bound enzymatic complex linked to the transmembrane flow of the protons down their concentration gradient (2). These processes are illustrated in Figure 4.4.

Abnormalities in any number of mitochondrial structures could potentially compromise the ability of OxPhos to provide enough energy to maintain metabolic
Chapter 6

The Warburg Dispute

Few topics have been more controversial or hotly debated in the cancer field than the role of mitochondrial function in the origin and progression of the disease. I would put this controversy on the top of Hal Hellman’s “Great Feuds” list in either medicine or science (1). The controversy, as I see it, has arisen largely from Warburg’s emphatic statement that cancer originates largely from injury to respiration. The mitochondrion is the key organelle responsible for cellular respiration where oxygen is consumed in the complete catabolism of organic fuel. Warburg emphasized that respiratory injury in cancer becomes irreversible since the respiration of tumor cells never returns to normal (2). Warburg went on to mention that the injury to respiration could not be so complete that the cells die, as no cancer cells could arise from dead cells.

Evidence of respiratory injury would be obvious in the cancer cells that express reduced mitochondrial adenosine triphosphate (ATP) production in association with decreased oxygen consumption, since O$_2$ is necessary for ATP synthesis through OxPhos. However, oxygen consumption is not reduced in some cancer cells. Indeed, O$_2$ consumption increases with increased malignancy in some tumor cells. Does this mean that respiration is normal or increased in such cells? Not necessarily. Warburg has attributed this phenomenon to defects in the coupling of respiration to ATP production (2). In other words, some cancer cells produce CO$_2$ and consume O$_2$, but produce insufficient energy through respiration.

Defects in the inner mitochondrial membrane of tumor cells dissipate the proton motive gradient, thus uncoupling the linkage between electron transport and ATP production through OxPhos. Uncoupling is a normal process in brown adipose tissue and is regulated by specific uncoupling proteins. Uncoupling proteins divert the proton motive gradient from ATP production to heat production (3, 4). As I have shown in the last chapter, heat is also observed in those tumor cells and tissues where thermal energy has been measured (5–7). Indeed, thermal energy is correlated with poor prognosis. The hotter the tumor, the faster is the growth. It is my belief that heat production in the tumor tissue could arise from upregulation of uncoupling proteins or from protein-independent uncoupling of the mitochondrial

Chapter 7

Is Respiration Normal in Cancer Cells?

Respiration is the process by which cells use O₂ to obtain their energy through OxPhos. If cancer cells have insufficient respiration, as I described in Chapters 4–6, it is not clear why so many published studies indicate that respiration is normal or is not severely impaired in cancer cells. How is it possible for cancer cells to express normal respiration if the organelle responsible for the phenomenon is damaged? I consider this a central issue in the field of cancer metabolism. If respiration is undamaged and functional in many tumor cells then Warburg’s theory of impaired respiration cannot reasonably explain the origin of cancer. The role of respiration in cancer cells festers as a persistent conundrum that must be addressed “head on.” It becomes difficult for me, or anyone for that matter, to discuss Warburg’s original theory if significant credible evidence exists showing that ATP is synthesized through normal OxPhos in cancer cells.

Why is it so important to establish the validity of the Warburg theory? If the Warburg theory is correct, then it should be possible to link all features of the disease directly or indirectly to respiratory damage or insufficiency. If the Warburg theory is correct in describing the nature of the disease, then the cancer field is marching in the wrong direction. On the other hand, if the Warburg theory is incorrect, then it becomes necessary to abandon this explanation for the origin of cancer. This would allow the cancer field to continue in the same direction. It is therefore essential for all those interested in the subject to evaluate carefully the evidence that the quantity and quality of respiration is similar in normal cells and tumor cells.

