REVIEW

The hypothesis of specific affinity of metabolic pathways inherent to onset of hibernation and reaction to critical stress stimuli

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In this publication we are discussing the discovered analogy between reactions of hibernating and non-hibernating animals to critical factors in the external environment. A hypothesis is formulated regarding the mechanisms responsible for the discovered analogy both at the cellular level and at the level of the whole organism.

> *"When I see a bird that walks like a duck and swims like a duck and quacks like a duck, I call that bird a duck."* attributed to James Whitcomb Riley

The question of what life is, what is considered its beginning and its end, apparently stands before the mankind since its appearance on Earth. And this question is still on the agenda. The deeper the researchers dig into the essence of biological processes, the more blurry the line separating life and death becomes. Concepts of "latent" or "suspended" life arise, visible signs of which previously would have been considered attributes of death. To denote such ambiguous living states, in 1873 a German scientist Wilhelm Preyer introduced a concept of anabiosis (αvα - again and βιος - life) - return to life. This concept carries the idea that the states of life and death, as they are understood, can be reversible, despite the fact that visible manifestations of life are absent (Goldovsky 1981). The conditions, under which life processes in an organism can be significantly inhibited, up to temporary cessation, are far beyond optimal for functioning. Suppression of life-sustaining functions is an adaptive reaction developed for surviving such restrictions. All these conditions are stressful to an

organism and cause physiologic changes which may be more or less able to offset the impact of stress.

There are two qualitatively different strategies for adaptation to stressful external conditions - increase in resistance and increase in tolerance (stamina, endurance) (Kulinsky & Olhovsky 1992). Phylogenetically more ancient tolerance strategy is characterized by subordination to the external environment. Metabolic basis for this strategy is the inhibition of metabolic processes, reduction in energy expenditure and oxygen consumption, minimization of functions, which inevitably lead to certain changes in homeostasis. However, the organism is resistant to them: they are not excessive, not harmful and are reversible. This particular strategy is utilized in cryptobiosis (Roots 2006). Currently, there is division of cryptobiotic states into Hibernation, Estivation, Anoxia, Freezing, and Diapause (Goldovsky 1981; Roots 2006) .

The ability to sustain prolonged anabiosis is widely known in microorganisms as well as in higher organisms (Goldovsky 1981; Feofilova 2003; Roots 2006; Blanco & Rahalinarivo 2010). It could be stated that mechanisms allowing for cryptobiosis are present in representatives of practically all groups of fauna and flora. The search for specific functional features of hibernating animals in active phase, which would distinguish them from non-hibernating ones, does not reveal such differences, while plenty of physiologic differences between animals in the state of hibernation and actively metabolizing ones exist. A careful study of the physiologic and biochemical processes responsible for implementation of hypometabolic states in hibernating animals suggests that during hibernation, in the body of a hibernating animal, changes are observed similar to those that occur in severe clinically pathologic cases (Roth & Oehler 2010), but the latter, as a rule, are irreversible. All

critical pathologic processes that require urgent intervention to preserve live, are very strong stressors and demand an immediate response. As early as in the works of H. Selye, attention was drawn to non-specificity and generality of organism's response to strong stressful stimulation (Selye 1998).

Human response to extreme stress and pathologic effects.

Human reaction to extreme stress and some pathologic states often manifests as shock, coma, and clinical death. These states, regardless of damaging effects, usually proceed through two major phases: erectile and torpid (Mazurkiewicz & Bagnenko 2004). Erectile (excitation) phase is associated with the initial response to a shocking agent which comprises massive release of catecholamines into the blood, with their concentration in the blood exceeding normal by 30–100 times (Hardaway 2006). Tachycardia, increased blood pressure, glycogenolysis, hyperglycemia are characteristic (Desborough 2000). Simultaneously with peripheral vasospasm, vasodilation in vital organs (heart, brain, liver) is observed, which can be considered an automatic reaction aimed at increasing energy supply to the vital organs.

Coagulopathy, sludging (Pories *et al.* 1962) and tissue hypoxia develop (Stalker 1970) which subsequently determine the severity of the shock state. Massive glycogenolysis in the absence of oxygen leads to lactic acidosis (Hardaway 2006). In turn, increased acidity reduces contractility of the heart muscle, which reduces the oxygen delivery to tissues, initiating the "death cycle" ("triad of death") - coagulopathy, acidosis, hypothermia (Lewis 2000). A comparative review of stages of hibernation onset in hibernating organisms points to similarity with the stages of critical shock onset in humans.

