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Towards Cancer Theory – Circadian and 11-Day Biological Clocks

Yuri B. Kirsta♦, DSc, Dmitry Y. Kirsta, BSc

Institute for Water and Environmental Problems, Siberian Branch of the Russian Academy of Sciences, Barnaul, Russia

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Abstract

Background: In the current study, we used the information-hierarchical system approach to examine human metabolism. Metabolism hierarchical structure, beginning from enzyme level, is controlled by the established information principle and divine section numbers. This structure represents a key mechanism of the hierarchical biological clock (HBC) of human body. Time cycles of HBC hierarchical levels are nested into each other according to strict dynamics schemes. The cycles form the HBC scales of 1, 6, 42 seconds, 24 hours (circadian rhythm), and 11 days and jointly make up the precision HBC similar to the conventional countdown (1 s, 1 m, 1 hr, 1 day, and 1 month).

Method: Diagnostic/prognostic studies of cancer require a detailed analysis of metabolic HBC disorders. We utilized the information-hierarchical system approach and the information principle in order to analyze HBC run under different dietary patterns.

Results: We characterized hierarchical metabolic systems with 24-hour and 11-day operation times. The 24-hour circadian rhythm comprised citrate, pentose, and fatty acid (anabolic or catabolic) biochemical cycles individually. The 11-day cyclicity referred to these cycles combined into a ternary system of the higher-rank hierarchical level. Disorder of systems operation should lead to a radical change in HBC run with subsequent transformation of normal cells into cancer cells.

Conclusion: Mutations of metabolic enzyme genes can damage HBC run, thereby leading to cancer and other chronobiological disorders. Organized rhythmicity of external factors (everyday food intake, 11-day periodical dietary pattern, and so forth) made it possible to heal cancer cells per se. Applying a particular kind of diet, the human lifespan could significantly increase. The proposed direction of cancer prevention and treatment can be called a cancer metabolism chronotherapy.

Keywords: Humans, Biochemical phenomena, Biological clocks, Neoplasms, Life expectancy

♦**Corresponding Author:**
Yuri B. Kirsta, DSc
Institute for Water and Environmental Problems SB RAS, 1 Molodezhnaya St., Barnaul, Russia
Tel: +7(3852) 66-65-07
Fax: +7(3852) 24-03-96
Email: kirsta@iwep.ru

Introduction

The current paper presents the results of long-term investigation of human metabolism rhythmicity, which started in the 1970s,[1] to promote a better understanding of

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cancer origin. We analyzed the hierarchically organized metabolic system of cells with its hierarchical biological clock (HBC) constructed during a long process of evolution. This precision clock regulates cellular and body's metabolism from ovum formation to human death. There is a great deal of literature focusing on the study and different mathematical interpretations of the hierarchical structure of evolutionary systems.[2-5] However, none of the studies concerns the information on system organization.

Analyzing the information-hierarchical organization (IHO) of human metabolism, we used the information-hierarchical system approach and the established information principle to explain the operation of IHO hierarchical levels (HLs).[6-9] HL functions based on cyclic basic processes (BPs) that determine the dynamics of all the metabolic reactions.

Method

Any diagnostic and prognostic studies on cancer as well as its treatment could be greatly improved by understanding the causes of its occurrence. The appearance of cancer cells means a damage to their metabolic HBC formed as a hierarchy of HLs/BPs cycles.

Operation cycles of HLs/BPs are nested into each other according to certain dynamics/quantization schemes (Figure 1).[6-9] "Quantization" means that the cycles of each HL represent indivisible elements at the next higher-rank HL. HL/BP organization is characterized by four types of information, H, $|H \ln H|$, R, and $|R \ln R|$ (Table 1).

