Thermodynamics in cancers: opposing interactions between PPAR gamma and the canonical WNT/beta-catenin pathway

Yves Lecarpentier1*, Victor Claes2, Alexandre Vallée3 and Jean-Louis Hébert4

Abstract
Cancer cells are the site of numerous metabolic and thermodynamic abnormalities. We focus this review on the interactions between the canonical WNT/beta-catenin pathway and peroxisome proliferator-activated receptor gamma (PPAR gamma) in cancers and their implications from an energetic and metabolic point of view. In numerous tissues, PPAR gamma activation induces inhibition of beta-catenin pathway, while the activation of the canonical WNT/beta-catenin pathway inactivates PPAR gamma. In most cancers but not all, PPAR gamma is downregulated while the WNT/beta-catenin pathway is upregulated. In cancer cells, upregulation of the WNT/beta-catenin signaling induces dramatic changes in key metabolic enzymes that modify their thermodynamic behavior. This leads to activation of pyruvate dehydrogenase kinase 1 (PDK-1) and monocarboxylate lactate transporter. Consequently, phosphorylation of PDK-1 inhibits the pyruvate dehydrogenase complex (PDH). Thus, a large part of pyruvate cannot be converted into acetyl-coenzyme A (acetyl-CoA) in mitochondria and only a part of acetyl-CoA can enter the tricarboxylic acid cycle. This leads to aerobic glycolysis in spite of the availability of oxygen. This phenomenon is referred to as the Warburg effect. Cytoplasmic pyruvate is converted into lactate. The WNT/beta-catenin pathway induces the transcription of genes involved in cell proliferation, i.e., MYC and CYCLIN D1. This ultimately promotes the nucleotide, protein and lipid synthesis necessary for cell growth and multiplication. In cancer, activation of the PI3K-AKT pathway induces an increase of the aerobic glycolysis. Moreover, prostaglandin E2 by activating the canonical WNT pathway plays also a role in cancer. In addition in many cancer cells, PPAR gamma is downregulated. Moreover, PPAR gamma contributes to regulate some key circadian genes. In cancers, abnormalities in the regulation of circadian rhythms (CRs) are observed. CRs are dissipative structures which play a key-role in far-from-equilibrium thermodynamics. In cancers, metabolism, thermodynamics and CRs are intimately interrelated.

Keywords: PPAR gamma, WNT/beta-catenin, Cancer, Circadian rhythms, Pyruvate dehydrogenase kinase, Pyruvate dehydrogenase complex, Aerobic glycolysis, Warburg effect, PI3 K-AKT pathway, Dissipative structures

Introduction
Schrödinger in his famous book “What is life” [1] provided us a new understanding of the thermodynamics in living systems. By applying this to the thermodynamics of physical, chemical and biological far-from-equilibrium systems, Prigogine and his colleagues opened new avenues for the exploration of dissipative structures which occupy a major place in the living world [2, 3]. Cancer is an exergonic process in which heat flows from the tumor to its surroundings [4]. The entropy production rate is increased in cancer cells and is characteristic of irreversible processes driven by changes in heat production, Gibbs energy, intracellular acidity, ionic conductance, membrane potential gradient [5]. Numerous cellular mechanisms can induce and develop carcinogenic processes. In most cancers, the WNT/beta-catenin pathway is upregulated while peroxisome proliferator-activated receptor gamma (PPAR gamma) is downregulated. This profile has been observed in several diseases...
[6] such as cancers [7, 8], type 2 diabetes [9], and certain neurodegenerative diseases (amyotrophic lateral sclerosis [10], Huntington’s disease [11], multiple sclerosis [12, 13] and Friedreich’s ataxia [14]). The opposite profile has been reported in arrhythmogenic right ventricular cardiomyopathy (ARVC) [15, 16], osteoporosis [17–19], and certain neurodegenerative diseases (Alzheimer’s disease [20], Parkinson’s disease [21], bipolar disorder [22, 23] and schizophrenia [24]). From a thermodynamic viewpoint and among numerous cellular processes involved in cancers, two major phenomena play a key role, i.e., aerobic glycolysis or the Warburg effect and disruption of circadian rhythms (CRs). The thermodynamic dysregulation induced by these two processes is consubstantial with metabolic abnormalities commonly found in cancers. PPAR dysfunction influences statistical mechanics by modifying thermodynamic force, thermodynamic flow, and rate of entropy production [5, 25]. We focus our review on the opposing interactions observed in cancers between the canonical WNT/beta-catenin pathway and PPAR gamma and their metabolic and energetic implications.

Canonical WNT/beta-catenin pathway
The canonical WNT/beta-catenin pathway plays an important role in metabolism, embryonic development, cell fate, and epithelial-mesenchymal transition (EMT) [26]. The canonical WNT activity is reflected by elevated levels of beta-catenin in the nucleus and/or cytoplasm, which can be detected by means of immunohistochemical staining, Western blotting and semiquantitative RT-PCR [27]. Its dysfunction is involved in numerous diseases, particularly in cancers [28–31]. The transcription factor beta-catenin/T-cell factor/l hood enhancer factor (TCF/LEF) represents the key effector of the canonical WNT pathway (Figs. 1, 2). The destruction complex consists of AXIN, tumor suppressor adenosomatous polyposis coli (APC), and glycogen synthase kinase-3 (GSK-3beta). The destruction complex exerts a tight control on the beta-catenin signaling. In the absence of WNT ligands (“off state”), the destruction complex phosphorylates beta-catenin which is then degraded in the proteasome. In the presence of WNT ligands (“on state”), the WNT receptor interacts with Frizzled (FZL) and LDL receptor-related protein 5/6 (LRP5/6). WNT receptor is associated with Dishevelled (DHS). This triggers the disruption of the destruction complex and prevents degradation of beta-catenin in the proteasome. Beta-catenin then translocates to the nucleus and interacts with TCF/LEF. This leads to the stimulation of the beta-catenin target genes (pyruvate dehydrogenase kinase (PDK), monocarboxylate lactate transporter-1 (MTC-1), MYC, CYCLIN D1, cyclooxygenase-2 (COX-2), AXIN) [32–35] (Fig. 1).

