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Regulation of Energy Homeostasis in Cancer

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Abstract

The disease called cancer is actually the abnormal uncontrolled growth and proliferation of cells in our body by mutation. Reprogramming of metabolism in order to carry on the growth and proliferation of cancer cells is one of the most important changes seen in cancer cells. Altered metabolism is among the main causes of cancer. Cancer cells consume a lot of energy therefore it starts seeking for alternative fuels and their metabolisms vary compared to normal cells. The most important of these differences is aerobic glycolysis known as the 'Warburg effect'. AMP-activated protein kinase (AMPK) is an energy sensor of our body and keeps it in a certain order. AMPK provides the balance between catabolism and anabolism. Another issue that needs to be mentioned in cancer metabolism is the p53 gene. The p53 gene is the most frequently mutated gene in cancer cells and is responsible for cell cycle and death. It is our circadian system that regulates metabolism in a 24-hour rhythm. In daily nutrition, the time of feeding is as important as the amount of energy intake. Our circadian system regulates glucose, lipid and energy metabolism, glucose homeostasis, as well as hunger and satiety cycles. Changes in metabolism occur when the order of the circadian system has been left. This situation causes the metabolic diseases. Circadian disruption has a carcinogenic effect on our body. We should try to protect our health by maintaining our circadian system. In this review we discuss the regulation of energy homeostasis with glucose, alternative ways, and circadian rhythm disruption in cancer cells.

Keywords: Cancer; Energy Homeostasis; Circadian Rhythm

Abbreviations: AMPK: AMP-Activated Protein Kinase; GLUT: Glucose Transporter; OAA: Oxaloacetate; LDH: Lactate Dehydrogenase; FAO: Fatty Acid Oxidation; ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; ACC: Acetyl-Coa Carboxylase-2; G6PD: Glucose-6-Phosphate Dehydrogenase; IARC: International Agency for Research on Cancer; SCN: Suprachiasmic Nucleus; per: Period; CRY: Cryptochrome; AMP: Adenosine Monophosphate; SIRT: Sirtuin; SCN: Suprachiasmatic Nuclei.

Introduction

Cancer cells are characterized by rapid growth, division and uncontrolled proliferation. If cells become resistant to apoptosis, abnormal clumps of cells called neoplasms appear [1]. One of the first changes seen in cancer cells is the alteration in their metabolism because cancer cells try to acquire nutrients through different mechanisms and additional ways to meet the increasing energy demand. This change in metabolism was discovered by Otto Warburg in

1920 [2]. Otto Warburg showed that cancer cells use high amounts of glucose as an alternative carbon source for anabolic reactions, as well as increased lactate production under aerobic glycolysis conditions. In other words, he observed that these cells had a high glycolysis rate even in the presence of oxygen, and he called this aerobic glycolysis [1,3-5]. In cancer cells, a large amount of lactate is produced regardless of the oxygen amount in the environment. For this reason, the metabolism of cancer cells is called aerobic glycolysis (Warburg effect) [4-6]. Healthy cells do not metabolize glucose to lactate in the presence of oxygen, they only resort to anaerobic glycolysis or the metabolism of glucose to lactic acid in the absence of oxygen.

Aerobic glycolysis in cancer cells has been investigated for many years and has been accepted as one of the metabolic distinguishing features of these cells [6]. Besides glucose, cancer cells look for other alternative ways to meet their needs. For this, they also use nutrients such as glutamine, amino acids, lactate, acetate and macromolecules. These differences in cancer cells are called metabolic reprogramming [6,7].

Cancer Cells Is Need Much More Energy

Using of Glucose and the Other Substitutions by Cancer Cells

There are two basic nutrients necessary for the survival of mammalian cells to carry on their activities. These nutrients are glucose and glutamine. Uptake of glucose into cells is provided by a family of proteins known as the glucose transporter (GLUT) [8]. Increased expression of GLUTs facilitates the survival of cancer cells. Regulated aerobic glycolysis provides rapid production of ATP for energy requirements at blood concentrations, nurtures anabolic processes in biomass production, supports metastasis by creating an lactate acid environment from pyruvate, is used to produce oxaloacetate (OAA), alanine and aspartate amino acids which are involved in the synthesis of biomolecules, meet the intermediate carbon requirement for the formation of macromolecules and mediates the controlled oxidation of carbon skeletons as well as the capture of NADH and FADH2. Briefly, it is a good source of nitrogen groups. For these reasons it provides to meet the most of the energetic and metabolic demands [7,8]. Glucose is actually the limiting nutrient for cancer cells, but in the absence of glucose, these cells can use glutamine, lipid, amino acids, and various metabolic intermediates. This is called metabolic flexibility. Cells rely on their metabolic flexibility to survive in the absence of glucose [9,10].

Glutamine in the Cancer Cells

The high need for glutamine in cancer cells was described by the American physiologist Harry Eagle in the 1950s [11]. Cancer cells can use glutamine via the glutamine transporter SCL1A5 located at the plasma membrane, or glutamine and other amino asids can be derived from the lysosomal degradation of extracellular proteins [7].