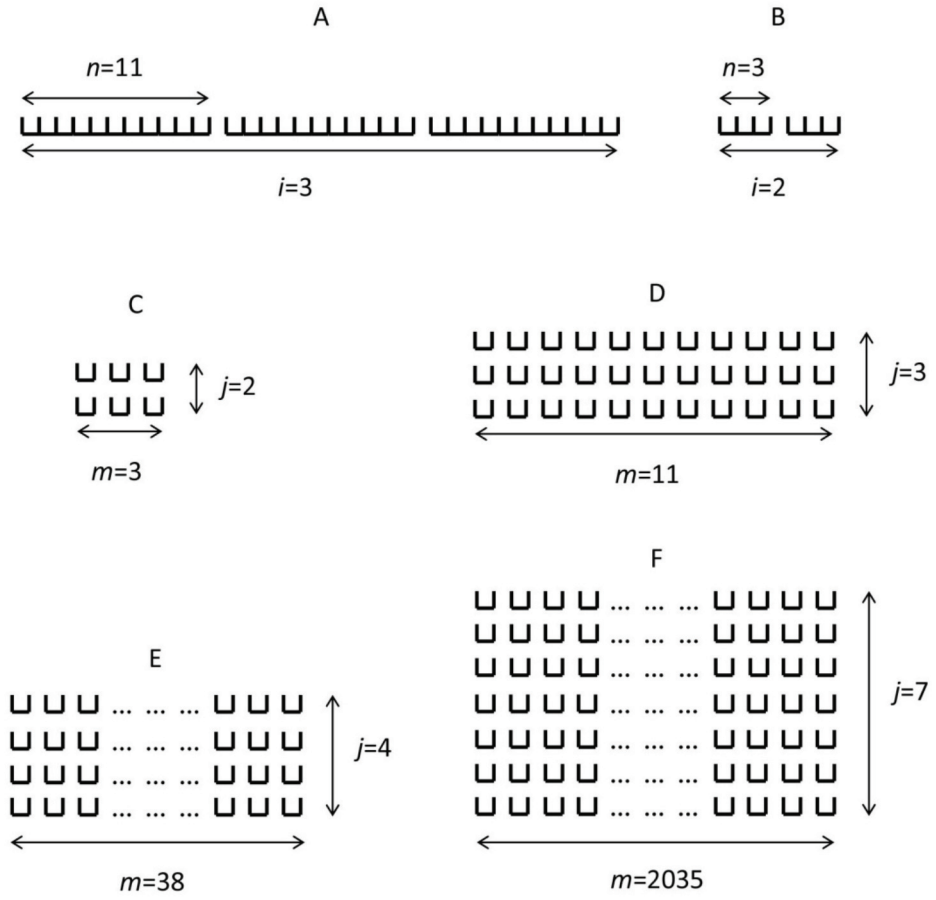

Figure 1. Dynamics/quantization schemes for one basic process (BP) with three (case A) and two (B) phases; for two (C), three (D), four (E), and seven (F) parallel BPs. The schemes are characterised by the information entropy H (see Table 1) equal to 0.682 (A), 0.618 (B), 0.382 (C), 0.318 (D), 0.276 (E), 0.204 (F); symbol ⊔ is the operation cycle of the lower-rank hierarchical level (HL) of human metabolism; *i, j, n*, and *m* depict the numerical characteristics of the schemes: *i*= number of phases for one BP; *j*= number of parallel BPs; *n*= number of lower-rank HL cycles in one phase for one BP; *m*= number of phases (lower-rank HL cycles) for each of the parallel BPs.
Sources: Ecol Model. 1992;62(4):259-74; Ecol Model. 2001;145(1):49-59

Table 1. Numerical characteristics of some dynamics/quantization schemes of BPs for hierarchical systems

Characteristics	Number *i* of phases (one BP), *i* = 3, 2		Number *j* of parallel BPs (interconnected BPs), *j* = 2, 3, 4, …, 7				
	3	2	2	3	4	…	7
N	33	6	6	33	152	…	14245
n	11	3	-	-	-	-	-
m	-	-	3	11	38	…	2035
H	0.682	0.618	0.382	0.318	0.276	…	0.203
R	0.318	0.382	0.618	0.682	0.724	…	0.797
$\|H \ln H\|$	0.261	0.297	0.368	0.364	0.355	…	0.324
$\|R \ln R\|$	0.364	0.368	0.297	0.261	0.233	…	0.181

N is the total number of recurring development cycles of the lower-rank HL in a cycle of the given HL and summed over all BPs, *N*=*ni* or *N*=*mj* (see Figure 1); *n* is the number of lower-rank HL cycles in one phase (distinct interval) for one BP; *m* is the number of lower-rank HL cycles for each of the parallel BPs in a cycle of the given HL; *i*= number of phases for one BP; *j*= number of parallel BPs; *H* and *R* are the information entropy and the ordering of HL organization, respectively, *H*+*R*=1; *H*=(ln *n*)/ln *N*, *R*=(ln *i*)/ ln *N* in the case of one BP or *H*=(ln *j*)/ ln *N*, *R*=(ln *m*)/ ln *N* for parallel BPs; $|H \ln H|$ and $|R \ln R|$ are absolute values of $H \ln H$ and $R \ln R$, respectively; ln is the natural logarithm. The value of *H* maximizes the overall information of HL with the resulting formation of both a widely known sequence of generalized divine section numbers and the *N*, *n*, *m* values.
BPs are the basic processes.
Sources: Ecol Model. 1992;62(4):259-74; Ecol Model. 2001;145(1):49-59; World Futures. 2003;59(6):401-20

BPs produce informative energy-matter *H*- and $|H \ln H|$-products composed of unequal free energies of newly created chemical bonds (or different synthesized molecules) and time *R*- and $|R \ln R|$-products composed of unequal times of correspondingly *H*- and $|H \ln H|$-products present in an HL operation cycle. Information of BP products is calculated as normalized Shannon information:

$$\text{Information} = -\frac{\sum_{i=1}^{k} p_i \times \ln p_i}{\ln k}, \quad (1)$$

,where *k* is the number of elements that comprise BP product, p_i is the unity fraction of element *i* in the product, $\sum_{i=1}^{k} p_i = 1$.

BP energy-matter products are employed at higher-rank HLs and thus, they combine all HLs into one IHO of human metabolism (Figure 2). Time cycles of HLs operation, successively nested into one another, make up the HBC. Thus, proper food and/or timely medication intake, according to HBC, should stabilize metabolic IHO and prevent carcinogenic transformation of cells.

Results

In this paper, we analyzed HL-4 and HL-5 systems of human cellular metabolism (Figure 2). Operation cycles of HL-4 and HL-5 made up 24-hour (circadian) and 11-day HBC scales, respectively.[8] Disorder of HL-4 and HL-5 functioning should have led to a radical change in HBC run with subsequent transformation of normal cells into cancer cells. For a better understanding of how HL-4 and HL-5 work, we also indicated their informative energy-matter *H*-products. In the course of biochemical reactions, these products are constructed by means of free energy of chemical bonds. We used the values of free energy in the standard conditions of reactions (metabolite concentration 1 mole, temperature 298 K, pH 7.0); thus, a slight increase was observed in the calculation error.

HL 4

HL-4 corresponds to recurrent operation of main metabolic cycles, including citrate, pentose, and fatty acid ones (Figure 2). The dynamics scheme of HL-4 comprises seven parallel BPs (Figure 1F). The coincidence of HL-4 cycle and diurnal rhythm of environmental factors (light, temperature, and others) is necessary to optimize the functioning of human metabolism.