PSEUDO-RESPIRATION

Just because cultured tumor cells consume O₂, release CO₂, transport electrons through the ETC, and produce ATP in their mitochondria does not mean that
Chapter 17

Metabolic Management of Cancer

If cancer is primarily a disease of energy metabolism, then rational strategies for cancer management should be found in those therapies that specifically target tumor cell energy metabolism. These therapeutic strategies should be applicable for the majority of cancers regardless of tissue origin, as nearly all cancers suffer from the same underlying disorder, that is, damaged respiration with compensatory fermentation. In this chapter, I review information showing how changes in availability of glucose and glutamine target both tumor cells and the tumor microenvironment. Numerous studies show that dietary energy reduction (DER) is a general metabolic therapy that significantly reduces growth and progression of numerous tumor types, including cancers of the mammary, brain, colon, pancreas, lung, and prostate (1–11). DER naturally lowers circulating glucose levels, which many tumors depend on for growth and survival. David Kritchevsky, as well as Stephen Hursting and Frank Kari, provide historical overviews and comprehensive evidence showing how dietary calorie reduction reduces growth and progression of many tumor types (1, 12–14). All oncologists should know that dietary energy reduction is the nemesis of many cancers. This therapeutic approach will be most effective soon after cancer is first diagnosed when most individuals are in good health.

In this chapter, I use the term dietary energy reduction to refer to either calorie restriction (CR) or dietary restriction. The term calorie restriction is often used interchangeably with the term dietary restriction since their therapeutic effects against tumors are due largely to the reduction in foods that provide energy to the body (11, 15). In the absence of energy molecules from foods, the body will generate energy from internal stores, largely involving fats and proteins. Carbohydrates will be synthesized from these molecules through gluconeogenesis. Humans evolved to function efficiently for extended periods in the absence of food (16). Therapeutic fasting enhances systemic energy conservation to achieve...

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a new homeostatic state. Respiratory insufficiency and genomic instability will prevent tumor cells from entering this new energy state.

DER is produced from a total reduction in dietary nutrients and differs from starvation in that DER reduces total calorie energy intake without causing anorexia or malnutrition (4, 11, 17–20). As a natural therapy, DER improves health, prevents tumor formation, and reduces inflammation (17, 19, 21–25). Reduced calorie intake is ideally suited as a therapy for reducing tumor growth without the adverse effects associated with conventional cancer therapies. Indeed, fasting can reduce the toxic effects of some chemotherapies (26). Research from Gary Meadows’ laboratory also shows that tumor metabolism and growth can be affected from restriction of certain amino acids (27, 28). I have addressed in Chapter 18 the issue of cachexia and how DER can also be used to target this energy state.

IS IT DIETARY CONTENT OR DIETARY COMPOSITION THAT PRIMARILY REDUCES TUMOR GROWTH?

Albert Tannenbaum first showed that the anticancer action of DER mostly involved CR itself rather than restriction of any specific dietary component (11, 20). On the basis of the data from his 1953 study with Herbert Silverstone, Tannenbaum stated that “Underfeeding or caloric restriction of mice bearing mammary carcinoma of spontaneous origin increased their life span, decreased the rate of growth of the tumors, hindered the formation of additional neoplasms of the mammae, and decreased the frequency of lung metastases” (29). It is clear from these and numerous other studies that the simple process of DER inhibits tumor growth and metastasis. We also showed that the therapeutic efficacy of DER against brain cancer could be significantly enhanced when combined with drugs that also target glycolysis (30).

We confirmed and extended the findings of Tannenbaum and coworkers in a series of orthotopic mouse brain tumor models treated with the reduced intake of the ketogenic diet (KD). We refer to this as a restricted or reduced intake ketogenic diet (KD-R). The KD-R produces antitumor effects similar to that of DER (15, 31–34). We showed that reduced intake of either a high carbohydrate diet or a high fat, low carbohydrate KD could reduce aggressive brain tumor growth to a similar degree (Fig. 17.1). The energy composition of a typical KD compared to a normal high carbohydrate, low fat diet is shown in Table 17.1.