Glutamine is a carbon source for energy production, it is used as a carbon source in the synthesis of macromolecules required in cell division, it can directly provide the required acetyl-CoA under hypoxia. Glutamine is a nitrogen source for biosynthetic reactions, the main route for the transport of reduced nitrogen into cells, takes part in nucleotide synthesis during proliferation with amido and amino groups as nitrogen source, it has the advantage of providing two nitrogen atoms in synthesizing amino acids and nucleotides that are involved in growth. Glutamine is a regulator of lipid production and a protector of redox homeostasis, it also increases the NADPH / NADP+ ratio and maintain cellular redox status and reduced glutathione (GSH) levels by converting to pyruvate [12,13]. As glutamine can activate alternative metabolisms, it is important for the survival of cancer cell. In glutamine deprivation, macropinocytosis is induced in cancer cells and a membrane crease system is used to capture extracellular material, thereby scavenging fluid and macromolecules [13].

Lactate for Energy Demanding of Cancer Cells

Lactate is the product of anaerobic glycolysis by lactate dehydrogenase (LDH). It is an intermediate with a high energy. It is taken up with the lactate monocarboxylase family carrier group [12]. The accumulation of lactate outside the cell causes an increase in hyaluronic acid and facilitates the spread of cancer cells. It helps survive damaged cells by reducing T cell activation and monocyte migration as well as triggers chemoattraction and cell invasiveness by altering tumor PH [8].

Over-expression of MCT1 in the lactate monocarboxylase family induces p53 loss and glucose deprivation. By blocking MCT1, MCT4, cancer cells can be prevented from accessing lactate [12]. One of the advantages of using lactate versus glucose is the shorter oxidative pathway of lactate and does not require ATP accumulation compared to glycolysis. In fact, catabolism of glucose to lactate results in low energy efficiency, thus increasing the rate of glucose consumption so that cells can meet their needs, which is the most common metabolic phenotype seen in cancer cells [9,14]. Figure 1 shows the glucose and lactate shuttle in a cancer cell.

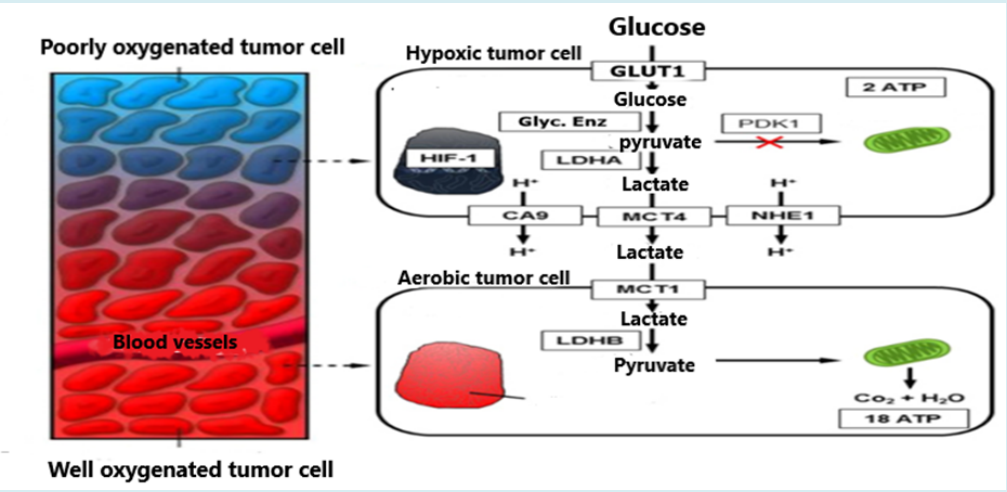

Figure 1: Lactate shuttle in a cancer cell [1].

Lipids – Fatty Acid Metabolism in Cancer Cells

In case of insufficient glucose in cancer cells, these cells try to meet their needs by fatty acid oxidation (FAO). Normal cells take up fatty acids through diet, while cancer cells show an increase in de novo fatty acid synthesis [4]. Lipids are essential components of membranes [5]. Lipids are one of the essential energy sources and act as secondary messengers in signal transmission in the cell. Therefore, cancer cells need fatty acids to complete their organelles and membranes [7,15].

Adenosine Monophosphate- Activating Protein Kinase (AMPK) and Cancer Metabolism

There are regulatory proteins that detect the levels of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to ensure the flow of energy in our body [16].

This is mainly achieved by the AMP-activating protein kinase (AMPK) system and this system becomes active at high AMP and low ATP concentrations. AMPK is a heterotrimeric protein complex involved in the regulation of metabolic and energy homeostasis [17]. The states of activity are due to the use of high ATP during muscle contraction or the metabolic stress that occurs in the case of hypoxia.

In healthy mammalian cells, AMP-activating protein kinase (AMPK) is activated by metabolic stress, hypoxia, ischemia, glucose deprivation, drug, xenobiotic species and with mechanisms including increases in cellular AMP, ADP and Ca^{2+} [16]. In the eukaryotic cell, the main energy sensor is AMP-activated protein kinase (AMPK) [18].