Citrate and pentose cycles were analyzed as HL-4 systems earlier.[7] The start-end separation of its parallel BPs operation was realized by inserting a proper HL-3 system. Fatty acid cycle is the specific HL-4 system, which is absent in plant metabolism. During seven repeated circulations of this cycle, one molecule of palmitic acid was synthesized. Human metabolism contains urea cycle (Figure 2). Urea HL-4 system also consists of seven reactions representing seven parallel BPs. Generally, HL-4 systems transfer the free energy of energy-carrying molecules to individual carbohydrate molecules that are key

to human metabolism. The examples of *H*-product formation at HL-4 are given below.

Citrate cycle

Its seven parallel reactions were carried out simultaneously in each of the 2035 phases of HL-4 dynamics scheme. They began with citrate, as the basis for building new chemical bonds, free energies of which form the *H*-product (succinyl-CoA):[10] $citrate_{mit}$ $\leftrightarrow$1 by ACO2 $cis\text{-}aconitate_{mit}$ + H_2O, $cis\text{-}aconitate_{mit}$ + H_2O $\leftrightarrow$2 by ACO2 threo-Ds-$isocitrate_{mit}$, [$citrate_{mit}$ $\leftrightarrow$ $citrate_{cyt}$] $\leftrightarrow$ 3 by ACO1 threo-Ds-$isocitrate_{cyt}$, threo-Ds-$isocitrate_{mit}$ + NAD^+ $\leftrightarrow$ 4 by IDH3(NAD+) 2-$oxoglutarate_{mit}$ + NADH + H^+ + CO_2, threo-Ds-$isocitrate_{mit}$ + $NADP^+$ $\leftrightarrow$ 5 by IDH2(NADP+) $oxalosuccinate_{mit}$ + NADPH + H^+, $oxalosuccinate_{mit}$ $\rightarrow$ 6 by IDH2(NADP+) 2-$oxoglutarate_{mit}$ + CO_2, threo-Ds-$isocitrate_{cyt}$ + $NADP^+$ $\leftrightarrow$ 7 by IDH1(NADP+) 2-$oxoglutarate_{cyt}$ + NADPH +