- In the blood of hibernating organisms, before the onset of hibernation, the content of catecholamines increases by 500–600%. The animals are overly excited and agitated.

- Heart rate acceleration, hypertension, glycogenolysis, lipolysis, hyperglycemia (Goldovsky 1981) are observed.

- There is pronounced coagulopathy. Blood clotting time may increase from 8 minutes to 150 minutes or more during hybernation (Smith, Lewis, & Svihla 1954).

- Metabolism in skeletal muscule and brain is suppressed (Frerichs *et al.* 1998). Bowel bulk and its functional activity sharply decline (Cramp *et al.* 2009).

- Body temperature decreases (Goldovsky 1981; Roots 2006).

- Upon entering the state of hibernation, initial acidosis is noticed, which is regulated in such a way that the intracellular acidosis in the dormant state is contained within brain and skeletal muscle cells, but is not observed in the liver and heart muscle cells (Malan, Rodeau, & Daull 1985).

- Torpidity is a necessary condition for hibernation (Goldovsky 1981; Roots 2006)

Undoubtedly, there are common physiologic findings observed at the onset of hibernation, state of shock, and clinical death. Perhaps these similarities are a reflection of a genetically programmed in virtually all animals, including humans, mechanism ensuring cryptobiosis. According to existing theories, in critical situations more ancient biological mechanisms are utilized (Orbeli 1949). Therefore, similar mechanisms should be observed during embryogenesis and early ontogeny. Before birth, the level of catecholamines

in the embryo's blood rises. Mobilization of energy stores leads to breakdown of glycogen (Glg) stored in the liver to glucose (Gupte 1968). The level of lactate (La) in blood increases, and metabolic acidosis ensues. It is known that embryos are highly resistant to hypoxia (Boyle, Meschia, & Wilkening 1992; Podrabsky *et al.* 2007), which is determined by two conjugated factors:

- selective reduction of oxygen consumption and aerobic metabolism in non-vital organs (skeletal muscle), followed by intensification of glycolysis in them and La production;

- balancing La production and its metabolism in organs with sustained non changeable aerobic exchange (Boyle *et al.* 1992).

Another characteristic feature of the early development period is resistance to cooling (Lokotko 1949). It is obvious that physiologic mechanisms assuring embryo's and organism's reactions to hypoxia and stress, at the early stages of development, have similarities with the processes occurring in animals during hibernation and with human responses to critical stressful insults.

The role of catecholamines

Catecholamines are physiologically active agents operating in the body as chemical mediators. Cells capable of synthesizing norepinephrine (NE) are found in many tissues, i.e. NE access is provided directly to each cell (Baulieu 1990). As a neurotransmitter, it affects local blood flow (vasoconstriction) (Backer *et al.* 2010), functional activity of organs and cell degradation (Dunser & Hasibeder 2009), activation of anaerobic glycolysis and release of La into blood by skeletal muscle (Qvisth *et al.* 2008). Massive surge of NE, as a hormone and a neurotransmitter, in stressful situations and during hypoxia, has multifactorial beneficial effect on the body. Its onset of action is

within seconds and can sometimes demonstrate features of anticipatory reactions. The released energy substrates can be used by all body tissues and cells, assisted by stimulation of blood circulation. However, prolonged exposure to NE can deplete energy reserves in animals preparing for hibernation, while they will be necessary during awaking. Consequently, during transition into state of cryptobiosis, quick neutralization of neurotransmitter action is needed in order to conserve energy substrates (Benedict & Grahame-Smith 1978).

It can be summarized that the impact of massive release of catecholamines, which is observed at the onset of hibernation as well as in the perinatal period and in the state of shock or clinical death, has a signaling function and provides all body systems, organs and cells with the maximum supply of energy substrates. Very important consequence of massive catecholamine surge is discontinuation of power supply to the most energy consuming but not live sustaining systems.

Providing a cell with stocks of energy substrates.

Power supply of a cell determines its survivability, and therefore, the onset of hibernation should be accompanied by provision of adequate amounts of energy substrate for all cells.In hibernating animals before dormancy, significant accumulation of Glg and lipids in critical tissues including hepatocytes is demonstrated (Malatesta *et al.* 2002). Glg accumulation in the liver is considered to be one of the major prerequisites for survival in animals capable of sustaining hypoxia and anoxia (Bickler & Buck 2007).