In any stress situation, when the energy state in the cell is compromised, it activates and reduces energy-consuming pathways, stimulating energy production and ensuring survival [17,19,20]. It directly and indirectly phosphorylates downstream targets of the activities of rate-limiting metabolic enzymes, transcription and translation factors, proliferation and growth pathways as well as epigenetic regulators. As a result, cell growth and proliferation are declined [19,20]. Although there are many signaling pathways for cell growth and proliferation, the most important of these signaling pathways is the mTOR 1 complex, which is blocked by AMPK activation [21]. AMPK acts as a fuel gauge and is activated by reducing the ATP/AMP ratio [22]. AMPK inhibits pathways that consume ATP while activates pathways that generate ATP [17,19]. AMPK transcriptionally reprograms cell metabolism during prolonged energy declines [23]. Another thing to say about AMPK is for appetite. AMPK is the basis of the balance between catabolism and anabolism in our body. In the presence of sufficient energy storage, muscle leptin stimulates AMPK and increases catabolism, while hypotalamus leptin can inhibit AMPK as a suppressor of hunger [18]. Hormones and AMPK are of great importance in the regulation of energy expenditure and food intake in response to environmental signals [19]. AMPK has a glucose sensor property, so AMPK activation occurs in glucose deficiency. As a result, it phosphorylates the enzymes that provide ATP formation, activates the catabolic pathways and suppresses the anabolic pathways. In addition, AMPK is associated with blood glucose detection and stimulating liver glucose production [16]. AMPK also directly phosphorylates and inhibits acetyl-CoA carboxylase-2 (ACC2) and acetyl-CoA carboxylase-1 (ACC1). Thus, it provides control of lipid metabolism and prevents fatty acid synthesis. Sustained AMPK activation limits glucose and lipid synthesis in cells and promotes fatty acid oxidation [23]. AMPK conserves ATP

by blocking anabolic pathways. Inhibits anabolic enzyme activities by phosphorylation [18]. Figure 2 shows the pathways in which AMPK is involved in cell metabolism. Cells lacking AMPK cannot adapt to nutrient concentrations in the disruption of energy balance [17].

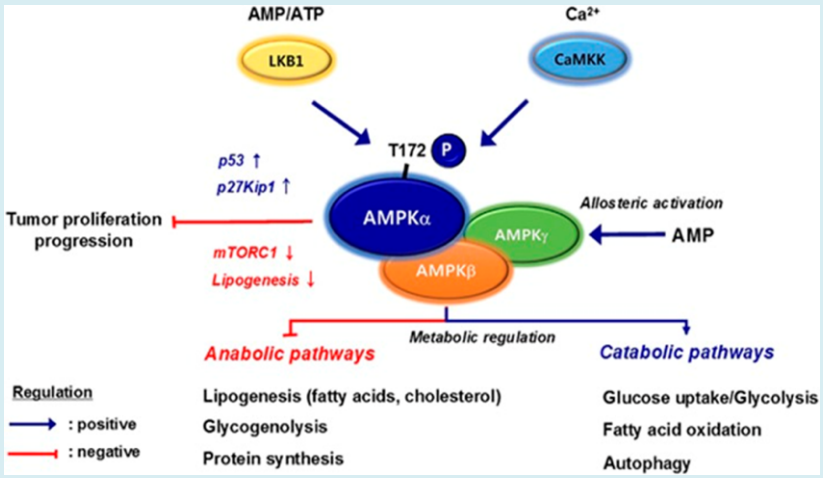

Figure 2: The role of AMPK in cancer cells [24].

Tumor Suppressor P53 and Metabolic Homeostasis

The p53 gene is the most frequently mutated gene in cancer cells. It regulates cell cycle and death. It tries to prevent tumor formation. It regulates the expression of proteins related to metabolism. Therefore, it maintains cell homeostasis [25,26]. P53 adapts in the presence or absence of nutrients to maintain metabolic homeostasis. After a period of fasting, p53 rises and tries to balance gluconeogenesis and ketogenesis to adapt to starvation [5]. P53 interacts with mTOR and AMPK to maintain metabolic homeostasis. Affects pathways in carbohydrate and lipid metabolism, controls autophagy [27]. The p53 gene inhibits glycolysis by regulating the transcription of many genes that modulate glycolysis [25,28-30]. It also takes part in regulating the p53 pentose phosphate pathway. It is very important that NADPH reduces oxidized glutathione and maintains redox regulation and is involved in the production of key components of nucleotide synthesis for DNA repair when cells are faced with DNA damage [25].

The mevolanate pathway is another mechanism in cancer progression. In case of nutrient starvation, p53 activates and inhibits fatty acid synthesis, increases lipid catabolism by increasing fatty acid oxidation (FAO) [25,31]. Increased lipid biosynthesis is seen in almost all cancer cells. On the other hand, mutant p53 reduces NADPH production, inhibits glucose-6-phosphate dehydrogenase (G6PD) activity, and inhibits lipid accumulation. As a result, lost in p53 activity or mutations in p53 may contribute to cancer progression by accelerating lipid accumulation [26]. Since p53 is activated in the presence of stress, it inhibits mTORC1 in order to stop the cell's growth, division and energy consumption in any poor condition [27,32].

Effect of Circadian Rhythm on Nutrition and Cancer

In our daily life, we are exposed to many changes such as hot, cold, light and dark. In order to adapt to these changes, our body has developed circadian timing systems over time. Nutrition, metabolism, gastrointestinal system, endocrine system, body temperature, cardiovascular activity regulations are regulated by changes due to light and darkness [16,33,34]. Health problems begin to occur when the order established by our circadian system is disturbed as well as when food intake decreases or increases abnormally. Obesity, diabetes, impaired glucose tolerance, concentration disorders, depression, cardiovascular diseases are the leading health problems that may occur. Cause the development of cancer [35-40]. The feeding times and daily activities are programmed to be during the day time. In 2007, a study was conducted on shift workers by the World Health Organization International Agency for Research on Cancer (IARC). As a result, it is concluded that the circadian systems of shift workers are disrupted and this disruption has a carcinogenic effect [41].