PPAR gamma
Peroxisome proliferator-activated receptor gamma is a ligand-activated transcriptional factor that belongs to the nuclear hormone receptor superfamily [36]. It heterodimerizes with the retinoid X receptor. PPAR gamma is expressed in numerous cell types, such as adipose tissues, muscles, brain, and immune cells. PPAR gamma activates the expression of many genes and regulates glucose homeostasis, insulin sensitivity, lipid metabolism, immune responses, cell fate and inflammation [37–39]. PPAR gamma agonists thiazolidinediones (TZDs)
improve insulin sensitivity in peripheral tissues [40] and ameliorate glucose tolerance and insulin sensitivity in type 2 diabetic patients [41]. TZDs act on the promoters of glucose transporter (GLUT-2) and glucokinase (GK) in pancreatic beta-cells and liver. Abnormalities of PPAR gamma are observed in several pathological states such as cancers, diabetes, obesity, and atherosclerosis. Some TZDs have been used for treating type 2 diabetes. PPAR gamma also plays an important role in regulating cardiovascular rhythms by controlling circadian variations of blood pressure and heart rate through BMAL1 [42, 43]. However, numerous side effects induced by TZD have been reported [44].

**Opposing effects of the canonical WNT/beta-catenin pathway and PPAR gamma**

The link between the WNT/beta-catenin pathway and PPAR gamma involves the TCF/LEF beta-catenin-binding domain and a catenin binding domain within PPAR gamma. In numerous mammalian cells, PPAR gamma and WNT/beta-catenin signaling behave in an opposite manner [45–50]. In some diseases, although the WNT/beta-catenin pathway is downregulated, PPAR gamma appears to be upregulated and vice versa (see: “Introduction”) [6]. In several cellular systems, beta-catenin is inhibited by PPAR gamma agonists [45, 47, 48, 51]. It has also been observed that inhibition of the WNT/beta-catenin pathway induces activation of PPAR gamma [15].

**Aerobic glycolysis in cancer cells: role of the canonical WNT signaling**

The role of the WNT/beta-catenin signaling in cancer development, especially in colorectal cancer, is now better understood [52, 53]. Upregulation of the WNT/beta-catenin pathway via TCF/LEF leads to cell proliferation, EMT, migration and angiogenesis [54–56]. In cancer cells, overactivation of the WNT/beta-catenin pathway induces aerobic glycolysis. This allows glucose utilization for cell proliferation [35]. Thus in a large part, glucose supply is fermented in lactate regardless of oxygen availability. This phenomenon is referred to as aerobic glycolysis or the Warburg effect [57].

In cancer, the behavior of two key enzymes involved in glucose metabolism is modified leading to the Warburg effect. Activation of PDK-1 is required for the Warburg aerobic glycolysis. Upregulation of WNT/beta-catenin signaling activates both PDK-1 and MCT-1 [35, 58]. PDK-1, a major regulator of glucose metabolism, phosphorylates the pyruvate dehydrogenase complex (PDH) which is inhibited and largely prevents the conversion of pyruvate into acetyl-CoA in mitochondria [59]. In colon cancer, PDK-1 is upregulated [35, 60], so that the conversion of pyruvate into acetyl-CoA in mitochondria is diminished with a consequent reduction of acetyl-CoA entering the tricarboxylic acid (TCA) cycle. This induces aerobic glycolysis in spite of the availability of oxygen. PDK-1 has also been observed to be upregulated in several other cancers [61, 62]. Cytosolic pyruvate is converted into lactate through activation of lactic dehydrogenase-A (LDH-A). Upregulation of both LDH-A and MCT-1 results in pyruvate being diverted towards the formation of lactate and the secretion of the latter outside of the cell, which favors angiogenesis [63] and ultimately leads to anabolic production of biomass i.e., nucleotide synthesis [64, 65]. The Warburg effect partly shunts the TCA cycle leading to aerobic glycolysis which is less efficient in terms of ATP production. The most cost effective way producing ATP is via glucose oxidation (ATP/O₂ = 6.4), since the pathway via free fatty acid beta-oxidation is less efficient (ATP/O₂ = 5.6). This takes about 11% more O₂ to produce the same amount of ATP from fatty acids as it does from glucose. Moreover, PDK-1 and 2 enhance angiogenesis [66, 67]. Blocking WNT reduces the PDK-1 level via the transcription regulation and reduces in vivo tumor growth [35]. Conversely, PPAR gamma activation selectively decreases PDK mRNA [68]. PDKs allow metabolic flexibility [69] and are transcriptionally regulated by insulin, glucocorticoids, thyroid hormone and fatty acids [70]. Several diseases presenting PDK abnormalities are often associated with type 2 diabetes, obesity, metabolic disorders, cardiomyopathies, neuropathies and cancers.
In colon cancer, activation of WNT/beta-catenin signaling decreases the oxidative metabolism in the TCA cycle and promotes cell proliferation [35]. In addition, the WNT/beta-catenin pathway induces the transcription of genes involved in cell proliferation, particularly CYCLIN D1 and MYC operating through the G1 phase [71–74]. MYC activates aerobic glycolysis and glutaminolysis and favors nucleotide synthesis [75, 76]. MYC also activates LDH-A, induces glutamine uptake into the cell and mitochondria, and stimulates aspartate synthesis which favors nucleotide synthesis [75] (Fig. 1). Moreover, MYC increases the hypoxia-inducible factor -1alpha (HIF1A) which controls PDK-1 [77]. Part of the pyruvate is converted into acetyl-CoA which in turn enters the TCA cycle and is converted into citrate. This promotes protein and lipid synthesis. Cellular accumulation of metabolic intermediates (aspartate, serine, glycine, and ribose) allows de novo nucleotide synthesis, which contributes to growth and proliferation.

Phosphofructokinase (PFK), an allosteric enzyme, is responsible for glycolytic oscillations. PFK can lead to instabilities beyond which a new state can be organized in time and in space [78]. A positive feedback is responsible for periodic behavior. These far-from-equilibrium oscillatory mechanisms come within the field of dissipative structures initially described by Illia Prigogine [79]. Elevated PFK-1 activity is characteristic of cancer cells and is induced in response to oncogenes [80].

Cancer cells are characterized by increased glucose consumption. High serum glucose levels may modulate cancer-related processes. Glucose itself can directly impact the canonical WNT pathway [81]. High glucose level enhances the nuclear translocation of beta-catenin in response to WNT activation. In cancer cells, glucose-induced beta-catenin acetylation favors the WNT pathway.