During embryogenesis in virtually all vertebrate species, a characteristic period of maximal accumulation of energy substrates in the liver preceding birth is observed (Randall & L'Ecuyer

1976; Margolis 1983; Devi, Habeebullah, & Gupta 1992). During the moment immediately preceding birth, Glg in the liver and other tissues of all animals begins to plummet (Devi *et al.* 1992). The level of La in the blood increases, and metabolic acidosis ensues (Polianchikova *et al.* 2009). Probably, this decrease in Glg is caused by disruption of embryonic oxygen regimen and is explained by redistribution of energy substrates among all cells. The likelihood of survival in animals resistant to anoxia is highly dependent on Glg stores in the liver. In case of total depletion of liver Glg, an animal does not survive in anoxic conditions (Nilsson 1990).

Specific features of the nervous system's reaction to hibernation and critical stress

Release of catecholamines and, consequently, activation of catabolic processes is regulated by the autonomic nervous system (ANS) (Appenzeller & Oribe 1997). A characteristic feature of ANS is that exclusion of innervation by the ANS results in significant increase in cells sensitivity to NE (Pokrovsky & Korotko 1998). It can be assumed that in case of severe depression of the central nervous system which is observed in hibernating animals during hibernation and in non-hibernating animals at the time of critical stress and hypoxia (Desborough 2000; Drew *et al.* 2001), such inhibition may encom pass the ANS as well. In that case, increase of cellular sensitivity to NE may play a major role in awakening of the animal from hibernation.

During hibernation, the hippocampus plays the most important role – it performs a "guarding" function and triggers central nervous system activation mechanism at termination of hibernation (Malan & mйdicale 1989). Cellular changes in the hippocampus during hibernation demonstrate

presence of structural rear rangements, as well as temporary loss of synaptic contacts between neurons, which persisted for 3h after induced excitation from hibernation. It seems that adjustments, both metabolic and morphologic (Magarinos *et al.* 2006), which occurred at the time of "switching on" hypometabolic state at the cellular level, require some time for reverse reorganization and return of the cells into active state. Changes in the cells of the hippocampus during hibernation are completely reversible (Anoshkina 2005).

Talking about ensuring viability of the cells of the nervous system under conditions of hypoxia and concomitant hibernation, feasibility of catecholamine release prior to slowing of metabolic processes in the body is explained by the necessity to provide the nervous system in an isolated state with energy substrates. In hyperglycemic state caused by catecholamine release, there is rapid accumulation of glucose in neurons and astrocytes in a parallel fashion (Simpson, Carruthers, & Vannucci 2007).

The role of lactate and lactic acidosis

In case of isolation of the nervous system cells, maintenance of viability of a neuron can be achieved by the use of La. La is accumulated by nervous tissue during lactic acidosis by means of ACNS (astrocyte-neuron lactate shuttle) (Aubert *et al.* 2005; Brooks & Hashimoto 2007; Boumezbeur *et al.* 2010), since La can be used instead of glucose to maintain viability of brain cells in critical situations (Quistorff, Secher, & Lieshout 2008).

The fact that La production and utilization of exogenous La by a cell are carried out via different metabolic pathways (Chatham, Rosiers, & Forder 2001) explains the ability of the cells of nervous and muscle tissues to survive in conditions of hypobiosis and vasoconstriction with the use of extracellular La, but with suppression of their own glycolysis. In addition to its function as the energy substrate, the role of La and metabolic acidosis for the nervous tissue may be a signaling function (Chesler 2003). It is natural to assume the role of La as a pseudo-hormone, which plays an important role in coordinating cellular and systemic functions (Philp, Macdonald, & Watt 2005). Besides, La can be quickly redistributed among tissues and delivered to those tissues in which it can be used as a substrate for gluconeogenesis and glycogenesis (Brooks & Hashimoto 2007). A possibility of La pyruvate exchange between mitochondria (Mt) and cytosol, i.e. Mt participation in the processes of gluconeogenesis, and stimulation of this process by NE (Brooks *et al.* 1999; Bari *et al.* 2004) are considered.