The circadian clock system in our body is divided into two parts. The suprachiasmic nucleus (SCN) of the hypothalamus is the main site where these rhythms occur. Circadian oxidizers that produce circadian rhythms is located in this region.

Secondly, there is the peripheral clock found in various tissues in the body (such as liver, adipose tissue, gastrointestinal tract, retina, heart) [33,34,37-39,42]. Mainly, the central clock regulates metabolism. Peripheral tissues, on the other hand, integrate signals from the central clock with environmental and behavioral factors (sleep, nutrition, light) and their own autonomous rhythm to keep metabolism in rhythm [35,37,39]. The circadian rhythm is determined by internal and external factors. While our central clock is affected by light, the rhythm in peripheral tissues is formed by the inputs from the central clock, external factors (nutrition, light, sleep, physical activity) and metabolites [34,35]. The proteins found in the SCN are period (per) and crypto chrome (cry). Alongside these proteins are the transcription factors Bmal1 and Clock. Mutation of Per1 causes more food consumption during the daytime [34]. SCN outputs can control energy homeostasis depending on the sympathetic and parasympathetic systems [33]. Although our circadian system has resilience, peripheral tissue clocks are sensitive to the composition and timing of the food consumed. When the timings in this order shift, chronic diseases occur over time. Figure 3 shows the internal and external factors affecting the circadian rhythm [35,39]. During the daytime, our body prepares itself for nourishment, gastric emptying and gastrointestinal motility are at their peak in the morning. Intestinal microbiota increases energy metabolism in the active phase in accordance with the daily rhythm, and helps detoxification in the resting phase. Appetite is time-controlled and delayed bedtime increases food consumption. The feeding/fasting cycles affect the phosphorylation of energy sensors. In high-fat diets, the nutrition/hunger cycles become atrophied, the energy consumed in the resting state increases, the circadian rhythm in the clock genes decreases [37,39]. During the day, fasting and fullness times activate adenosine monophosphate (AMP) kinase and mTOR pathways, which have an significant role in metabolic homeostasis [34]. Resetting the disrupted circadian rhythm, treatment methods can be established to prevent conditions such as cancer and immune system dysfunction. The primary reset mechanism is with the master clock in the upper chiasmic core. The second mechanism occurs in response to mealtime during the nutritional fasting cycle [38].

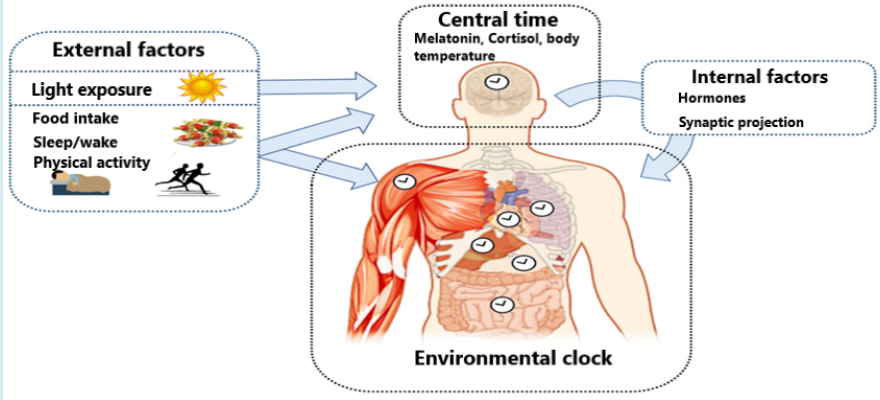

Figure 3: Internal and external factors affecting circadian rhythm [35].

Hormones that are very crucial in our metabolism such as insulin, glucagon, adiponectin, corticosterone, leptin, grehlin (known as hunger hormone and stimulates food intake) have a circadian rhythm. This rhythm affects our metabolic balance [33,37]. Adipose tissues secrete hormones and metabolites that play a role in energy balance along with incoming appetite signals. Leptin is released through the circadian cycle. Its secretions is at its peak at night [40]. One of the important hormones affected by the circadian system is melatonin. It takes part in biological and physiological regulations of the body. Its main role is to regulate the circadian rhythm by maintaining the biological clock in the body. These hormones are stimulated by darkness at night and suppressed by light during the day. Nowadays, melatonin levels start to drop as there is much more artificial light exposure at night [33,40,42]. The active time of the day is the period of energy intake and expenditure. During this period, we have insulin sensitivity and high glucose tolerance. It is forming increased of blood insulin level, glucose uptake by cells, glycogen synthesis and faty deposits in this period. The sleep phase of the day is our resting period. In this phase, usually stored energy is used. Glucose intolerance and insulin resistance occur in sleep disorders such as aging, shift working hours, and excessive exposure to artificial light at night [43]. Figure 4 shows the cycle of our body, depending on day and night, as well as the protein and transcription factors found in our central clock.