**Aerobic glycolysis and vitamin C**

It has been recently described a novel antitumoral mechanism of vitamin C [82]. Mutation of the proto-oncogene KRAS is often present in colon and pancreatic cancer. In KRAS mutant colorectal cancer, this mechanism involves the Warburg metabolic disruption. In the absence of vitamin C, pyruvate kinase PKM2 is phosphorylated, then translocates to the nucleus and binds the beta-catenin/TCF/LEF transcriptional factor. This promotes the MYC transcription which in turn enhances GLUT-1 and Poly(adenosine diphosphate-ribose) Tract Binding Protein (PTB) expression. In the presence of vitamin C which enters into the cell via GLUT-1, RAS is detached from the cell membrane which blocks the PKM2 phosphorylation. This induces downregulation of GLUT-1 and PKM2 expression via disruption of the beta-catenin/TEF/LEF transcriptional complex. This leads to downregulation of MYC and inhibition of the Warburg pathway. Thus, vitamin C uncouples the Warburg metabolic switch in KRAS mutant colon cancer.

**Thermodynamics and lawless-disorderly cancer growth**

From a thermodynamic viewpoint, the lawless-disorderly cancer growth and the orderly fetal growth share some similar features [83]. Hypoxic conditions reported in cancer cells for their growth requirements resemble to those observed during normal fetal growth, which requires a relatively low oxygen tension. For both cancerous and fetal growth, low energy requirements are linked to the tumorigenic arm of acute inflammation [83], as in wound healing. Moreover, the production of lactate under aerobic glycolysis conditions is characteristic of the human placenta [84], a tissue in which the population of contractile myofibroblasts is important [85]. In cancer (mammary carcinoma, epithelial cells in cancerous mammary glands), fibrotic lesions (Dupuytren’s nodules, hypertrophic scars) [86], and normal placental stem villi [87], the main myosin motor in myofibroblasts is the non muscle myosin (NMM). Kinetics of contractile NMM crossbridges are dramatically slow [88] and their entropy production rate is extremely low [89]. The presence of numerous myofibroblasts is associated with the aerobic glycolysis metabolism. In epithelial cancers, myofibroblasts represent a significant part of the stroma reaction. Myofibroblasts, epithelial cells, and connective tissue cells participate to cancer invasion, with loss of epithelial characteristics and acquisition of mesenchymal properties. This refers to as EMT [26] which greatly influences the invasive carcinoma progression and in which the canonical WNT pathway plays a key role. WNT3a favors myofibroblast differentiation by upregulating the transforming growth factor (TGF-beta1). This occurs through SMAD2 in a beta-catenin-dependent manner [90]. Importantly, it has been recently demonstrated that aerobic glycolysis is induced in response to TGF-beta1 [91].

**Activation of WNT/beta-catenin pathway and inactivation of PPAR gamma in cancers**

WNT/beta-catenin signaling has been found to be activated in cancers [92, 93]. WNT1 was first discovered as a proto-oncogene in a breast cancer mouse model. Increased expression of beta-catenin may be due to factors such as mutations in beta-catenin, abnormalities in the beta-catenin destruction complex, mutations in APC, overexpression of WNT ligands, and loss of inhibition or decreased activity of regulatory pathways. Alterations in gene expression of CTNNBI which encodes beta-catenin, have been reported in numerous cancers such as breast
colorectal, melanoma, prostate and lung tumors. WNT 1, WNT2 and WNT7A ligand-proteins are overexpressed in glioblastoma, esophagael cancer and ovarian cancer respectively. Proteins of the TCF/LEF family and WNT5A may also induce cancer. Repression of WNT/ beta-catenin signaling can prevent EMT and inhibit metastasis. Mutations of the WNT pathway components are associated with many cancers, particularly with colorectal cancer. APC deficiency and beta-catenin mutations upregulate the WNT/beta-catenin pathway and prevent beta-catenin degradation. This leads to excessive stem cell renewal and cell proliferation that predisposes to tumor genesis particularly for colorectal cancer [94]. Nuclear accumulation of beta-catenin drives cancer cell proliferation. In colon cancer, beta-catenin-TCF/LEF signaling is activated [95], and activation of the WNT pathway via APC gene mutations favors cell proliferation [96]. Mutations in PPAR gamma are linked with human colon cancer [97].

Several studies have presented evidence for a protective role of PPAR gamma against cancer. In colon cancer, PPAR gamma downregulates the oncogene beta-catenin and suppresses cell proliferation [98]. In contrast, other studies have implicated PPAR gamma in the promotion and development of cancer [8]. Thus, PPAR gamma activation by specific agonists can induce growth inhibition, apoptosis and differentiation of numerous tumor cells. On the contrary, overexpression of PPAR gamma has been reported in tumors of colon, breast, prostate, stomach, salivary gland, cervix, ovary, bladder, lung, testes and the neural crest element of sympathetic nervous system [7]. The biological significance of PPAR gamma in cancer remains controversial. Activation of PPAR gamma can induce either tumor suppressive or promoting responses. On the one hand, PPAR gamma can act as a tumor inhibitor in colon cancer [99–105], in breast cancer [106–110], in urological cancer [110–115], in lung cancer [116–118], and in gastric cancer [119–122]. On the other hand, PPAR gamma can act as a tumor promotor in colon cancer [123–126], in breast cancer [127–132], and in urological cancer [133–135]. There is no clear unifying accepted mechanism explaining these contradictory evidences concerning either the protective role of PPAR gamma or their role on promotion/development of cancer. This might be partly explained by cell type-specific effects, organ-specific effects, receptor-independent effects according to the PPAR gamma agonist used. This might also be due to specific pharmacokinetic properties of PPAR gamma ligands or the stage of cancer development at which the PPAR gamma ligand is administered [8]. These arguments are hypotheses, and for the time being, no universal mechanism is able to explain the contradictory effects of PPAR gamma ligands on cancers.

Role of PI3K-AKT pathway in aerobic glycolysis and cancers

Hyperactivation of phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) pathway is associated with an increased rate of glucose metabolism in tumor cells [136]. AKT signaling directly acts on aerobic glycolysis in cancer cells. AKT regulates the localization of GLUT1 in the plasma membrane and hexokinase expression. It also activates phosphofructokinase-1 (PFK-1) which directly phosphorylates PFK-2. This leads to produce fructose-2,6-bisphosphate, an activator of PFK-1. AKT activation causes an increase in aerobic glycolysis or Warburg effect in cancer. PI3K-AKT pathway promotes cell survival, cell growth, cell proliferation, cell migration and angiogenesis in response to extracellular signals including hormones and growth factors. This pathway is stimulated by the binding of extracellular ligands to a receptor tyrosine kinase (RTK) located in the plasma membrane (Fig. 1). This signaling is upregulated in certain cancers. Through phosphorylation of GSK-3beta, PI3 K-AKT favors the G1 phase of the cell cycle. GSK-3beta phosphorylation decreases the degradation of beta-catenin in the proteasome. Thus, TCF/LEF transcription factor is activated which in turn favors transcription of the target gene CYCLIN D1 [137]. Consequently, by decreasing the GSK-3beta activity, AKT pathway behaves similarly to the WNT pathway. Aberrant activation of PI3K-AKT is often associated with cancers, including glioblastomas, ovarian, pancreatic and breast cancers [138]. AKT mRNA is increased in breast and prostate cancer. PI3K-AKT contributes to angiogenesis by acting on the vascular endothelial growth factor in endothelial cells and on the endothelial nitric oxide synthase. This activates vasodilation and vascular remodeling [139]. Moreover, the PI3K-AKT pathway increases the hypoxia-inducible transcription factor [140].