Thus, the distinguishing feature of animals capable of undergoing cryptobiosis, lies in the fact that the initial enhancement of glycolysis, caused by massive release of catecholamines, is a temporary phenomenon. Shortly thereafter, the activity of the enzymes of glycolysis in the liver declines. Cessation of glycolysis first occurs in the liver, which makes sense for preservation of stocks of Glg (Kelly & Storey 1988). It is the increase in concentration of extracellular La that can inhibit glycolysis (Isaacson, Solís, & Nicoll 1993). Another feature of lactic acidosis is increase in the electrochemical gradient created by La /H+ transport across the membrane. Gradient is considered metabolic energy which is independent of ATP, but can be used by a cell (Kandel, Schwartz, & Jessell 2000; Basu, Mukherjee, & Adhya 2008) under conditions of suppression of ATP production by the La in Mt (Ereciska *et al.* 1993). Lactic acidosis accompanying hibernation and stress states is directly related to the dynamics of intracellular calcium ion (Ca^{2+} i) content.

Effect of Ca²⁺ on the metabolic processes in a cell

$(Ca^{2+}i)$ concentration changes rapidly, depending on the state of the cell. The same changes occur in the nucleus (Nicotera *et al.* 1989). Phosphorylation and dephosphorylation, which alter enzymatic activity and occur during changes in metabolic states, are also dependent on $(Ca^{2+}i)$ (Padilla *et al.* 2002; Storey & Storey 2004). Increase in calcium concentration in tissues is characteristic for animals resistant to anoxia (Jackson 2002). Regulation of Ca^{2+} concentration inside the cell is carried out by coordinated action of the endoplasmic reticulum (ER) and Mt, which have an independent ability to deposit excess Ca^{2+} and release it – i.e., they regulate cellular metabolism (Duchen 2000; Walsh *et al.* 2009). This regulation is ensured by Ca^{2+} exchange between them (Csordás *et al.* 2010) for which contact between the organelles is required (Filippin *et al.* 2003).

It should be noted that NE has a property of intracellular signaling chain activation which ultimately causes the release of Ca^{2+} from intracellular ER (Alexandrov *et al.* 2008) into the cytosol. Accumulation of Ca^{2+} in the cytosol causes its deposition in Mt and leads to reversible inhibition of their functional activity (Buja *et al.* 1983), and to reversible blockade of the respiratory chain (Baker, Hodgkin, & Ridgway 1971). Taking into consideration dependence of Ca^{2+} accumulation in Mt on H^+ gradient created by respiratory chain reactions (Vasington & Murphy 1962), it can be assumed that intramitochondrial concentration of Ca^{2+} $(Ca^{2+}m)$ can be regulated by decrease in oxidative processes. In view of the data on participation of ER in activation of apoptosis (Rosati *et al.* 2010), it is obvious that disruption of concordant Mt and ER activity in a cell in regulating $(Ca^{2+}i)$ may serve as a signal to launching apoptosis. Change in $(Ca^{2+}i)$ concentration regulates the colloidal state of the cytoplasm, which is directly related to the regulation of metabolic activity of the cell (Pollack 2001). Sol/gel ratio at different concentrations of Ca^{2+} in cytosol alters Mt and ER aggregation, regulates levels of energetic exchange and biosynthesis (Distelhorst & Shore 2004; Brough, Schell, & Irvine 2005). With decrease in Mt locomotor activity (Hajnóczky *et al.* 2007), their linear aggregation (Mironov 2006) and increase in matrix density are observed – so-called "giant" Mt, which can be found in the liver of hibernating animals and in pathologic conditions. Their formation is a reversible process (Chedid, Jao, & Port 1980; Volkova & Turdyev 1987). Similar morphologic changes are also characteristic for plant and animal cells which have undergone long-term incubation under conditions of low temperature or anoxia (Vartapetian *et al.* 2003).

Thus, increase in La and $(Ca^{2+}i)$ concentrations may serve as a signal for cessation of oxidative processes, reduction in metabolic activity of the major cellular energy producers – Mt, and their restructuring.

Mitochondria and their role in regulating metabolic status of a cell.

Mt are very dynamic organelles. They change the state of the inner membrane, cristae, and morphology of the network depending on the energy state of the cell, actively reproduce and migrate inside the cytosol (Schäfer & Reichert 2009). Currently, bacterial origin of Mt is practically undoubted (Kurland & Andersson 2000; Dyall, Brown, & Johnson 2004). Perhaps, the original ancestors of Mt were parasitic organisms. Very similar in properties and metabolism, parasitic cellular aerobic bacteria Wolbachia, the closest relatives of Mt, are being studied (Oehler, Bourtzis, & International 2011). Unlike Mt, Wolbachia have

their own glycolysis gene, so they are not completely dependent on the host cell under hypoxic conditions, whereas Mt become vulnerable in oxygen depleted environment.