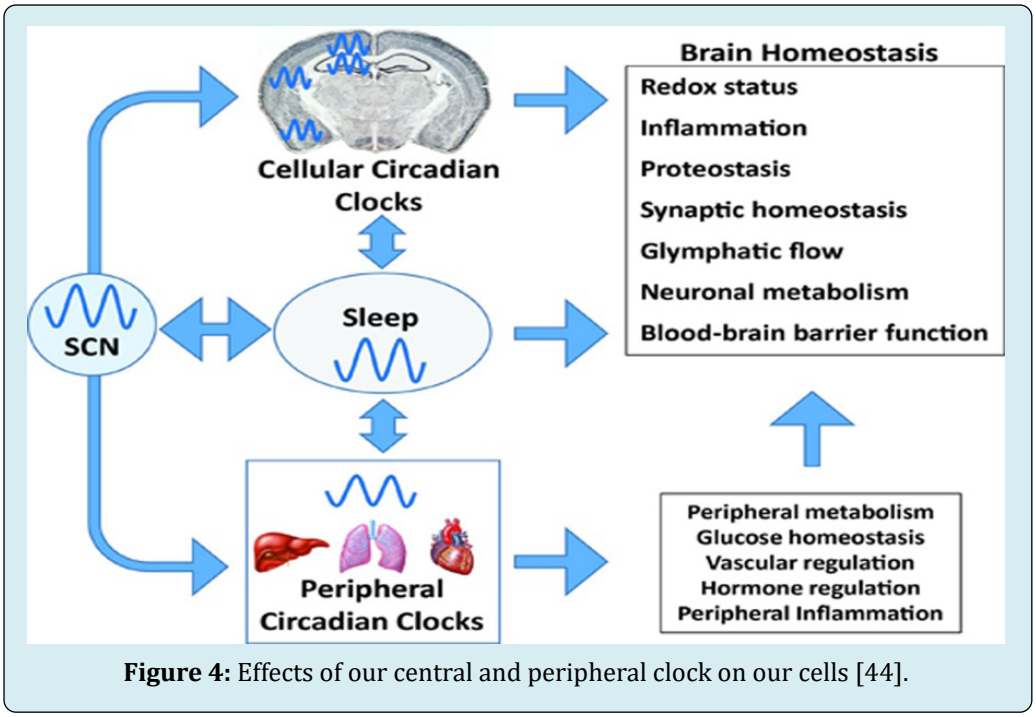

Figure 4: Effects of our central and peripheral clock on our cells [44].

The oxidation-reduction reactions taking place in the cell, the interactions between hormone receptors and genes are the main roles that regulate energy metabolism. The other group that has important functions in our circadian clock system is the sirtuin (SIRT) genes [40]. Sirtuin1 (SIRT1) is a homologue of the NAD+-dependent histone deacetylase SIR2, which is found in transcriptional silencing, genome stability and is very important in calorie restriction (Froy, 2010). SIRT1 is involved in metabolic processes such as lipid metabolism, insulin sensitivity, gluconeogenesis, and modulates BMAL1 activity. SIRT3 and SIRT5 are involved in regulating intracellular pathways such as fatty acid oxidation and oxidative phosphorylation [33,40].

Consumption of food regularly at certain times of the day is very important for the organism and for rhythmic gene expression [40]. Over time, the addition of high-calorie foods (refined foods, increased sugar consumption, corn syrup, etc.) into our lives and their involvement into 3 meals a day, the increase in sedentary life has led to an increase in obesity and various diseases [34]. Gastrointestinal discomfort such as bloating, constipation and diarrhea may occur in situations that disrupt the circadian rhythm such as shift working hours and travels. Recently, one of the main causes of metabolic disorders is thought to be disruptions in the circadian system, and treatment approaches are being developed. These approaches are called chronopharmacology, chronon nutrition, and chronon exercise [40].

Suprachiasmatic Nuclei (SCN) Misalignment Can Occur when the Timing of Eating Is Changed.

Diseases may occur as a result. Breakfast is a very important meal in the cooperation of the central clock and peripheral tissues [37]. Delaying the intake of food can lead to negative consequences. For instance, eating lunch at 16.00 instead of 13.00 causes an increase in glucose and a decrease in carbohydrate oxidation in case of fasting [35].

Although the sensitivity of cells to glucose is at its highest point in the morning, insulin secretion peaks in the afternoon (12.00-18.00) and is at its lowest point at night while sleeping. The rhythm in peripheral insulin sensitivity is due to the basic intracellular pathways and circulating factors accompanying glucose uptake. The storage of glycogen in the muscles lacks the circadian rhythm. Studies showed that healthy individuals have weaker glycemic control in the evening and at night, glucose tolerance shows a circadian rhythm, and peripheral insulin sensitivity is affected by internal and external factors [35]. Inappropriate sleep timing negatively affects carbohydrate and lipid metabolism.

It is seen that daytime sleep increases glucose and insulin and increases triglyceride levels. When daytime sleep becomes a habit, a 3% decrease in energy expenditure is observed, which creates a condition more conducive to weight gain in night shift workers [35]. Changing sleep patterns can

cause improper circadian regulation. Improper circadian alignment also causes changes in appetite hormones [45]. Figure 5 shows the circadian clock that our body has set up and the circadian clock that has been disrupted due to external factors.