The phosphatase and tensin homologue (PTEN) represents the main brake of the PI 3'-OH kinase (PIK3)-AKT pathway [141]. PI3K generate phosphatidylinositol-3,4,5-triphosphate (PIP3) from PIP2. AKT is activated by PIP3. PTEN is a PIP3-phosphatase and its activity is opposed to that of PI3K. PI3K-AKT signaling is a major pathway which is activated in cancer. PTEN appears to be relevant against cancer progression and represents a target for somatic cancer inactivation. In some cancers (endometrial, breast, and colorectal cancers), PI3K and PTEN mutations coexist. PTEN also induces a decrease in cancer cell proliferation due to cell cycle arrest in the G1 phase.

Prostaglandins, WNT and PPAR gamma

Several studies have established the role of prostaglandin E2 (PGE2) by activating the WNT/beta-catenin pathway. The link between PGE2 and the canonical WNT
pathway suggests that chronic inflammation induced by a prolonged increase of PGE2 could lead to activation of WNT signaling resulting in cell proliferation and cancer. PGE2 enhances the beta-catenin-dependent transcription [142, 143]. PGE2 promotes colon cancer cell growth through the beta-catenin pathway. Thus, blockade of WNT/beta-catenin signaling can be of interest for cancer treatment. In treatment of colorectal cancer, nonsteroidal anti-inflammatory drugs (NSAIDs) induce beneficial effects [144], partly due to their interaction with the beta-catenin pathway and their inhibition of the PGE2 synthesis. PGE2 modulates the WNT activity in hematopoietic stem cell (HSC) in zebrafish. Inhibition of PGE2 synthesis blocks alterations in HSC induced by WNT. PGE2 modifies the WNT signaling cascade at the level of beta-catenin degradation through the cAMP/PKA pathway. WNT activation in stem cells requires PGE2 [145]. Dimethyl-prostaglandin E2 increases HSC in vivo. In addition, dimethyl-prostaglandin E2 leads to the formation of components of the WNT pathway [146]. WNT signaling upregulates interleukin (IL)-7R and IL-2Rbeta. In neuroectodermal (NE-4C) stem cells, PGE2 interacts with the canonical WNT signaling through PKA and PI3K [147]. In WNT-induced cells, beta-catenin is increased and the WNT-target genes (Ctnnb1, Ptg2, Ccnd1, Mmp9) are significantly upregulated after PGE2 use. PPAR gamma and proinflammatory enzyme pathways are interrelated. Decreased expression of PPAR gamma and high levels of COX-2 have been reported in many cancers [148]. TZDs decrease COX-2, inhibit growth of non-small-cell lung cancer cells in vitro, and block tumor development. TZDs diminish COX-2 and PGE2 through PPAR gamma. The PPAR gamma activator 15dPGJ2 plays an anti-inflammatory role in a PPAR gamma-dependent manner, decreasing COX-2, PGE2 and iNOS expression [149].

Circadian rhythms (CRs), cancers, metabolism and thermodynamics
CRs can be defined as endogenous, entrainable free-running periods that last approximately 24 h. CRs are far-from-equilibrium dissipative structures and are due to a negative feedback produced by a protein on the expression of its own gene [150–152]. They operate in far-from-equilibrium manner if affinity of the studied system is \( \propto RT \) (R is the universal gas constant and T is the absolute temperature), and generate order spontaneously by exchanging energy with their external environment [2, 153]. In mammals, CRs involve several major critical transcription factors such as circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl-hydrocarbon receptor nuclear translocator-like1 (BMAL1), period 1 (PER1), period 2 (PER2), and period 3 (PER3) [154, 155]. Transcription/translation autoregulatory feedback loops with both activating and inhibiting pathways are involved in CRs [156, 157].

Circadian rhythms govern numerous physiological and metabolic functions [158]. Thus, CRs are observed in sleep-awake and feeding patterns, energy metabolism, body temperature, hormone secretion, heart rate and blood pressure. Following epidemiological and genetic probes, it has been suggested that disruption of CRs may be directly linked to cancer, leading to aberrant cellular proliferation [159]. Since numerous connections between the circadian clock and cellular metabolism have been reported, it is thought that the abnormal metabolism observed in cancer may be a consequence of disrupted CRs. CRs within the cell regulate the timing of many important life cycles [160]. The phase diffusion constant depends on the free-energy dissipation per period. Oscillations are driven by multiple irreversible cycles that hydrolyze fuel molecules such as ATP. The free energy consumed per period is proportional to the number of phase coherent periods. A decreased BMAL1 function modifies the behavior of genes involved in the canonical WNT pathway [161]. Beta-catenin induces PER2 degradation altering circadian clock gene in intestinal mucosa of ApcMin/+ mice [162]. A decreased expression level of PER1 and/or PER2 has been reported in numerous cancers: breast cancer [163], prostate cancer [164], pancreatic cancer [165], colorectal cancer [166], chronic myeloid leukemia [167], and glioma [168, 169].

Peroxisome proliferator-activated receptors interferes with the mammalian clock and energy metabolism [170]. PPARs are rhythmically expressed in mammalian tissues [171] and directly interact with the core clock genes. PPAR gamma exhibits variations in diurnal expression in mouse fat, liver and blood vessels [42]. Deletion of PPAR gamma in mouse impairs diurnal rhythms [172]. PPAR gamma plays an important role in the coordinated control of circadian clocks, metabolism and cardiac performance. PGC-1 alpha, a transcriptional co-activator that regulates energy metabolism, is rhythmically expressed in the liver and skeletal muscle of mice. PGC-1 alpha upregulates the expression of the clock genes BMAL1 and Rev-erb alpha. Mice lacking PGC-1 alpha show changes in CRs and metabolism [173]. PGC-1 alpha acts as a stress sensor in cancer cells. In maintaining metabolic homeostasis, PGC-1 alpha favors cancer cell survival [174]. PGC-1 alpha interferes in a very complex manner with nuclear receptors such as Rev-erb, ROR, PPARs [175]. PPAR alpha and gamma up-regulate the expression of Rev-erb alpha and BMAL1 by binding to their promoters. PGC-1 potentiates ROR alpha transcriptional activity and enhances both Rev-erb alpha and BMAL1 transcription. Moreover after serum shock,
GSK-3beta-mediated stabilization of Rev-erb alpha plays a key role to initiate, maintain and synchronize CRs.