Based on the fact that, in critical conditions, the most ancient defense mechanisms awake (Orbeli 1949), a defense response of bacterial type can be expected from Mt in unfavorable conditions. Under normal conditions, during the Mt life cycle, a mitochondrial permeability transition pore (MTP) opens and closes on their inner membrane, depending on Ca^{2+} dynamics (Petronilli *et al.* 1999). MTP can assume a low-conductivity or a high-conductivity state (Savina 1992). In animals in the state of hibernation, mitochondrial pore is open in the low-conductivity state (Savina 1992). However, in cells of non- hibernating animals, hypoxia-induced disappearance of inter membrane potential leads to opening of MPT in the high-conductivity state and to release of pro-apoptotic proteins from the inner membrane of Mt. This in turn leads to destruction of the outer "host" membrane and apoptosis (Bröker, Kruyt, & Giaccone 2005). Such a mechanism of aggressive impact by the parasitic bacteria on the host cells via release of specific substances has many analogues in the world of protozoa (Bassler & Losick 2006).

It should be highlighted how remarkable the process of apoptosis is. Studies of apoptosis at the ultra-structural level demonstrate that one of the first ultra-structural signs of apoptosis in the cells is fragmentation of Mt inside the outer membrane, while release of caspases occurs after rearranging of Mt cristae into separate compartments. Only after these transformations, swelling of Mt and release of caspases are observed (Sun *et al.* 2007), which may point to initial transformation of Mt inside of the outer membrane and subsequent dissolution of the outer membrane. The next step in the transformation

of Mt is their condensation into very small electron-dense organelles (Goyal *et al.* 2007) with closely packed lamellar structures (Saprunova 2008). Such tiny ultra condensed Mt are found in cells under anoxic conditions (Plattner *et al.* 1970; Solodovnikova *et al.* 2006).

In experiments dealing with introduction of strong cellular protective agents that block apoptosis, or with the use of mitochondrial toxins, an unusual picture was observed – complete disappearance of Mt (Xue, Fletcher, & Tolkovsky 2001). Many small oval or round electron-dense structures surrounded by a single-layer membrane was noted in the cytoplasm. Internally, these structures were composed of densely packed membranes (Lyamzaev *et al.* 2008). Upon incubation of the "free of Mt" cells in a solution without mitochondrial poisons, there was complete restoration of the mitochondrial cellular apparatus, even superior to that prior to poisonous exposure (Saprunova 2008).

Under stressful conditions, most bacteria, both aerobic and anaerobic, form special dormant forms. One of such forms is an endospore. In each of the bacterial cells, a single endospore is usually formed, however, ability of some bacteria to form several spores inside a primary bacterial cells has been discovered (Siunov *et al.* 1999). Interestingly, the genetic material does not pass into an endospore in its entirety. Upon formation of the spore, destruction (lysis) of the "parent" cell wall occurs, and the spore is released into the medium (Gusev & Mineeva 1985). The process of sporulation is reversible during most stages. It can be stopped by substances which inhibit protein synthesis, such as antibiotics (Fajardo-Cavazos & Nicholson 2006). It is possible that ultra-condensed Mt represent exactly these dormant forms. It is not excluded that apoptosis is

not the mechanism of cell's "suicide", but the mechanism of Mt self-preservation.

On the other hand, in animals during hibernation, the opposite changes are observed. Mt coalesce into extended structures - the "giant" Mt with condensed matrix. A specific mitochondrial network is formed. In Mt isolated from the liver of hibernating animals, such a state did not change in response to incubation at elevated temperature and concentration of energy substrate (Brustovetsky *et al.* 1993b). However, Ca^{2+}-dependent activation of respiration of Mt in hepatocytes of a hibernating animal causes swelling of the organelles and increase in respiration (Brustovetsky, Egorova, & Gnutov 1993a), which points to both morphologic and metabolic restructuring of the Mt during hibernation. "Giant" aggregated Mt are very characteristic for the tissue cells of animals both during hibernation and under conditions of hypoxia and hypothermia (Yamada 1968; Vartapetian *et al.* 2003). It is particularly noted that the process of Mt coalescence consists of two stages. The outer membranes merge first. This merge occurs even in conditions of Mt isolation from the cell, which may confirm the ability of Mt to synthesize substances able to dissolve the outer "host" membrane. During the next stage, Mt merge the inner membranes, yielding a unified Mt (Hoppins *et al.* 2009). I.e., the process goes in the opposite direction as compared with the changes taking place in apoptosis. Of note, some single-celled organisms are also able to form colonies within a common mucous membrane (Kirk 2005).