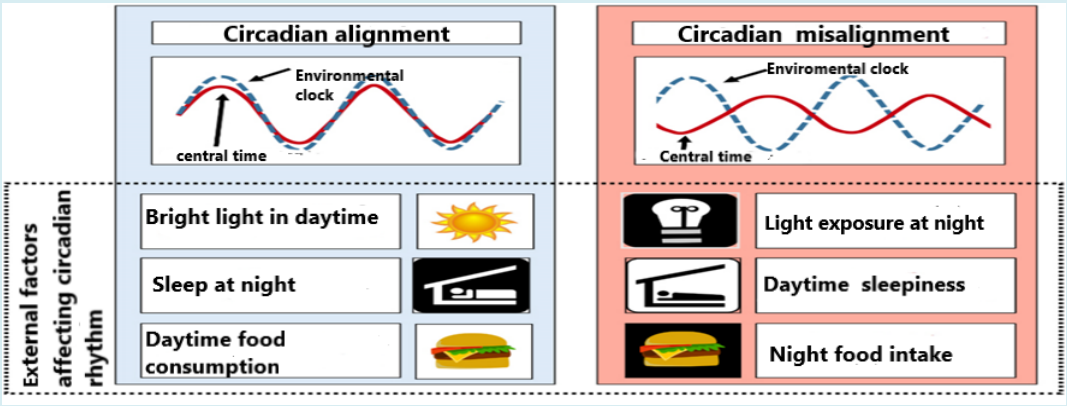

Figure 5: External factors in the circadian rhythm [35].

Circadian Rhythm and Cancer

The light center is the timing mark for our clock. It affects the time of food intake and the phases of the peripheral clocks. When we are exposed to bright light during the day, our melatonin secretion increases at night. Exposure to bright light in the morning appears to improve carbohydrate metabolism and fat loss. Exposure to bright light during the day can have positive results, but on the contrary, exposure to bright light in the evening can have just as much negative results. These negative results include increase insulin resistance, increase postprandial insulin, glucose, glucagon-like peptide 1 (GLP1) levels, impair carbohydrate digestion; increase the risk of cancer and metabolic diseases [35].

Homeostasis of cancerous tissues and cells, uncontrolled proliferation, evasion from the triggered immune system, and high energy demand shows the relationship between circadian rhythm and cancer (Figure 6) [46,47].

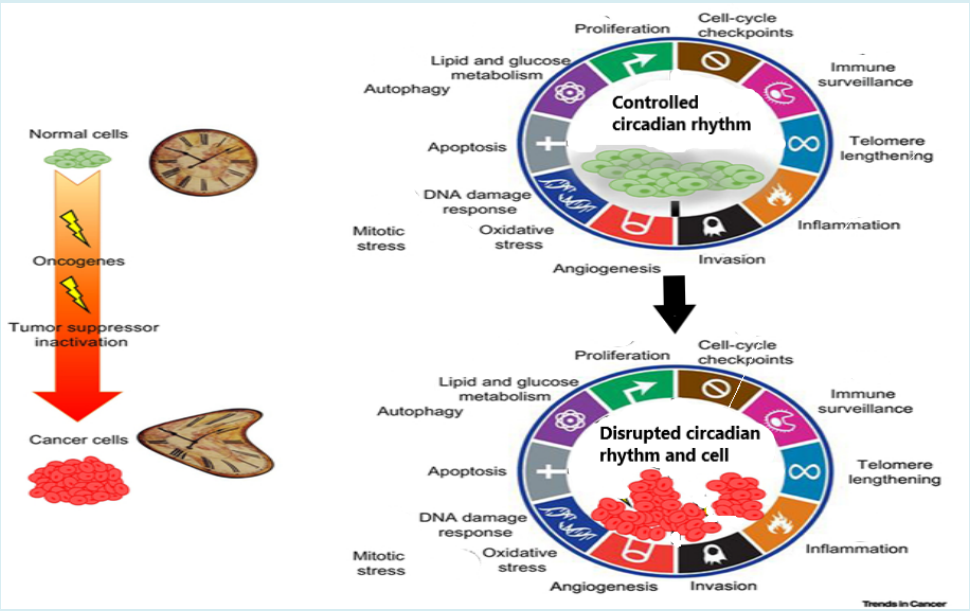

Figure 6: Disruption of circadian rhythm and results on cancer cells [47].

Thousands of genes from different cells express the circadian rhythm. In other words, processes such as DNA damage repair or protein folding Cause homeostasis. Disruption of the circadian rhythm disturbs the cellular process and creates a suitable environment for tumor genesis [48]. The circadian regulation controls the expression of factors with paracrine or endocrine function. Some tumors produce excessive amounts of these endocrine factors (hormones, neurotransmitters, etc.) and disrupt the circadian rhythm.

The relationship between chronic circadian rhythm disorder and cancer has been demonstrated in the development of human breast and prostate cancer [49]. In animal studies, it has been shown that tumor-free distal organs are affected by tumors that disrupt circadian rhythms [50]. On the other hand, changes in circadian gene expression affect the life expectancy of cancer patients [51]. Disruption of the circadian gene expression changes the tumor microenvironment. It also changes the circadian rhythm [52]. As a result, components such as oncogenes, tumor suppressors, hormones, and cytokines as hemostasis regulators control the homeostasis balance by disrupting the circadian rhythm.

Conclusion

Metabolism alterations are one of the main changes seen in cancer cells for acquiring nutrients and meeting the increasing energy demand. Glucose and the alternative sources such as glutamine provides rapid production of ATP and support metastasis by creating an lactate acid environment from pyruvate therefore it provides energy for the cancer cells. On the other hand, glutamine can be involved in the survival of cancer cell by synthesizing macromolecules required in cell division. In addition to the role of nutrients in metabolism and cancer cell survival, the p53 that regulates cell cycle and death adapts in the presence or absence of nutrients to maintain metabolic homeostasis as well. The emerging connection between the circadian clock and cancer is another raising new hopes for cancer prevention. Circadian rhythm that control fasting and fullness times activate kinase pathways which have an significant role in metabolic homeostasis. In addition circadian rhythm affects our metabolic balance by regulating hormones that are very crucial in our metabolism. The circadian rhythm is expressed by the thousands of genes involved in DNA damage repair or protein folding, therefore changes in circadian rhythm disturbs the cellular processes and leads tumor formation. Therefore, we can say that regulation of energy homeostasis in cancer cells are maintained by multi-pathways and effects. This are included simple intermediate molecules which are related with each other in complex rail way. The health homeostatic system should be save, however cancer cells should be live with proliferation. We need more information about mix pathways and all regulations to overcome of energy regulation on cancer cell.