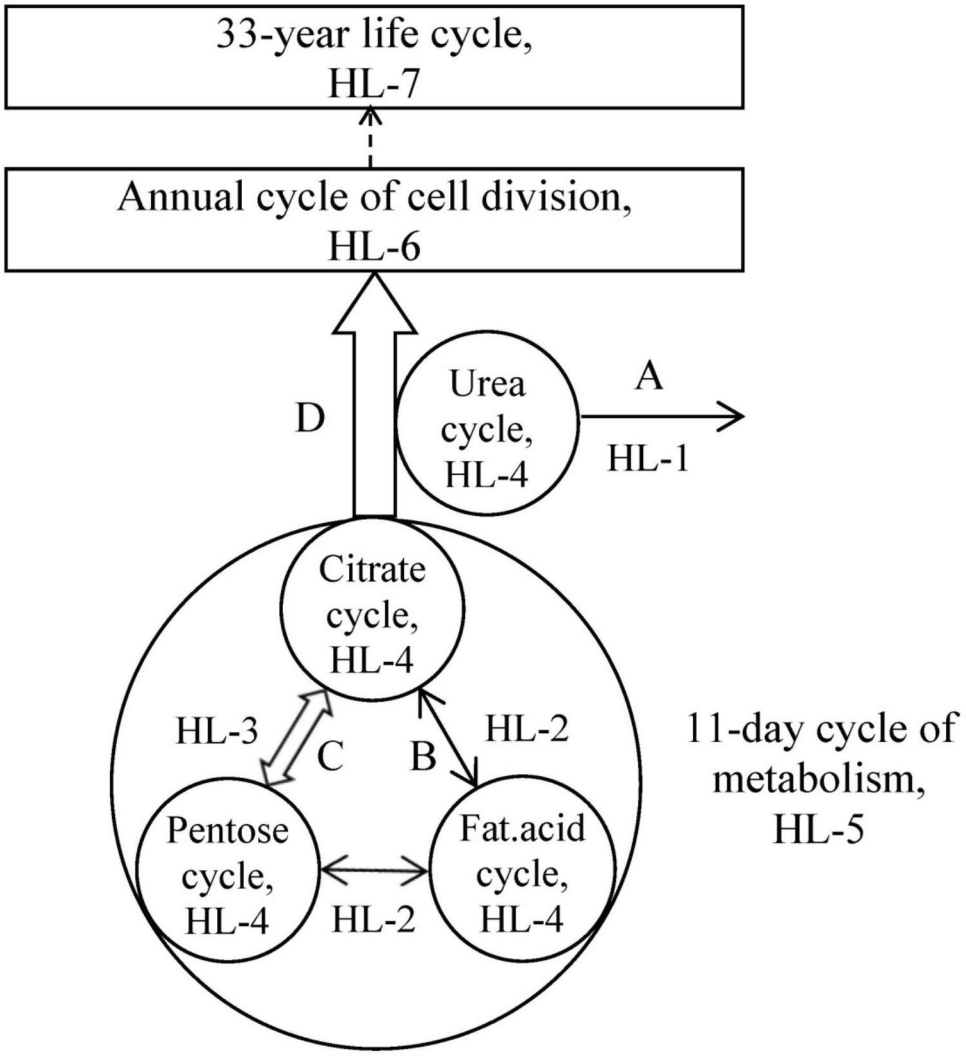

Figure 2. Diagram of the information-hierarchical organization of human metabolism. Sign "A" indicates the HL-1 system with the 1 s cycle. "B" represents the HL-2 systems having the dynamics scheme of one basic process (BP) with 2 phases (Figure 1, Table 1) and the 6-7 s cycle. "C" indicates the HL-3 system having the same scheme of one BP with 2 phases and the 42 s cycle: the systems represent glycolysis (beginning from D-glyceraldehyde 3-phosphate) or gluconeogenesis (ending with D-glyceraldehyde 3-phosphate). "D" is the specific HL-3 network of systems with the above-mentioned scheme; the network produces amino acids, ribonucleotides, and deoxyribonucleotides to run the HL-6 system with peptides, RNA, and DNA synthesis. A small circle around the names of biochemical cycles denotes the corresponding metabolic HL-4 systems with the scheme of seven parallel BPs and the operation cycle of 24 hours. A large cycle around the three small ones denotes the metabolic HL-5 system with the scheme of three parallel BPs and 11-day cycle; these BPs are represented by three HL-4 system operation. The rectangle shows HL systems of increasing integration with operation cycles of 1 year and 33 years.

Sources: Ecol Model. 2001;145(1):49-59; World Futures. 2003;59(6):401-20

$H^+ + CO_2$, [2-oxoglutarate$_{cyt}$ ↔ 2-oxoglutarate$_{mit}$] + ThPP.E + E.Lip.S_2 + CoA-SH + NAD^+] → 0 by OGDH succinyl-CoA$_{mit}$ + CO_2 + ThPP.E +E.Lip$<^{SH}_{SH}$ + NADPH + H^+. The "mit" and "cyt" indices denote mitochondrial and cytosolic substrates, respectively. ACO1 and ACO2 are aconitases 1 and 2; IDH1, IDH2, and IDH3 – isocitrate dehydrogenase isozymes 1, 2, and 3, which depend on NAD^+ or $NADP^+$; OGDH – 2-oxoglutarate dehydrogenase complex.

The inclusion of 7th cytosolic reaction in citrate cycle was confirmed by the occurrence of cancer due to mutations of IDH1 (cytosolic isocitrate dehydrogenase) genes.[11] Cancer is caused by damaging citrate HL-4 system and HBC run. The last of above-listed reactions (designated as 0) represent HL-2 system implemented after seven parallel BPs of citrate HL-4 system. It is indistinguishable in citrate system due to the quantization of metabolic IHO (see Method). This reaction is necessary for obtaining succinyl-CoA in mitochondria from mitochondrial and cytosolic 2-oxoglutarate formed in fourth, sixth, and seventh reactions. To separate the beginning and end of each of the 2035 phases in citrate HL-4 system operation (Figure 1F), the binding-separating HL-3 system was used. The latter consisted of 6+1=7 one- and two-substrate successive reactions of HL-2:[10] succinyl-CoA + GDP + Pi ↔ 1,2 succinate + GTP + CoA-SH + FAD ↔ 3 fumarate +$FADH_2$ + H_2O ↔ 4 *S*(=L)-malate + NAD^+ ↔ 5 oxaloacetate + NADH + H^+ + acetyl-CoA + H_2O ↔ 6,7 citrate + CoA-SH. The stable 42-second operation cycle of this HL-3 system ensures its strict 2035-fold embedding into 24-hour HL-4 cycle.

HL-4 systems of seven parallel BPs form one *H*-product.[7] The latter is not constructed from energy-carrying molecules ATP, $FADH_2$, NADH, H^+, as it occurs in HL-3 systems. The *H*-product of citrate cycle is succinyl-CoA built by attaching two carbohydrates and one thioethereal bond to carbohydrate fragment CH_3-CO- introduced into citrate cycle by acetyl-CoA. The standard free energies of carbohydrates (at their complete oxidation to CO_2) and of thioethereal bond are about 480 kJ/mol per atom C and 32 kJ/mol, respectively.[13,14] Hence, we have the ratio of two *H*-product structural elements [480 kJ/mol×(2 mol) = 960 kJ] : [32 kJ/mol×(1 mol) = 32 kJ] or 0.968:0.032 in unit fractions. Substituting the fractions in Eq. (1) gives information H=0.204 required by the dynamics scheme of seven parallel BPs (Table 1).

Pentose cycle

Pentose HL-4 system in cytosol is similar to reversed Calvin system in plants.[7-8] Its seven reactions convert ribulozo-5-phosphate (as the basis for adding carbohydrate and phosphate) to fructose-1,6-diphosphate representing the *H*-product. Pentose HL-4 system could work during both gluconeogenesis and glycolysis owing to the reversibility of its reactions. This reversibility maintains its dynamics scheme of seven parallel BPs (Figure 1F) in different (anabolic or catabolic) modes of metabolism and ensures the run of cellular HBC.