**Conclusions**

Cancers exhibit thermodynamic and metabolic alterations and abnormal CRs. In many cancers but not all, the canonical WNT/beta-catenin pathway is upregulated, while PPAR gamma is downregulated, the two systems behaving in an opposite manner. Overactivation of the WNT pathway results in cell proliferation due to the activation of certain target genes of beta-catenin, such as MYC and CYCLIN D1. This promotes protein synthesis and angiogenesis. PDK and MCT-1 are also target genes of beta-catenin, explaining the significant decrease in the transformation of pyruvate into acetyl-CoA in mitochondria and the formation of intracellular lactate, which will be extruded out of the cell. This is referred to as aerobic glycolysis or the Warburg phenomenon. The expression of PPAR gamma is decreased due to the overactivation of WNT/beta-catenin signaling. Circadian rhythms, dissipative structures which are governed by the laws of far-from-equilibrium thermodynamics are disrupted in cancers. They are influenced by both the WNT/beta-catenin pathway and PPAR gamma. Changes in thermodynamics, metabolism and circadian rhythms are tightly linked in cancers.

**Abbreviations**

acetyl-CoA: acetyl-coenzyme A; APC: adenomatous polyposis coli; ARVC: arrhythmogenic right ventricular dysplasia/cardiomyopathy; BMAL1: brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; CLOCK: circadian locomotor output cycles kaput; COX-2: cyclooxygenase-2; DSH: dishevelled; EMT: epithelial-mesenchymal transition; FZD: frizzled; G: glucokinase; GLUT-glucose transporter; GSK-3beta: glycogen synthase kinase-3beta; HSC: locomotor output cycles kaput; COX-2: cyclooxygenase-2; DSH: dishevelled; EMOT: epithelial-mesenchymal transition; FZD: frizzled; G: glucokinase; GLUT-glucose transporter; GSK-3beta: glycogen synthase kinase-3beta; HSC: hematopoietic stem cell; LDH: lactate dehydrogenase; LRP5/6: low-density lipoprotein receptor-related protein 5/6; MCT-1: monocarboxylate lactate transporter-1; NSAI: nonsteroidal anti-inflammatory drug; PER: period; PPAR: peroxisome proliferator-activated receptor; PGC-1 alpha: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; P3k-Akt: phosphatidylinositol 3-kinase-protein kinase B; PFK-1: phosphofructokinase-1; PDK: pyruvate dehydrogenase kinase; RTK: receptor tyrosine kinase; TCF/LEF: T cell factor factor/lymphoid enhancer factor; TZD: thiazolidinedione; TGF-beta1: transforming growth factor; TCA: tricarboxylic acid.

**Authors' contributions**

YL, VC, AV and J-LH have contributed equally to this review. All authors read and approved the final manuscript.

**Author details**

1. Centre de Recherche Clinique, Hôpital de Meaux, 6-8 rue Saint Fiacre, 77100 Meaux, France. 2. Department of Pharmaceutical Sciences, University of Antwerp, Wilrijk, Belgium. 3. Experimental and Clinical Neurosciences Laboratory, INSERM U1084, University of Poitiers, Poitiers, France. 4. Institut de Cardiologie, Hôpital de la Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France.

**Acknowledgements**

We would like to thank Dr. Christophe Locher, President of the “Fédération de la Recherche Clinique de Grand Hôpital de l’Est Franclilien”, and Mr. Vincent Gobert, Administrative Manager of the Clinical Research Center, Meaux Hospital, Meaux, France, for their valuable support in making the necessary research facilities available for this study. The manuscript has been revised by Brian Keogh, Ph.D.

**Competing interests**

The authors declare that they have no competing interests.

**Publisher’s Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 28 November 2016 Accepted: 20 March 2017 Published online: 12 April 2017

**References**

1. Schrödinger E (1944) What is life?: Cambridge University Press, Cambridge
2. Prigogine I, Nicolis G, Babloyantz A (1974) Nonequilibrium problems in biological phenomena. Annu NY Acad Sci 231:99–105
3. Prigogine I (1986) Life and physics. New perspectives. Cell Biophys 9:217–224
4. Atkins PW (1990) Physical chemistry. Oxford University Press, Oxford, pp 1–486
5. Kondepudi D, Prigogine I (1999) Modern thermodynamics from heat engines to dissipative structures. Wiley, New York, pp 1–486
6. Lecarpentier Y, Claes V, Duthoit G, Hebert JL (2014) Circadian rhythms, Wnt/beta-catenin pathway and PPAR-alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. Front Physiol 5:429
7. Krishnan A, Nair SA, Pillai MR (2007) Biology of PPAR gamma in cancer: a critical review on existing lacunae. Curr Mol Med 7:532–540
8. Youssef J, Badr M (2011) Peroxisome proliferator-activated receptors and cancer: challenges and opportunities. Br J Pharmacol 164:68–82
9. Lecarpentier Y, Claes V, Valleé A, Hebert JL (2017) Interactions between PPAR gamma and the canonical Wnt/beta-catenin pathway in type 2 diabetes and colon cancer. PPAR Res 5:1–9
10. Lecarpentier Y, Valleé A (2016) Opposite interplay between PPAR gamma and canonical Wnt/Beta-catenin pathway in amyotrophic lateral sclerosis. Front Neurol 7:100
11. Godin JD, Poizat G, Hickey MA, Maschat F, Humbert S (2010) Mutant huntingtin-impaired degradation of beta-catenin causes neurotoxicity in Huntington’s disease. EMBO J 29:2433–2445
12. Drew PD, Xu J, Racke MK (2008) PPAR-gamma: therapeutic potential for multiple sclerosis. PPAR Res 2008:627463
13. Yuan S, Shi Y, Tang SJ (2012) Wnt signaling in the pathogenesis of multiple sclerosis-associated chronic pain. J Neuroimmune Pharmacol 7:904–913
14. Coppola G, Marmolin D, Lu D, Wang Q, Cnop M et al (2009) Functional genomic analysis of frataxin deficiency reveals tissue-specific alterations and identifies the PPARGamma pathway as a therapeutic target in Friedreich’s ataxia. Hum Mol Genet 18:2452–2461
15. Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD et al (2006) Suppression of canonical Wnt/beta-catenin signaling by nuclear pioglitazon recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest 116:2012–2021
16. Djouadi F, Lecarpentier Y, Hebert JL, Charron P, Bastin J et al (2009) A potential link between peroxisome proliferator-activated receptor signalling and the pathogenesis of arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Res 84:83–90
17. Canalis E (2013) Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches. Nat Rev Endocrinol 9:575–583
18. Rawadi G, Roman-Roman S (2005) Wnt signalling pathway: a new target for the treatment of osteoporosis. Expert Opin Ther Targets 9:1063–1077
19. Korvala J, Juppner H, Makite O, Sochet T, Schnabl D et al (2012) Mutations in LRP5 cause primary osteoporosis without features of OI by reducing Wnt signaling activity. BMC Med Genet 13:26
20. Valleé A, Lecarpentier Y (2016) Alzheimer disease: crosstalk between the canonical Wnt/beta-catenin pathway and PPARs alpha and gamma. Front Neurosci 10:459
21. Berwick DC, Harvey K (2012) The importance of Wnt signalling for neurodegeneration in Parkinson's disease. Biochem Soc Trans 40:1123–1128

