

## Commentary

# Switching Diseased Cells from Cytosolic Aerobic Glycolysis to Mitochondrial Oxidative Phosphorylation: A Metabolic Rhythm Regulated by Melatonin?

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## Abstract

This commentary reviews the concept of the circadian melatonin rhythm playing an essential role in reducing the development of diseases such as solid tumors which adopt cytosolic aerobic glycolysis (Warburg effect) to support their enhanced metabolism. Experimental data shows that solid mammary tumors depend on aerobic glycolysis during the day but revert to mitochondrial oxidative phosphorylation at night for ATP production. This conversion of diseased cells during the day to a healthier phenotype at night occurs under control of the melatonin rhythm. When the nocturnal melatonin rise is inhibited by light exposure at night, cancer cells function in the diseased state 24/7. The ability of melatonin to switch cancer cells as well as other diseased cells, e.g., Alzheimer disease, fibrosis, hyperactivation of macrophages, etc., from aerobic glycolysis to mitochondrial oxidative phosphorylation may be a basic protective mechanism to reduce pathologies.

Many diseased cells adopt cytosolic aerobic glycolysis for the rapid generation of ATP and high throughput production of other biomolecules.<sup>1-4</sup> This phenomenon was described by Warburg more than 100 years ago and bears his name, i.e., the Warburg effect.<sup>5</sup> When discovered, and for many years thereafter, this unique metabolism was thought to be a characteristic of only solid tumor cells.<sup>6</sup> Subsequent research has revealed otherwise. Cytosolic aerobic glycolysis is common to a number of diseases and is believed to be a necessary pathophysiological feature of these cells. Switching these cells from cytosolic aerobic glycolysis to mitochondrial oxidative phosphorylation typical of healthy cells would significantly reduce their pathology resulting a more normal cell phenotype. Thus, molecules/drugs that promote this switch may have significant anti-pathological activity and would impact a number of diseases that use aerobic glycolysis to support their elevated metabolism.<sup>1-6</sup>

When aerobic glycolysis is adopted by healthy cells such that they become pathological, it has been assumed that these newly-diseased cells display aerobic glycolysis 24/7.<sup>6</sup> This may not be the case, however; when the metabolism of xenografted human mammary cancers growing in immune-compromised rats were sampled at 4-hour intervals over a 24-hour light:dark cycle, the tumors exhibited all the features of aerobic glycolysis, i.e., high glucose uptake, elevated lactate secretion, increased ATP synthesis, etc., during the day. Remarkably, however, cancer cells collected at night were not using aerobic glycolysis but rather had reverted back to mitochondrial oxidative phosphorylation.<sup>7</sup> This marked rhythmic change had not been reported previously. The failure to observe this rhythm may be related to the fact that cancers are routinely examined during the day rather than at night, which would require the collection of the tumors in darkness. Also, this day:night difference would not occur in cultured cancer cells where they are not under the influence of the circadian melatonin rhythm.

Of special interest is that the switch from daytime aerobic glycolysis to nighttime mitochondrial oxidative phosphorylation was dependent on the nocturnal rise in circulating melatonin levels.<sup>7</sup> When tumor-bearing rats were exposed to light-at-night which severely blunted the nocturnal rise in circulating melatonin, nighttime mitochondrial oxidative phosphorylation did not occur such that cytosolic glycolysis was featured in these tumors collected both in the day and the subjective night, i.e., they displayed a pathological-type metabolism throughout the 24-hour period. Moreover, the tumors exhibited an increased growth rate relative to those in a regular light:dark cycle with a daily nocturnal rise in melatonin.

This finding has important implications. It suggests that at least this tumor type only functions with a cancer phenotype during the day while at night the same cells are of a healthier phenotype. Thus, cancer cells are only part-time cancerous and part-time healthy cells.<sup>8</sup> In the absence of a nocturnal rise in melatonin, however, the cells function with the cancer phenotype throughout each 24-hour period.<sup>7</sup>