It is important to mention that mouse body weight was similar in the two unrestricted groups and was reduced to a similar level (about 20% reduction) in the two restricted diet groups. This is very important as some mouse strains gain weight on the KD, while other mouse strains might lose weight on the KD. It is not possible to accurately compare the effects of different diets on tumor growth if the diets differentially influence body weight. Use of isocaloric diets is relevant only if the diets maintain similar body weights in the test subjects. If body weights differ in mice fed isocaloric diets, the diets are not metabolically equivalent.

We showed that it is better to use body weight rather than degree of CR as the independent variable for assessing the influence of DER on tumor growth in mice. For example, a 20% reduction in a KD causes less body weight reduction than does
Is It Dietary Content or Dietary Composition that Primarily Reduces Tumor Growth? 293

(a) SD

(b) KD

UR R

Figure 17.1 Influence of diet on the intracerebral growth of the CT-2A brain tumor. The visual representation (a) and quantitative assessment (b) of the tumor growth in C57BL/6J mice receiving the standard high carbohydrate diet (SD) or the ketogenic diet (KD) under either unrestricted (UR) or restricted (R) feeding as we described (15). Unrestricted feeding is the same as AL feeding. Values in (b) are expressed as means with 95% confidence intervals, and n = the number of mice examined in each group. The dry weights of the tumors in the R-fed mice were significantly lower than those in the unrestricted UR-fed mice at P < 0.01. The results show that DER significantly reduces tumor growth whether the mice are fed a standard high carbohydrate diet (SD) or a high fat, low carbohydrate KD. No adverse effects were seen in the mice maintained on the 30–40% DER. Body weights were similar for mice in both UR groups and were reduced similarly in both R groups (15). Despite a reduction in total body weight, the R-fed mice were more healthy and active than the UR-fed mice as assessed by ambulatory and grooming behavior. No signs of vitamin or mineral deficiency were observed in the DER-fed mice according to standard criteria for mice. These findings are consistent with the well-recognized health benefits of mild to moderate diet restriction in rodents and in humans (32, 33). Source: Modified from data presented in Reference 33. See color insert.

Table 17.1 Composition (%) of a Standard Diet High Carbohydrate Diet and a Typical Ketogenic Diet

<table>
<thead>
<tr>
<th>Components</th>
<th>Standard Diet (SD)</th>
<th>Ketogenic Diet (KD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td>Fat</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>Protein</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Energy (kcal/g)</td>
<td>4.4</td>
<td>7.2</td>
</tr>
<tr>
<td>F/(P+C)*</td>
<td>0.07</td>
<td>4</td>
</tr>
</tbody>
</table>

*F/(P + C) = ratio of fats to protein + carbohydrates.

a 20% reduction in a high carbohydrate diet. It is difficult to compare the influence of one diet with another diet on tumor growth if the components of the two diets are metabolized differently. When body weight is used as the independent variable, data interpretation becomes more accurate (15, 34). Our results show that brain tumor growth is influenced more by diet energy content than by diet nutrient composition.
Gerald Krystal and coworkers also showed that a low carbohydrate, high protein diet could slow tumor growth and prevent cancer initiation (35). Their results showed that reduced glucose and body weight were associated with reduced tumor growth. While this study is conceptually important, it was not clear if the therapeutic effects of the low carbohydrate diet were due to reduced carbohydrate, high protein, or a general CR. The findings of reduced body weight and blood glucose suggest to me that the therapeutic effect is due more to CR than to carbohydrate or protein restriction (36).

**DIETARY ENERGY REDUCTION AND THERAPEUTIC FASTING IN RODENTS AND HUMANS**

The DER-induced inhibition of brain tumor growth in mice is directly correlated with reduced levels of glucose and elevated levels of ketone bodies (15). Ketone bodies [\(\beta\)-hydroxybutyrate (\(\beta\)-OHB) and acetoacetate] become an alternative fuel for tissue energy metabolism when glucose levels are reduced as would occur during consumption of very low calorie diets or water-only fasting (37–39) (Fig. 17.2). Acetone is also a by-product of ketone synthesis, but acetone is not used for energy and is released in the breath or urine. \(\beta\)-OHB is the major circulating ketone body and is used primarily for energy metabolism when glucose levels become reduced. Although \(\beta\)-OHB is metabolized to acetoacetate in most tissues except liver, tissue uptake from the circulation is faster for \(\beta\)-OHB than for acetoacetate (40). A greater number of surface receptors for \(\beta\)-OHB than for acetoacetate might account for the more rapid uptake of \(\beta\)-OHB (17, 41).