22. Gould TD, Manji HK (2002) The Wnt signaling pathway in bipolar disorder. Neuroscientist 8:497–511

23. Valverezan AJ, Klein PS (2012) GSK-3 and Wnt signaling in neurogenesis and bipolar disorder. Front Mol Neurosci 5:1

24. Panacione I, Napoletano F, Forte AM, Kozalidis GD, Del Casale A et al (2013) Neurodevelopment in schizophrenia: the role of the wnt pathways. Curr Neuropharmacol 11:535–558

25. Lecarpentier Y, Krokidis X, Martin P, Pinaud T, Hebbert J et al (2008) Increased entropy production in diaphragm muscle of PPAR alpha knockout mice. J Theor Biol 250:99–102

26. Heuberger J, Birchmeier W (2010) Interplay of cadherin-mediated cell adhesion and canonical wnt signaling. Cold Spring Harb Perspect Biol 2:a002915

27. Igota S, Tosa M, Murakami M, Egawa S, Shimizu H et al (2013) Identification and characterization of Wnt signaling pathway in keloid pathology. Int J Med Sci 10:344–354

28. Moon RT, Kohn AD, De Ferrari GV, Kaykas A (2004) WNT and beta-catenin signalling and canonical Wnt signaling. Cold Spring Harb Perspect Biol 2:a002915

29. Pate KT, Stringari C, Sprowl-Tanio S, Wang K, TeSlaa T et al (2014) Wnt peroxisome proliferator-activated receptor gamma signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. EMBO J 33:1454–1473

30. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S (2011) The peroxisome proliferator-activated receptor: a family of nuclear receptors role in various diseases. J Adv Pharm Technol Res 2:236–240

31. Elbrecht Y, Chen Y, Cullinan CA, Hayes N, Leibowitz M et al (1996) Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. Biochem Biophys Res Commun 224:431–437

32. Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM et al (1997) The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. Proc Natl Acad Sci USA 96:5522–5527

33. Angers S, Moon RT (2009) Proximal events in Wnt signal transduction.

34. He TC, Sparks AB, Rago C, Hermeking H, Zawel L et al (1998) Identification of beta-catenin levels via a proteasome-mediated and adenomatous polyposis coli-independent pathway. J Biol Chem 273:35583–35594

35. Takada I, Kozukenko AP, Katso S (2009) Wnt and PPARgamma signaling in osteoblastogenesis and adipogenesis. Nat Rev Rheumatol 5:442–447

36. Lu D, Canon DA (2010) Repression of beta-catenin signaling by PPAR gamma ligands. Eur J Pharmacol 636:198–202

37. Loo JW, Wang H, Zuo Y, Farmer SR (2006) Functional interaction between peroxisome proliferator-activated receptor gamma and beta-catenin. Mol Cell Biol 26:5827–5837

38. Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM et al (1997) The peroxisome proliferator-activated receptor gamma and beta-catenin. Nat Rev Cancer 8:1192–1205

39. Warburg O (1956) On the origin of cancer cells. Science 123:309–314

40. PPAR-gamma signaling and metabolism: the good, the bad and the future. Nutr Metab (Lond) 11:10

41. Picard F, Auwerx J (2002) PPAR(gamma) and glucose homeostasis. Annu Rev Nutr 22:167–197

42. Wang N, Yang G, Jia Z, Zhang H, Aoyagi T et al (2008) Vascular PPAR-gamma controls circadian variation in blood pressure and heart rate through BMAL1. Cell Metab 8:482–491

43. Lecarpentier Y, Claes V, Hebert JL (2010) PPARs, cardiovascular metabolism, and function: near- or far-from-equilibrium pathways. PPAR Res. doi:10.1155/2010/783273

44. Ahmadlal M, Suh JM, Liddle C, Atkins AR et al (2013) PPAR-gamma signaling and metabolism: the good, the bad and the future. Nat Med 19:557–566

45. Gerhold DL, Liu F, Jiang G, Lu Z, Xu J et al (2002) Gene expression profile of adipocyte differentiation and its regulation by peroxisome proliferator-activated receptor-gamma agonists. Endocrinology 143:2106–2118

46. Bhatia GD, Domann FE, Moore SA; Robbins ME (2002) Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. Mol Endocrinol 16:2793–2801

47. Sharma C, Pradeep A, Wong L, Rana A, Rana B (2004) Peroxisome proliferator-activated receptor gamma activation can regulate beta-catenin levels via a proteasome-mediated and adenomatous polyposis coli-independent pathway. J Biol Chem 279:35583–35594

48. Lee IK (2014) The role of pyruvate dehydrogenase kinase in diabetes and obesity. Diabetes Metab J 38:181–186

49. Osthus RC, Shim H, Kim S, Li Q, Reddy R et al (2000) Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. J Biol Chem 275:21797–21800