References

1. Kalyanaraman B (2017) Teaching the Basics of Cancer Metabolism: Developing Antitumor Strategies by Exploiting the Differences Between Normal and Cancer Cell Metabolism. Redox Biology 12: 833-842.

2. Warburg O (1925) The Metabolism of Carcinoma Cells. Cancer Research 9: 148-163.

3. Kreuzaler P, Panina Y, Segal J, Yuneva M (2020) Adapt and Conquer: Metabolic Flexibility in Cancer Growth, Invasion and Evasion. Molecular Metabolism 33: 83-101.

4. Kroemer G, Pouyssegur J (2008) Tumor Cell Metabolism: Cancer's Achilles' Heel. Cancer Cell 13: 472-482.

5. Krstic J, Reinisch I, Schupp M, Schulz TJ (2018) P53 Functions in Adipose Tissue Metabolism and Homeostasis. International Journal of Molecular Sciences 19(9): 2622.

6. Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: The Metabolic Requirements of Cell Proliferation. Science 324(5930): 1029-1033.

7. Vernieri C, Casola S, Foiani M, Pietrantonio F, de Braud F, et al. (2016) Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions. Cancer Discovery 6(12): 1315-1333.

8. Pavlova NN, Thompson CB (2016) The Emerging Hallmarks of Cancer Metabolism. Cell Metabolism 23(1): 27-47.

9. Danhier P, Bański P, Payen VL, Grasso D, Ippolito L, et al. (2017) Cancer Metabolism in Space and Time: Beyond the Warburg Effect. Biochim Biophys Acta Bioenerg 1858(8): 556-572.

10. Frezza C (2020) Metabolism and Cancer: The Future is now. Br J Cancer 122(2): 133-135.

11. Eagle H (1955) Nutrition Needs of Mammalian Cells in Tissue Culture. Science 122(3168): 501-514.

12. Keenan MM, Chi JT (2015) Alternative Fuels for Cancer Cells. Journal of Cancer 21(2): 49-55.

13. Boroughs LK, DeBerardinis RJ (2015) Metabolic Pathways Promoting Cancer Cell Survival and Growth. Nat Cell Biol 17(4): 351-359.

14. Vazquez A, Kamphorst JJ, Markert EK, Schug ZT, Tardito S, et al. (2016) Cancer Metabolism at a Glance. J Cell Sci 129(18): 3367-3373.

15. Wang Y, Xia Y, Lu Z (2018) Metabolic Features of Cancer Cells. Cancer Communications 38(1):1-6.

16. Hardie DG, Ross FA, Hawley SA (2012) AMPK: A Nutrient and Energy Sensor that Maintains Energy Homeostasis. Nat Rev Mol Cell Biol 13(4): 251-262.

17. Chaube B, Bhat MK (2016) AMPK, A Key Regulator of Metabolic/Energy Homeostasis and Mitochondrial Biogenesis in Cancer Cells. Cell Death Dis 7(1): e2044.

18. Tetik, Ş (2020) Nutritional Biochemistry. (Ed. Tetik S.) Nobel Medicine Press, pp: 177-195.

19. Viollet B (2017) The Energy Sensor AMPK: Adaptations to Exercise, Nutritional and Hormonal Signals. Hormones, Metabolism and the Benefits of Exercise 97: 13-24.

20. Yan Y, Zhou XE, Xu HE, Melcher K (2018) Structure and Physiological Regulation of AMPK. Int J Mol Sci 19(11): 3534.

21. Fay JR, Steele V, Crowell JA (2009) Energy Homeostasis and Cancer Prevention: The AMP-Activated Protein Kinase. Cancer Prev Res 2(4): 301-309.

22. Chaube B, Malvi P, Singh SV, Mohammad N, Viollet B, et al. (2015) AMPK Maintains Energy Homeostasis And Survival In Cancer Cells Via Regulating P38/PGC-1αmediated Mitochondrial Biogenesis. Cell Death Discov 1: 15063.

23. Garcia D, Shaw RJ (2017) AMPK: Mechanism of Cellular Energy Sensing and Restoration of Metabolic Balance. Mol Cell 66(6): 789-800.

24. Kim J, Yang G, Kim Y, Kim J, Ha J (2016) AMPK Activators: Mechanisms of Action and Physiological Activities. Exp Mol Med 48(4): e224.

25. Lacroix M, Riscal R, Arena G, Linares LK, Le Cam L (2020) Metabolic Functions of the Tumor Suppressor P53: Implications in Normal Physiology, Metabolic Disorders, and Cancer. Mol Metab 33: 2-22.

26. Parrales A, Iwakuma T (2016) P53 as a Regulator of Lipid Metabolism in Cancer. Int J Mol Sci 17(12): 2074.

27. Berkers CR, Maddocks OD, Cheung EC, Mor I, Vousden KH (2013) Metabolic Regulation by P53 Family Members. Cell Metab 18(5): 617-633.