Pentose cycle reactions are as follows:[10] D-ribulose 5-P ↔1 D-ribose 5-P, D-ribulose 5-P ↔2 D-xylulose 5-P, D-ribose 5-P + D-xylulose 5-P ↔3 D-sedoheptulose 7-P + D-glyceraldehyde 3-P, D-xylulose 5-P + D-erythrose 4-P ↔4 D-glyceraldehyde 3-P + β-D-fructose 6-P, β-D-fructose 6-P + D-erythrose 4-P ↔5 D-sedoheptulose 7-P + D-glyceraldehyde 3-P, D-glyceraldehyde 3-P ↔6 glycerone-P, glycerone-P + D-glyceraldehyde 3-P ↔7 β-D-fructose 1,6-P_2. All the seven reactions proceed simultaneously in each of the 2035 phases of their dynamics scheme (Figure 1F). The start-end separation of the phases is possible through the binding-separating HL-3 system of 6+1=7 one- and two-substrate successive HL-2 reactions:[10] β-D-fructose 1,6-P_2 + H_2O →1 β-D-fructose 6-P + Pi ↔2 α-D-glucose 6-P + $NADP^+$ ↔3 D-6-P-glucono-1,5-lactone + NADPH + H^+ + H_2O →4 D-6-P-gluconate + $NADP^+$ ↔5,6,7 D-ribulose 5-P + NADPH + H^+ + CO_2. Reactions 5-7 are as follows:[12] D-6-P-gluconate is oxidized (5) to 3-keto-6-phosphogluconate that is decarboxylated (6) to a 1,2-enediol of ribulose 5-P and then converted (7) to D-ribulose 5-P. The operation cycle of this HL-3 system is equal to that of one phase of pentose HL-4 cycle (Figure 1F). Its 42-

second duration corresponds to 2035-fold embedding of HL-3 cycles into 24-hour HL-4 cycle, similar to the citrate cycle case.

Considering the catabolic operation of pentose HL-4 cycle, during one phase of its dynamics scheme (Figure 1F), pentose cycle receives six molecules of α-D-glucose 6-P through HL-3 system of six reactions (D-glucose ↔…↔ D-ribulose 5-P) and produces D-glyceraldehyde 3-P with other metabolites.[10] Obviously, only six molecules of glucose give a full balance of input and output of cycle reactants. The glycolytic part of HL-3 network could operate with pentose cycle functioning simultaneously. Such joint work is possible once there are two oppositely directed reactions of β-D-fructose 1,6-P_2 + H_2O → fructose 6-P + Pi and fructose 6-P + ATP → β-D-fructose 1,6-P_2 + ADP in separate parts of the cell.

During the anabolic operation of pentose HL-4 cycle, its 5th reaction (see above) should be replaced by the reverse one (D-sedoheptulose 7-P + D-glyceraldehyde 3-P $\leftrightarrow_{5a}$ β-D-fructose 6-P + D-erythrose 4-P) with the resulting excess of β-D-fructose 6-P. The latter is converted to glucose through two HL-2 reactions (β-D-fructose 6-P ↔ α-D-glucose 6-P ↔D-glucose);[10] hence, the join work of pentose cycle and HL-3 systems of gluconeogenesis is possible.

The *H*-product of pentose cycle is β-D-fructose 1,6-P_2.[9] Similar to Krebs cycle in plants,[6] this product is created by addition of energy-containing components to ribulose-5-phosphate. The proportion of the added carbohydrates and phosphates in β-D-fructose 1,6-P_2 is 1:1. The standard free energy of hydrolyzed phosphate bond is about 16 kJ/mol and that of carbohydrates is 480 kJ/mol per carbon atom.[13-15] The ratio of these energies is 480:16 kJ/mol or 0.968:0.032. Substituting these fractions in Eq. (1), we obtain information 0.204 for the *H*-product of pentose cycle, which is required by the dynamics scheme of seven parallel BPs (Figure 1F, Table 1).

Fatty acid cycles

Anabolic fatty acid HL-4 system of seven parallel BPs is located in cytosol. Its BPs simultaneously lengthen seven separate chains with 2, 4, 6,..., 14 carbon atoms, respectively, until the palmitic acid molecules are formed.[14] Seven HL-3 systems attach two-carbon fragments to carbon chains in each phase of its dynamics scheme (Figure 1F). HL-3 operation cycle is repeated 2035 times during 24 hours. HL-3 systems include seven one- and two-substrate successive reactions, similar to HL-3 network: $acyl_n$-enzyme + malonyl-CoA $\leftrightarrow_1$ $acyl_n$-malonyl enzyme + CoA-SH $\leftrightarrow_2$ 3-oxoacyl$_{n+2}$-enzyme + CO_2 + NADPH + H^+ $\leftrightarrow_{3,4}$ D-3-hydroxyacyl$_{n+2}$-enzyme + $NADP^+$ $\leftrightarrow_5$ trans-2,3-dehydroacyl$_{n+2}$-enzyme + H_2O + NADPH + H^+ $\rightarrow_{6,7}$ [acyl-enzyme $E<^{Cys\text{-}SH}_{ACP\text{-}S\text{-}Rn+2.}$ → $E<^{Cys\text{-}S\text{-}Rn+2}_{ACP\text{-}SH}$] +$NADP^+$. Indexes "n", n=2, 4, 6,..., 14, denote the number of carbon atoms in growing fatty acid chains, enzyme (E) – fatty acid synthase, Cys – active cysteine residue, S – sulphur, ACP – acyl carrier protein, R_{n+2} – extended fatty acid chain with n+2 carbon atoms. The interconnection of these HL-3 systems, as seven parallel BPs and separation of the beginning and end of 2035 phases (Figure 1F), is ensured by successive elongation of the carbon chains up to palmitic acid R_{16}.

The *H*-product of anabolic fatty acid system is the carbon chain R_{14+2} in synthase complex $E<^{Cys\text{-}S\text{-}R14+2}_{ACP\text{-}SH}$. It is formed in each phase of HL-4 operation cycle via the free energies of two-carbon fragment (480×2 = 960 kJ/mol) and thioester bond (32 kJ/mol),[13,14] which are added to the chain R_{14}. Substituting the unit fractions corresponding these energies (960:32 kJ/mol gives 0.968:0.032) in Eq. (1), we obtain information *H*=0.204 required by HL-4 dynamics scheme (Figure 1F).