50. van de Wetering M, Sancho E, Verweij C, de Lau W, Oving I et al (2002) The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. Cell 111:241–250
73. Nusse R (2008) Wnt signaling and stem cell control. Cell Res 18:523–527
74. Niehrs C, Aebischer SP (2012) Mitotic and mitogenic Wnt signalling. EMBO J 31:2705–2713
75. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY et al (2008) Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci USA 105:18782–18787
76. Dang CV (2010) Rethinking the Warburg effect with Myc micromanaging glutamine metabolism. Cancer Res 70:859–862
77. Kim JW, Gao P, Liu YC, Semenza GL, Dang CV (2007) Hypoxia-inducible factor 1 and dysregulated c-Myc cooperatively induce vascular endothelial growth factor and metabolic switches hexokinase 2 and pyruvate dehydrogenase kinase 1. Mol Cell Biol 27:7381–7393
78. Goldbeter A (1973) Patterns of spatiotemporal organization in an allosteric enzyme model. Proc Natl Acad Sci USA 70:3255–3259
79. Prigogine I, Nicolis G (1971) Biological order, structure and instabilities. Q Rev Biophys 4:107–148
80. Mor I, Cheung EC, Vousden KH (2011) Control of glycolysis through regulation of PFK1: old friends and recent additions. Cold Spring Harb Symp Quant Biol 76:211–216
81. Chocarro-Calvo A, Garcia-Martinez JM, Ardila-Gonzalez S, De la Vieja A, Garcia-Jimenez C (2013) Glucose-induced beta-catenin acetylation enhances Wnt signaling in cancer. Mol Cell 49:474–486
82. Aguilera G, Munoz-SagastiBelza M, Torrejon B, Borrego-Palacios A, Del Puerto-Nevedo L et al (2016) Vitamin C uncouples the Warburg metabolic switch in KRAS mutant colon cancer. Oncotarget 7:49754–49765
83. Khamti M (2016) Is cancer a severe delayed hypersensitivity reaction and histamine a blueprint? Clin Transl Med 5:35
84. Bax BE, Bloxam DL (1997) Energy metabolism and glycolysis in human placental trophoblast cells during differentiation. Biochim Biophys Acta 1310:283–292
85. Feller AC, Schneider H, Schmidt D, Parwaresch MR (1985) Myofibroblast differentiation and reversal of malignant changes in colon cancer through PPARgamma. Nat Med 4:1046–1052
86. Grommes C, Landeeth GE, Heneka MT (2004) Antineoplastic effects of peroxisome proliferator-activated receptor gamma agonists. Lancet Oncol 5:419–429
87. McAlpine CA, Barak Y, Matise I, Cormier RT (2006) Intestinal-specific PPARgamma deficiency enhances tumorigenesis in ApcMin/+ mice. Int J Cancer 119:2339–2346
88. Muller E, Sarraf P, Tontonoz P, Evans RM, Martin KJ et al (1998) Terminal differentiation of human breast cancer through PPARgamma. Mol Cell 1:465–470
89. Clay CE, Namam AM, Atsumi G, Willingham MC, High KP et al (1999) Influence of J series prostaglandins on apoptosis and tumorigenesis of breast cancer cells. Carcinogenesis 20:1905–1911
90. Pignatelli M, Cocca C, Santos A, Perez-Castillo A (2003) Enhancement of BRCA1 gene expression by the peroxisome proliferator-activated receptor gamma in the MCF-7 breast cancer cell line. Oncogene 22:5446–5450
91. Elstner E, Muller C, Koshizuka K, Williamson EA, Park D et al (2006) Ligands for peroxisome proliferator-activated receptorgamma and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells in vitro and in BNX mice. Proc Natl Acad Sci USA 95:8806–8811
92. Inoue K, Kawahito Y, Tsuboouchi Y, Kohnno M, Yoshimura R et al (2001) Expression of peroxisome proliferator-activated receptor gamma in renal cell carcinoma and growth inhibition by its agonists. Biochem Biophys Res Commun 287:727–732
93. Guan YF, Zhang YH, Breyer RM, Davis L, Breyer MD (1999) Expression of peroxisome proliferator-activated receptor gamma (PPARgamma) in human transitional bladder cancer and its role in inducing cell death. Neoplasia 1:330–339
94. Lodolitskly C, Umerez MS, Jasins MA, Casabe A, Sandes E et al (2006) Bacillus Calmette-Guerin induces the expression of peroxisome proliferator-activated receptor gamma in bladder cancer cells. Int J Mol Med 17:269–273
95. Radhakrishnan SK, Gartel AL (2005) The PPAR-gamma agonist pioglitazone post-transcriptionally induces p21 in PC3 prostate cancer but not in other cell lines. Cell Cycle 4:582–584
96. Mueller E, Smith M, Sarraf P, Kroll T, Ayer A et al (2000) Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. Proc Natl Acad Sci USA 97:10990–10995
97. Yang FG, Zhang ZW, Xin DQ, Shi CJ, Wu JP et al (2005) PPARgamma activating receptor gamma ligands induce cell cycle arrest and apoptosis in human renal carcinoma cell lines. Acta Pharmacol Sin 26:753–761
98. Tsuboouchi Y, Sano H, Kawahito Y, Mukai S, Yamada R et al (2000) Inhibition of human lung cancer cell growth by the peroxisome proliferator-activated receptor-gamma agonists through induction of apoptosis. Biochem Biophys Res Commun 270:400–405
99. Lee SY, Hur GY, Jung KH, Jung HC, Kim JH et al (2006) PPAR-gamma agonist increase gefitinib’s antitumor activity through PTEN expression. Lung Cancer 51:297–301
100. Yao CJ, Lai GM, Chan CT, Cheng AL, Yang YY et al (2006) Dramatic synergistic antitumor effect of clinically achievable doses of lovastatin and troglitazone. Int J Cancer 118:773–779
119. Sato H, Ishihara S, Kawashima K, Moriyama N, Suetsugu H et al (2000) Expression of peroxisome proliferator-activated receptor (PPAR)gamma in gastric cancer and inhibitory effects of PPARgamma agonists. Br J Cancer 83:1394–1400

120. Takahashi N, Okumura T, Motomura W, Fujiimoto Y, Kawabata I et al (1999) Activation of PPARgamma inhibits cell growth and induces apoptosis in human gastric cancer cells. FEBS Lett 455:135–139

121. Lu J, Imamura K, Nomura S, Mafune K, Nakajima A et al (2005) Chemo-preventive effect of peroxisome proliferator-activated receptor gamma on gastric carcinogenesis in mice. Cancer Res 65:4769–4774

122. Liao SY, Zeng ZR, Leung WK, Zhou SZ, Chen B et al (2006) Peroxisome proliferator-activated receptor-gamma Pro12Ala polymorphism, Heli-cobacter pylori infection and non-cardia gastric carcinoma in Chinese. Aliment Pharmacol Ther 23:283–294

123. Saez E, Tontonoz P, Nelson MC, Alvarez JG, Ming UT et al (1998) Activation of peroxisome proliferator-activated receptor gamma promotes the development of colon tumors in C57BL/6 J-APC-Min+/- mice. Nat Med 4:1053–1057