Most likely, concurrent synchronization of the inner membrane potential (Kurz *et al.* 2010) can facilitate the merging process and synchronization of energy supply among all cellular Mt under conditions of reduction of metabolic processes throughout the cell, as well as boosting Mt's ability to transfer information within and between cells.

Adaptive changes in Mt are aimed at minimal energy use and are easily reversible, allowing for transition from one physiologic state to another, which is observed even in isolated Mt (Hackenbrock 1966).

All "behavior" of Mt suggests that, in critical situations, they are able to "take care of themselves". Mt are able to release fragments of their DNA into the cytosol when the pore is open, providing for synthesis of essential proteins (Patrushev *et al.* 2004), and replication of mitochondrial DNA is not inhibited even by irradiation, unlike nuclear DNA (Cleaver 1992).

The level of oxygen consumption by Mt during hibernation can be reduced by more than 80% (Kayes *et al.* 2009). However, in organisms incapable of hypobiosis, ischemia and hypoxia cause a dramatic increase in formation of reactive oxygen species (ROS) in Mt with disruption of the respiratory chain and oxidative phosphorylation. The rate of ROS production is directly dependent on the degree of respiratory chain blockade (Belenichev, Cherniy, & Kolesnik 2009). I.e., absence of a mechanism of coordinated reduction of metabolic function in a cell and Mt is suggested.

Nevertheless, regulation of stress dysfunction of Mt does exist by effects of various substances, including regulatory peptides isolated from resistant to stress animals from widely separated phylogenetic groups (Turdyev *et al.* 1984). This suggests existence of biologically common specific cellular mechanisms responsible for stress endurance.

If the activity of the biochemical reactions catalyzed by enzymes and comprising the metabolic status of an organism is relatively independent of temperature (Hochachka & Somero 2002), the noted difference in enzymatic activity in the mitochondrial

membrane between active and hibernating animals may be related to the physical state of the membranes. Reduction in energy metabolism is accompanied by decrease in membrane permeability (Politoff, Socolar, & Loewenstein 1969). In homeothermic animals capable to hibernation, properties of the mitochondrial membranes during hibernation were similar to those of poikilotherms (Lyons & Raison 1970; Raison *et al.* 1971).

Protective properties of membranes during hibernation.

All cell membranes possess the property of phase transition from a "liquid" to a "solid" state. Phase transition of membrane lipids is a particularly important functional and adaptive property (Hazel 1995). This transition in itself induces a change in the enzymatic activity of proteins (Hazel & Williams 1990). Such changes are quite reversible in stress-resistant and capable of hibernation organisms (Azzam, Hallenbeck, & Kachar 2000).

The temperature which causes phase transition may be raised or lowered, depending on the characteristics of substances which interact with the membranes (Xü *et al.* 1983). Increasing Ca^{2+} concentrations can lead to increase in the temperature of phase transition, pH changes can also initiate phase transition (Pollack & Chin 2008). At the same time, substances with anesthetic properties lower the temperature of phase transition (Heimburg & Jackson 2007; Blicher *et al.* 2009). Thus, phase transition of cell membranes may facilitate changes in ion permeability, activity of enzyme systems, isolation and "conservation" of the cell. However, cell preparation to implementation of this transition, the temperature of the transition, and synchronization of timing of the transition in different parts of the membrane must play critical roles in ensuring preservation of cellular structures

and reversibility of the process. It is known that the temperature of phase transition depends on the fatty acid composition of the membranes. Saturated fatty acids differ from unsaturated ones by higher melting points, while unsaturated fatty acids may reduce the temperature of the transition and ensure "fluidity" of the membranes. Membranes contain both types of fatty acids and changes in their composition alter physical properties of the membranes (Rawicz *et al.* 2000). It is assumed that fatty acid composition of membrane lipids, rather than the phase transition itself, determines cells tolerance to low temperature stress (James *et al.* 1972). In stress-tolerant organisms and those most resistant to low temperature, cells are able to modify their membrane composition during acclimatization and decrease in metabolic rate (Crockett 2008).