28. Franklin DA, He Y, Leslie PL, Tikunov AP, Fenger N, et al. (2016) P53 Coordinates DNA Repair with Nucleotide Synthesis by Suppressing PFKFB3 Expression and Promoting the Pentose Phosphate Pathway. Sci Rep 6: 38067.

29. Kawauchi K, Araki K, Tobiume K, Tanaka N (2008) P53 Regulates Glucose Metabolism through an IKK-NF-Kb Pathway and Inhibits Cell Transformation. Nat Cell Biol 10(5): 611-618.

30. Schwartzenberg-Bar-Yoseph F, Armoni M, Karnieli E (2004) The Tumor Suppressor P53 Down-Regulates Glucose Transporters GLUT1 and GLUT4 Gene Expression. Cancer Res 64: 2627-2633.

31. Assaily W, Rubinger DA, Wheaton K, Lin Y, Ma W, et al. (2011) ROS-Mediated P53 Induction of Lpin1 Regulates Fatty Acid Oxidation in Response to Nutritional Stress. Mol Cell 44(3): 491-501.

32. Feng Z, Zhang H, Levine AJ, Jin S (2005) The Coordinate Regulation of the P53 and Mtor Pathways in Cells. Proc Natl Acad Sci U S A 102(23): 8204-8209.

33. Froy O (2010) Metabolism and Circadian Rhythms-Implications for Obesity. Endocr Rev 31(1): 1-24.

34. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, et al. (2014) Meal Frequency and Timing in Health and Disease. Proc Natl Acad Sci USA 111(47): 16647-16653.

35. Poggiogalle E, Jamshed H, Peterson CM (2018) Circadian Regulation of Glucose, Lipid, and Energy Metabolism in Humans. Metabolism 84: 11-27.

36. Verlande A, Masri S (2019) Circadian Clocks and Cancer: Time-Keeping Governs Cellular Metabolism. Trends Endocrinol Metab 30(7): 445-458.

37. Micó V, Díez-Ricote L, Daimiel L (2017) Nutrigenetics and Nutrimiromics of the Circadian System: The Time for Human Health. Int J Mol Sci 17(2013): 2-24.

38. Mindikoglu AL, Abdulsada MM, Jain A, Choi JM, Jalal PK, et al. (2020) Intermittent Fasting from Dawn to Sunset for 30 Consecutive Days is Associated with Anticancer Proteomic Signature and Up Regulates Key Regulatory Proteins of Glucose and Lipid Metabolism, Circadian Clock, DNA Repair, Cytoskeleton Remodeling, Immune System and Cognitive Function in Healthy Subjects. J Proteomics 217: 103645.

39. Potter GD, Cade JE, Grant PJ, Hardie LJ (2016) Nutrition and the Circadian System. Br J Nutr 116(3): 434-442.

40. Serin Y, Acar Tek N (2019) Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy

Balance. Ann Nutr Metab 74(4): 322-330.

41. Shaw E, Leung GKW, Jong J, Coates AM, Davis R, et al. (2019) The Impact of Time of Day on Energy Expenditure: Implications for Long-Term Energy Balance. Nutrients 11(10): 2383.

42. Srour B, Plancoulaine S, Andreeva VA, Fassier P, Julia C, et al. (2018) Circadian Nutritional Behaviours and Cancer Risk: New Insights from the Nutrinet-Sante Prospective Cohort Study. Int J Cancer 143(10): 2369-2379.

43. Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ (2014) Melatonin, Energy Metabolism, and Obesity: A Review. J Pineal Res 56(4): 371-381.

44. Musiek ES, Holtzman DM (2016) Mechanisms Linking Circadian Clocks, Sleep, and Neurodegeneration. Science 354(6315): 1004-1008.

45. Depner CM, Stothard ER, Wright KP Jr (2014) Metabolic Consequences of Sleep and Circadian Disorders. Curr Diab Rep 14(7): 507.

46. Hanahan D, Weinberg RA (2011) Hallmarks of Cancer: The Next Generation. Cell 144: 646-674.

47. Sulli G, Lam MTY, Panda S (2019) Interplay between Circadian Clock and Cancer: New Frontiers for Cancer Treatment. Trends Cancer 5(8): 475-494.

48. Mure LS, Le HD, Benegiamo G, Chang MW, Rios L, et al. (2018) Diurnal Transcriptome Atlas of a Primate Across Major Neural and Peripheral Tissues. Science 359 (6381): eaao0318.

49. Salamanca Fernández E, Rodríguez Barranco M, Guevara M, Ardanaz E, Olry de Labry Lima A, et al. (2018) Night-Shift Work and Breast and Prostate Cancer Risk: Updating the Evidence from Epidemiological Studies. An Sist Sanit Navar 41(2): 211-226.

50. Hojo H, Enya S, Arai M, Suzuki Y, Nojiri T, et al. (2017) Remote Reprogramming of Hepatic Circadian Transcriptome by Breast Cancer. Oncotarget 8(21): 34128-34140.

51. Ye Y, Xiang Y, Ozguc FM, Kim Y, Liu CJ, et al. (2018) The Genomic Landscape and Pharmacogenomic Interactions of Clock Genes in Cancer Chronotherapy. Cell Syst 6(3): 314-328.

52. Walton ZE, Patel CH, Brooks RC, Yu Y, Ibrahim Hashim A, et al. (2018) Acid Suspends the Circadian Clock in Hypoxia through Inhibition of mTOR. Cell 174(1): 72-87.