Catabolic fatty acid HL-4 system of seven parallel BPs performs a fatty acid β-oxidation in mitochondria. Note that synthesis and oxidation of fatty acids do not intersect because they take place in different cell compartments. Seven BPs shorten seven chains (with n=4, 6, 8, ... , 16 carbon atoms, respectively) obtained from the initial palmitic acid molecules. Each phase of its dynamics scheme (Figure 1F) includes parallel operation of seven HL-3 systems. Each HL-3 system consists of seven one- and two-substrate successive reactions:[10] $acyl_n$-CoA + FAD.E $\leftrightarrow_1$

trans-2,3-dehydroacyl$_n$-CoA + FADH$_2$.E $\leftrightarrow_2$ L-3-hydroxyacyl$_n$-CoA + NAD$^+$ $\leftrightarrow_3$ 3-oxoacyl$_n$-CoA + NADH + H$^+$ + CoA-SH $\leftrightarrow_4$ acyl$_{n-2}$-CoA + acetyl-CoA + oxaloacetate + H$_2$O $\leftrightarrow_{5,6}$ [citrate$_{mit}$ $\rightarrow$ citrate$_{cyt}$] + ATP $\leftrightarrow_7$ acetyl-CoA$_{cyt}$ + oxaloacetate + ADP + Pi. Indexes "n", n=16, 14, 12,..., 4 indicate the number of carbon atoms in the shortening fatty acid chains. Converting the parallel operation of seven HL-3 systems into seven parallel BPs of HL-4 is carried out by successively shortening the palmitic acid chain (similar to HL-4 of fatty acid synthesis).

The *H*-product of catabolic fatty acid system (β-oxidation) consists of the free energies of thioester bond and two-carbon acetyl fragment included in the acetyl-CoA (see the 7th reaction above). Using the same energy values as in anabolic fatty acid system, we obtain information *H*=0.204 required by HL-4 dynamics scheme (Figure 1F).

Urea cycle

This cycle takes place in the liver and kidneys. It represents HL-4 systems that include seven reactions:[10] HCO_3^- + NH_4^+ + 2×ATP $\leftrightarrow_{1,2}$ carbamoyl-P + 2×ADP +Pi + L-ornithine $\leftrightarrow_3$ L-citrulline + L-aspartate +ATP $\leftrightarrow_{4,5}$ L-argininosuccinate + AMP + PPi $\leftrightarrow_6$ L-arginine + fumarate + H$_2$O $\rightarrow_7$ L-ornithine +urea. There are no binding-separating HL-3 systems in it. The enumerated seven reactions are turned into seven parallel BPs by the intracellular medium per se, from which one carbon atom is taken (as HCO_3^-) and then returned (as urea). The start-end separation of 2035 phases in urea HL-4 operation cycle is ensured by removing the synthesized urea molecule out of the cycle, which is similar to the palmitic acid molecule in anabolic fatty acid system. The phases rhythmically coincide with HL-3 operation cycles due to receiving the amino groups from HL-3 network (Figure 2).

The *H*-product of urea cycle is formed by the free energies of four-carbon fragment and two amino groups NH_2 in the L-ornithine molecule, which are added to the HCO_3^- molecule entering the cycle. The energy of a bond between four-carbon fragment and one amino group could be estimated from the reversible reaction L-glutamate + ATP + NH_3 $\leftrightarrow$ L-glutamine + ADP + Pi. To form this bond, the energy of one ATP (30.5 kJ/mol) is needed.[10,13] Consequently, the total bond energy of the two amino groups equals 30.5×2=61 kJ/mol. The energy of one carbohydrate 480 kJ/mol[13,14] results into 480×4=1920 kJ/mol for four-carbon fragment. These free energies are in proportion 61:1920 kJ/mol or 0.031:0.969 in unit fractions. Substituting these in Eq. (1), we reach information *H*=0.2, which is consistent with the required value 0.204 (Figure 1F, Table 1).

HL 5

HL-5 system of human metabolism is composed of any three of the four HL-4 systems (citrate, pentose, anabolic fatty acid, and catabolic fatty acid cycles), which operate as three parallel BPs (Figures 1D, 2). Metabolic reactions of unused HL-4 system therefore turn into a part of HL-3 network. HL-5 exists independently of altering the anabolic and catabolic modes of cellular metabolism. In HL-5, one of the used pentose, anabolic fatty acid, or catabolic fatty acid HL-4 systems could be replaced by another, depending on the food character and cell type. HL-5 system also includes the urea HL-4 system as separating one. Note that human/animal HL-5 differs greatly from plant HL-5 having only two parallel BPs.[7,8] According to the dynamics scheme of three parallel BPs (Figure 1D), HL-5 operation cycle is equal to 1×11=11 days.

Different combinations of HL-4 systems in HL-5 do not affect the functioning of HL-5 and higher-rank HLs of human metabolism. This is a result of the information principle, according to which the functioning of lower-rank HLs is indivisible for the current one. Such a quantized organization of HLs provides for stable functioning of metabolism and the run of its HBC. We can consider certain possible variants of HL-5 system (Figure 2), which exist in different cells or at different nutrition.

HL-5 of fat catabolism

Fatty acids are the source of energy in cells and are obtained by splitting triglycerides in the cytoplasm. After moving into mitochondria, fatty

acids are oxidized by catabolic fatty acid system. Excess acetyl-CoA obtained from fats with short chains (from 4 to 16 carbon atoms) supports the work of citrate cycle. Due to excess acetyl-CoA, pentose cycle stops functioning. The latter is blocked, for example, via inhibiting its HL-2 reaction α-D-glucose 6-P ↔ D-6-P-glucono-1,5-lactone by an increased concentration of acyl-CoA.[10] As a result, the HL-5 system is formed by citrate cycle together with anabolic and catabolic fatty acid cycles.