124. Yang K, Fan KH, Lamprecht SA, Edelmann W, Kopelovich L et al (2005) Peroxisome proliferator-activated receptor gamma agonist troglitazone promotes survival of naive UCB T cells via the Wnt/beta-catenin pathway and alters immune reconstitution after UCBT. Blood Cancer J 4:e178

125. Li L, Kim HT, Nellore A, Patsoukis N, Petkova V et al (2014) PPARgamma E2 promotes survival of naive UCBC T cells via the Wnt/beta-catenin pathway in mice with gastritis. Pathobiology 82:133–141

126. Manning BD, Cantley LC (2007) AKT/PKB signaling: navigating downstream. Cell 129:1261–1274

127. Karar J, Maity A (2011) P13 K/Akt/mTOR pathway in angiogenesis. Front Mol Neurosci 4:51

128. Georgescu MW (2010) PTEN tumor suppressor network in P3K-Akt pathway control. Genes Cancer 1:1170–1177

129. Castellone MD, Teramoto H, Williams BO, Druey KM, Gutkind JS (2005) Prostaglandin E2 promotes colon cancer cell growth through a Gs-alpha-beta-catenin signaling axis. Science 310:1504–1510

130. Shao J, Jung C, Liu C, Sheng H (2005) Prostaglandin E2 Stimulates the beta-catenin/T cell factor-dependent transcription in colon cancer. J Biol Chem 280:26565–26572

131. Ricchi P, Zarrilli R, Di Palma A, Acquaviva AM (2003) Nonsteroidal anti-inflammatory drugs in colorectal cancer: from prevention to therapy. Br J Cancer 88:803–807

132. Goessling W, North TE, Loewer S, Lord AM, Lee S et al (2009) Genetic interaction of PGE2 and Wnt signaling regulates developmental specification of stem cells and regeneration. Cell 136:1136–1147

133. Papadaki I, Mylona E, Giannopoulou I, Markaki S, Keramopoulos A et al. (2017) Feedback of the drosophila period gene product on circadian cycling of its messenger RNA levels. Nature 434:536–540

134. Goodwin BC (1965) Oscillatory behavior in enzymatic control processes. Adv Enzyme Regul 3:425–438

135. Lefebvre AM, Chen I, Desreumaux P, Najib J, Fruchart JC et al (1998) Beta-adrenergic receptor stimulation and expression of peroxisome proliferator activated-receptors alpha and gamma in heart. Circulation 98:797–800

136. Simons AL, Orcutt KP, Madsen JM, Scarbrough PM, Spitz DR (2012) Oxidative stress in cardiomyocytes. Hypertension 42:844–850

137. Reppert SM, Weaver DR (2002) Coordination of circadian timing in mammals. Nature 418:1249–1260

138. Goodwin BC (1965) Oscillatory behavior in enzymatic control processes. Adv Enzyme Regul 3:425–438

139. Yang X, Wood PA, Ansell CM, Ohmori M, Oh EY et al (2009) Beta-catenin gene expression in intestinal mucosa of ApcMin/+ mice. J Biochem 145:289–297

140. Winter SL, Boscoyan-Collins L, Pinnaduwage D, Andrulis IL (2007) Expression of the circadian clock genes Per1 and Per2 in sporadic breast tumors. Neoplasia 9:797–800

141. Cao Q, Gery S, Dashi A, Yin D, Zhou Y et al (2009) A role for the clock gene per1 in prostate cancer. Cancer Res 69:7619–7625

142. Cao Y, Wang H, Ouyang Q, Tu Y (2015) The free energy cost of accurate biochemical oscillations. Nat Phys 11:772–778

143. Yang X, Wood PA, Ansell CM, Ohmori M, Oh EY et al (2009) Beta-catenin gene expression in intestinal mucosa of ApcMin+/- mice. J Biochem 145:289–297

144. Winter SL, Boscoyan-Collins L, Pinnaduwage D, Andrulis IL (2007) Expression of the circadian clock genes Per1 and Per2 in sporadic breast tumors. Neoplasia 9:797–800

145. Cao Y, Wang H, Ouyang Q, Tu Y (2015) The free energy cost of accurate biochemical oscillations. Nat Phys 11:772–778
165. Suzuki T, Sato F, Kondo J, Liu Y, Kusumi T et al (2008) Period is involved in the proliferation of human pancreatic MIA-PaCa2 cancer cells by TNF-alpha. Biomed Res 29:99–103
166. Mostafaei N, Kallay E, Sauerzapf E, Bonner E, Kiwanek S et al (2009) Correlated downregulation of estrogen receptor beta and the circadian clock gene Per1 in human colorectal cancer. Mol Carcinog 48:642–647
167. Yang MY, Yang WC, Lin PM, Hsu JF, Hsiao HH et al (2011) Altered expression of circadian clock genes in human chronic myeloid leukemia. J Biol Rhythms 26:136–148
168. Fujioka A, Takashima N, Shigeyoshi Y (2006) Circadian rhythm generation in a glioma cell line. Biochem Biophys Res Commun 346:169–174
169. Xia HC, Niu ZF, Ma H, Cao SZ, Hao SC et al (2010) Deregulated expression of the Per1 and Per2 in human gliomas. Can J Neurol Sci 37:365–370
170. Chen L, Yang G (2014) PPARs integrate the mammalian clock and energy metabolism. PPAR Res 2014:653017
171. Yang X, Downes M, Yu RT, Bookout AL, He W et al (2006) Nuclear receptor expression links the circadian clock to metabolism. Cell 126:801–810
172. Yang G, Jia Z, Aoyagi T, McClain D, Mortensen RM et al (2012) Systemic PPARgamma deletion impairs circadian rhythms of behavior and metabolism. PLoS ONE 7:e38117
173. Liu C, Li S, Liu T, Borjigin J, Lin JD (2007) Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism. Nature 447:477–481
174. Tan Z, Luo X, Xiao L, Tang M, Bode AM et al (2016) The role of PGC1alpha in cancer metabolism and its therapeutic implications. Mol Cancer Ther 15:774–782
175. Duez H, Staels B (2010) Nuclear receptors linking circadian rhythms and cardiometabolic control. Arterioscler Thromb Vasc Biol 30:1529–1534

Submit your manuscript to a SpringerOpen journal and benefit from:

► Convenient online submission
► Rigorous peer review
► Immediate publication on acceptance
► Open access: articles freely available online
► High visibility within the field
► Retaining the copyright to your article

Submit your next manuscript at ► springeropen.com