![Diagram of glucose and ketone bodies]

**Figure 17.2** Glucose and ketone bodies. Glucose is the major metabolic fuel for most tissues and cells and is the sole fuel for brain during normal physiological conditions. When DER lowers glucose levels, ketone bodies, produced in the liver, will substitute for glucose as a major energy metabolite (38, 42). A [H] is removed from \(\beta\)-OHB (left structure) to form acetoacetate (center structure). A carbon and two oxygen molecules are removed from acetoacetate to form acetone (right structure). Acetone is a nonenzymatic metabolite of ketone synthesis and is eliminated through the lungs.
KETOGENIC DIETS

KD were developed originally to manage epileptic seizures in children, but they are also effective in managing brain cancers, especially when administered in reduced amounts to reduce glucose levels (15, 43–46). KD consumption can also lower blood glucose levels in some persons. This is usually due to self-restriction because of diet unpalatability. Additionally, the high fat composition of the KD can reduce overall consumption through an effect on expression the cholecystokinin peptide. Intestinal cells release cholecystokinin in response to high fat diets. Cholecystokinin activates vagal sensory neurons to inhibit feeding behavior (47). We also showed that simply feeding mice less total food in the form of DER reduces circulating glucose levels, while elevating circulating levels of ketone bodies (15, 36, 37, 48). The efficacy of the KetoCal KD is optimal for brain cancer management when the ratio of dietary fats to combined carbohydrate/protein is 4:1 (49) (Table 17.1). I believe that this 4:1 ratio will be effective in targeting energy metabolism in most tumors that rely heavily on glucose for survival and growth. Reduced glucose availability will target aerobic glycolysis and the pentose phosphate shunt, critical metabolic pathways required for the survival and proliferation of many tumor types (50).

We found that the KD reduced growth and vascularization in mouse astrocytoma, but only when the diet was administered in reduced amounts that also lowered body weights (15, 34, 51). The KD had no therapeutic efficacy against tumor growth when consumed ad libitum (AL) or in unrestricted amounts. The data in Figure 17.1 show that unrestricted consumption of the KD has no inhibitory influence on mouse astrocytoma growth. The data in Figure 17.3 show that blood glucose levels remain high in mice that consume the KD in unreduced amounts. If glucose levels remain high, body weights remain stable or increase (36). When the KD is fed to mice in unrestricted amounts, blood glucose levels remain high and ketones are largely excreted in the urine. We clearly showed, however, that blood ketones were higher in tumor-bearing mice under DER than under AL feeding (34). Under DER, ketones are retained in the body for use in metabolism rather than excreted in the urine. This information is critical when designing metabolic therapies for tumor management.

It is also important to mention that Dr. Adrienne Scheck and colleagues reported growth inhibition of the mouse GL261 glioma cells from a KD fed to mice in unrestricted amounts. These findings suggest that some tumors might be susceptible to KD growth inhibition without CR or glucose reduction (52). Drs. Scheck and Mohammed Abdelwahhab also reported at the 2011 meeting of the American Association of Cancer Research (AACR) that the KD can improve survival in mice receiving radiation therapy for brain cancer. It is my belief, however, that the anticarcinogenic effects of the KD will be best when the diet is consumed in lower amounts rather than in higher amounts, as the unrestricted consumption of the KD can produce adverse events due to the high fat content of the diet (49, 53). Adverse events are reduced when the KD is consumed in restricted amounts.