The dynamics scheme of HL-5 requires combining three different HL-4 cycles in each of its 11 phases (Figure 1D). Due to quantized organization of HLs, three HL-4 systems in HL-5 should not be separated from each other by two or more cycles of HL-3 systems.[6] Catabolic fatty acid cycle (β-oxidation) is connected to citrate one via their common reaction in mitochondria:[10] acetyl-CoA + oxaloacetate + H_2O ↔ citrate + CoA-SH. In turn, the connection of catabolic fatty acid cycle and anabolic one is performed in cytosol by HL-2 reactions: acetyl-CoA + $E<^{\text{Cys-SH}}_{\text{ACP-SH}}$ ↔ $E<^{\text{Cys-SH}}_{\text{ACP-S-CO-CH3.}}$ → $E<^{\text{Cys-S-CO-CH3}}_{\text{ACP-SH}}$ + CoA, as well as acetyl-CoA + E-BIOTIN-CO_2^- ↔ malonyl-CoA + E-BIOTIN. Thus, each 24-hour phase in 11-day HL-5 cycle of fatty acid catabolism represents the simultaneous execution of 24-hour operation cycles of three HL-4 systems in accordance with HL-5 dynamics scheme.

HL-5 of carbohydrate catabolism

HL-5 system is formed under conditions of carbohydrate consumption and aerobic glycolysis. It includes three parallel HL-4 systems: citrate, pentose, and anabolic fatty acid cycles. Pentose and citrate cycles are connected by one HL-3 system of glycolysis: D-glyceraldehyde 3-P ↔… ↔ pyruvate → acetyl-CoA or D-glyceraldehyde 3-P ↔…↔ pyruvate ↔ oxaloacetate. Anabolic fatty acid cycle is connected to citrate one through HL-2 reaction [$citrate_{mit}$ ↔ $citrate_{cyt}$] + ATP + CoA-SH ↔ acetyl-CoA + oxaloacetate + ADP + Pi and two HL-2 reactions indicated for the fat catabolism HL-5 system mentioned above. The anabolic fatty acid HL-4 system is switched off owing to, in particular, the inhibition of acyl-CoA transfer into mitochondria by high malonyl-CoA concentrations.

HL-5 of protein catabolism

Amino acids are used by cells for producing energy via citrate cycle, for protein and ketone bodies synthesis and for gluconeogenesis. Protein catabolism HL-5 system can include citrate, anabolic fatty acid, and pentose cycles. It is similar to the carbohydrate catabolism HL-5 system, yet with gluconeogenesis instead of glycolysis. The connection of pentose cycle to citrate one is by the first HL-3 system of gluconeogenesis. The latter has 6+1=7 one- and two-substrate successive HL-2 reactions:[10] citrate + ATP + CoA-SH $\leftrightarrow_1$ acetyl-CoA + oxaloacetate + ADP + Pi + GTP $\leftrightarrow_2$ [$P\text{-enolpyruvate}_{mit}$ ↔ $P\text{-enolpyruvate}_{cyt}$] + GDP + CO_2 + H_2O $\leftrightarrow_3$ 2-P-D-glycerate $\leftrightarrow_4$ 3-P-D-glycerate + ATP $\leftrightarrow_5$ 1,3-P_2-D-glycerate + ADP + NADH + H^+ $\leftrightarrow_{6,7}$ D-glyceraldehyde 3-P + NAD^+ + Pi. On a number of occasions, the two first reactions can be replaced as follows: [$citrate_{mit}$ ↔ $citrate_{cyt}$] + ATP + CoA-SH $\leftrightarrow_1$ acetyl-CoA + oxaloacetate + ADP + Pi + GTP $\leftrightarrow_2$ P-enolpyruvate + GDP + CO_2. The second HL-3 system of gluconeogenesis begins with HL-2 reaction pyruvate + E-BIOTIN-CO_2^- $\leftrightarrow_1$ oxaloacetate + E-BIOTIN and operates as part of HL-3 network.

HL-5 at starvation

During prolonged fasting, HL-5 system can be formed from citrate, catabolic fatty acid, and pentose cycles with an alternation of gluconeogenesis and glycolysis. Fatty acid catabolism supplies energy for HL-5 system operation. The conjunction of catabolic fatty acid cycle and citrate one is performed similarly to HL-5 of fat catabolism. Pentose cycle connects with citrate one through HL-3 system of gluconeogenesis or HL-3 system of glycolysis alternately. The regular switching of gluconeogenesis-glycolysis is required to provide cells with necessary metabolites and support the function of HL-5.

Role of urea cycle

Urea cycle plays the role of binding-separating HL-4 system for all the variants of HL-5 system. It is connected with citrate cycle by two HL-2 reactions: 2-oxoglutarate + L-aspartate $\leftrightarrow_1$ L-

glutamate + oxaloacetate + ATP + NH_3 ↔2 L-glutamine +Pi + ADP. The first one takes 2-oxoglutarate with five carbon atoms from citrate cycle; whereas, the second one returns oxaloacetate with four carbon atoms in citrate cycle. In other words, one carbon atom is moved from the cycle to HL-3 network. In turn, urea cycle removes one carbon atom (urea) out of metabolic IHO. In the following, we will see that carbon atom taken from citrate cycle is a component of *H*-product at HL-5. It does not directly enter urea cycle, which is why the latter does not participate in *H*-product construction at HL-5. In view of the fact that this product must be created by all BPs together, urea cycle cannot be one of HL-5 parallel BPs and turns into the separating system in HL-5 (Figure 2). It separates HL-5 systems of different cells from each other and ensures coordination of their work throughout the body by physiological matching of liver and kidney function to the external diurnal rhythm.