This marked melatonin-dependent rhythm of gross cellular metabolism may be involved with other pathological cells that also exhibit cytosolic aerobic glycolysis during the day.<sup>1-3,9</sup> For example, we recently proposed that melatonin converts proinflammatory M1 macrophages to M2 anti-inflammatory macrophages, i.e., “pathological” macrophages, to non-pathological macrophages.<sup>9</sup> This occurs simultaneously with the changes in glucose metabolism in activated hyperinflammatory macrophages (M1; which use aerobic glycolysis) versus non-activated anti-inflammatory macrophages (M2; which use oxidative phosphorylation) and illustrates the ability of melatonin to modulate glucose metabolism.<sup>10</sup>

Here, we propose that this major day:night difference in cancer cell metabolism as well as in other cells with disordered metabolism that display aerobic glycolysis may be under the

control of the circadian melatonin rhythm. Mechanistically, this may be achieved when melatonin directly or indirectly (possibly via inhibition of HIF1 $\alpha$ ) downregulates the enzyme pyruvate dehydrogenase kinase (PDK) which normally markedly inhibits the pyruvate dehydrogenase complex (PDC).<sup>8</sup> PDC activity is essential for the intra-mitochondrial conversion of pyruvate, a glucose metabolite, to acetyl-coenzyme A (Fig. 1); this causes the cells to metabolize pyruvate in the cytosol with the development of aerobic glycolysis and associated metabolic changes including the marked upregulation of the pentose phosphate pathway for nucleotide synthesis and elevated production of other biomolecules (Fig. 1).<sup>9</sup> If this is a general feature of the nighttime rise in melatonin, which the evidence indicates it may be, it may partially account for the large number of diseases seemingly inhibited by melatonin, e.g., solid tumors, Alzheimer disease, fibrosis, etc.,<sup>1-6</sup> all of which exhibit the Warburg effect.

The hypothesis has implications for diseases in different population groups as well. There are a number of pathologies of the elderly which are/may be related to the loss of the melatonin rhythm,<sup>11</sup> perhaps the best known of which is the disturbed sleep:wake rhythm.<sup>12</sup> Other pathologies, however, also occur more frequently in the elderly, e.g., cancer, neurodegenerative diseases, etc., which are temporally associated with the loss of the melatonin cycle and the breakdown of circadian rhythms. Without adequate nocturnally-produced melatonin, aerobic glycolysis-dependent diseases would continuously function pathologically 24/7, which would hasten their progression and severity. Likewise, this may also occur in younger individuals who are exposed to sufficiently bright light-at-night where the melatonin rhythm is suppressed or disrupted.<sup>13, 14</sup> The ability of melatonin to impact pathological cells that use aerobic glycolysis and convert them to a more healthy cellular phenotype that utilizes mitochondrial oxidative phosphorylation may be an essential mechanism of the disease-

inhibiting actions of this indoleamine. If this observation is valid, many diseased cells may only function as a pathological phenotype during the day and may actually be a healthier cell at night, provided there is a nighttime rise in circulating melatonin.

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Fig. 1 An illustration of differential glucose metabolism and ATP production in healthy and diseased cells. In healthy cells, the glucose metabolite, pyruvate, enters the mitochondria to be converted to acetyl-coenzyme A. This ensures optimal function of the tricarboxylic acid (TCA) cycle and mitochondrial respiration with ample ATP production. In diseased cells, pyruvate is primarily metabolized to lactate in the cytosol. This occurs because pyruvate cannot be converted to acetyl-coenzyme A in the mitochondria due to the upregulation of pyruvate dehydrogenase kinase (PDK) which inhibits pyruvate dehydrogenase complex (PDC) (indicated by the red "X"). Cytosolic aerobic glycolysis (Warburg effect) leads to the accelerated rate of ATP production and increased activity of the pentose phosphate pathway (PPP). These combined actions cause the synthesis of abundant nucleotides and other biomolecules. This Warburg-type metabolism is common of many pathological conditions, e.g., cancer, Alzheimer disease, atherosclerosis, etc. We hypothesize that the nocturnal melatonin rise or the administration of exogenous melatonin converts diseased cells that use aerobic glycolysis to a more normal phenotype with high mitochondrial ATP synthesis. Melatonin allows increased PDC activity (dashed line) since the enzyme is disinhibited due to the direct or indirect suppression of PDK. The conversion of cells using aerobic glycolysis to cells using oxidative phosphorylation may be a mechanism by which melatonin interferes with the progression of these diseases.