Influence of mutations

All the considered HL-5 systems include citrate cycle as a mandatory component. That is why mutations in the genes encoding citrate cycle enzymes disrupt HBC run and lead to the transformation of cells into cancer ones. Moreover, significant violation of citrate cycle operation is lethal to cells. Consider the situation in further details.

Defects of citrate cycle enzymes do not usually disrupt its operation as HL-4 system. They primarily change the duration of its operation and therewith disturb the required nesting of HL-4 cycles in HL-5 cycle (and then in HL-6 and HL-7 ones). Disturbed nesting means losing control of HL-5 and higher-rank HLs over HL-4 provokes fast cell division and turns cells into benign or malignant tumor.[15] We see this with mutations in fumarase, succinate dehydrogenase,[16] isocitrate dehydrogenases IDH1, IDH2[17] and in some other enzymes.[18] While disrupting the operation of citrate cycle and HL-5 system, pentose cycle continues to function and forms the excessive amounts of pyruvate and lactate. This case is known as the Warburg effect associated with the transformation of normal cells into tumor-forming cells.

H-product of HL-5

During HL-5 operation cycle, the free energies of carbohydrates are distributed among two functionally contrast chemical compounds that represent structural elements of *H*-product. One of them is further employed in cellular metabolism and the other one is removed from the cell. The first element is the palmitic acid molecule with 16 carbon atoms; it is formed in anabolic fatty acid cycle and then used in other metabolic reactions. The second element is one carbon atom removed from citrate cycle and the cell via the urea binding-separating HL-4 system (see above). These *H*-product elements have the ratio of carbon atom amounts of 16:1 or 0.941:0.059 in unit fractions. Substituting two latter values in Eq. (1), we have information H=0.32 needed in the case of three parallel BPs (Figure 1D, Table 1). Once catabolic fatty acid cycle replaces the anabolic one in HL-5 system, the first element of *H*-product changes from the palmitic acid molecule to 8 acetyl-CoA molecules synthesized during the cycle operation. Given two carbon atoms in each acetyl-CoA molecule, we again obtain the proportion of carbon atoms 16:1 and the same information H=0.32.

For note, energy-matter *H*-products of any HL should be formed from products of the lower-rank HL. As is known, when malonyl-CoA is decarboxylated in anabolic fatty acid cycle, the carbon atom released as CO_2 is the one obtained from E.BIOTIN.CO_2^-. Thus, palmitic acid is formed according to the information principle, in other words, by using the carbon atoms from acetyl-CoA as the element of *H*-product of lower-rank HL.

Discussion

We analyzed IHO of normal and cancer cellular metabolism composed of hierarchically subordinated metabolic HL systems. IHO multiscale rhythmicity represents the precision metabolic/biological clock, the scales of which are hierarchically composed (1 s, 6 s, 42 s, 24 hours, and 11 days) similar to traditional time counting (1 s, 1 m, 1 hr, 1 day, and 1 month).

The rate of metabolic/biological clock should agree with the main environmental rhythms to optimize cell functioning. Any three of the four HL-4 systems (citrate, pentose, anabolic fatty acid, and catabolic fatty acid ones) simultaneously adjust their 24-hour cycles to the diurnal rhythm of nutrition by means of negative and positive metabolic feedbacks. Together, they form the higher-rank system of HL-5 with 11-day operation cycle. Damage to cellular IHO at HL-4 or HL-5 by internal or external mutagenic factors provokes transformation of the native cells into the cancer ones with uncontrolled growth.

It is useful to point out one important feature of HL-5. HL-5 is composed of three HL-4 systems (citrate, pentose, and fatty acid ones) which operate in parallel (Figures 1D, 2). There is a theoretical possibility to change HL-5 structure into another, yet with four HL-4 systems (citrate, pentose, anabolic fatty acid, and catabolic fatty acid ones). Their parallel work can be organized using, presumably, a specific diet.[19] Time cycle of HL-5 will then include 38 cycles of HL-4, instead of former 11 (Figures 1D, 1E). It results in the same increase (by 38/11=3.45 times) in human lifespan up to 33×3.45 = 114 years (Figure 2). The new HL-5 of four BPs will be at a higher risk of cancer, and therefore evolutionarily unfavorable. This is due to the impossibility to replace any HL-4 systems (if damaged by enzyme mutations) in the new HL-5 by alternate HL-4 system, in contrast to the current HL-5 of three BPs.

Specifically organized rhythmicity of external factors (for instance, 11-day periodical dietary pattern, special everyday food intake, exposure to 1-, 6-, 42-second multiperiodic magnetic field) makes it possible to heal cancer cells per se. Such a treatment differs from traditional methods aimed at cell destruction. Healing of cancer cells is achieved by multiscale synchronization of their metabolic/biological clock with external factor rhythmicity, which is similar to the adaptation of our body to time zone changes after flights. For the same reason, an exposure to proper external rhythmicity could prevent cancer after the treatment with stem cells, the clock of which disagrees with the recipient one. Certainly, such a therapy can be added to drug, radiation, or other therapies to increase their efficiency.[20,21] Thus, we have the new direction of cancer prevention and treatment that could be called a cancer metabolism chronotherapy.

Conclusion

The information-hierarchial system approach outlines the new direction of medical investigations. This approach can be used not only for cancer prevention and for treatment of cancer cells per se, but also for solving different medical problems such as chronotherapeutic drug delivery, progeria treatment, and increase of human life duration.

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Conflict of Interest

None declared.

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