Fatty acids, mainly unsaturated, in turn serve as modulators of intracellular signal transfer through activation or inhibition of Ca^{2+} concentration in the cell (Dalton, Hughes, & Barritt 1984), which is a consequence of regulation of permeability of cell membranes and changes in activity of the enzyme system. Of particular interest is uncoupling of respiration and phosphorylation in Mt which is dependent on threshold increase of fatty acid concentration. This effect is found in a specific range of fatty acid concentrations (Vaartjes & Bergh 1978) and may participate in transferring of Mt to another metabolic level.

The opportunity to modulate fatty acid composition of the membranes, as an adaptation to changing environmental conditions, is widely used by homoiotherms, including bacteria. This process was called Homeoviscous adaptation (Sinensky 1974).

In animals unable to hibernate, during decline of body temperature, a sharp increase in the

permeability of cell membranes and intensification of lipid peroxidation occurs (Carey, Andrews, & Martin 2003). In hibernating animals, similarly to poikiloterms, cells regulate membrane permeability (Wang *et al.* 2002). Such regulation is designed to maintain intracellular processes at a low level, to maintain the electrochemical potential of the Mt membranes, maintain membrane permeability to H^+, but to isolate the cell from penetration by damaging agents.

Role of H^+ transport in maintaining organism stability during hibernation

H^+ transfer is one of the most important processes occurring in a living cell and ensuring bioenergetic processes. Uptake and release of Ca^{2+} by the cell membranes is coupled with uptake and release of H^+. Accordingly, cessation of Ca^{2+} uptake by the cell must be accompanied by cessation of H^+ release (Serowy *et al.* 2003). However, animals in hibernating state demonstrate significantly depressed but not completely terminated release of H^+ from the cells (St-Pierre, Brand, & Boutilier 2000; Trzcionka *et al.* 2008), in the background of absent Ca^{2+} uptake. During hypobiosis, inhibition of electron transport chain in the Mt is observed, and release of H^+ from the Mt matrix decreases (Boutilier & St-Pierre 2002; Barger *et al.* 2003), but the proton conductivity of the inner membrane is not reduced during the entire period of hypobiosis (Bishop, St-Pierre, & Brand 2002; Boutilier & St-Pierre 2002), indicating continuation of metabolic processes in Mt at a low level. Loss of proton gradient leads to apoptosis (Kroemer, Dallaporta, & Resche-Rigon 1998).

Phase changes in membrane lipids, facilitating transition of a cell into hypometabolic state, are accompanied by structural changes in the water layer adjacent to the membrane (Steveninck &

Ledeboer 1974). Perhaps, restructuring of the juxta-membrane water layer during the transition of cell cytoplasm into "gel" state provides for alignment of the water molecules into specific "chains" (Decoursey 2003) and is designed to provide instant lateral movement of H^+ and, consequently, transfer of energy and information over long distances. Such a transfer is carried out along membrane surface by "hopping" H^+ via Grotthuss mechanism, i.e. without direct repositioning of water molecules (Cukierman 2006; Markovitch *et al.* 2008). This mechanism is similar to the characteristic mobility of electrons in Fe^{2+}/Fe^{3+} and differs in speed which is several orders of magnitude higher than ion conductivity. Such a mechanism is widespread in bacteria and increases the velocity of signal transfer as well as shortens the "useless" path of H^+ in the external volume (Mulkidjanian *et al.* 2005). There are proven facts of energy coupling between separate Mt during their close contact with each other, because inter-mitochondrial contacts are formed by connecting not only the outer but the inner membranes of contacting Mt (Yaguzhinsky & Krasinskaya 1987). This process can provide unhindered intercellular transport of H^+. Accordingly, while maintaining the H^+ current along the membranes within a cell, between cells, or along the membranes of nerve cells (Osenniy & Kuryndina 1975), an interconnection among all cells may continue, supporting integrity of the organism while minimizing life-sustaining processes intrinsic to hibernation state.

Under assumption that the mitochondrial reticulum represents an intracellular transmission system (Skulachev *et al.* 2004), specific morphological changes in Mt typical for animal cells in hibernation and in hypoxic or hypothermic conditions can be explained. These changes are manifested by formation of extended structures – a

specific mitochondrial network (Brustovetsky *et al.* 1993b).

In bacteria, a similar mechanism exists for communication and coordination of activity in a bacterial community. The mechanism is called "Quorum sensing", since a certain "critical" number of cells in the community is required for its implementation. Information transfer between bacterial cells by Quorum sensing may be achieved in a fraction of a second via electron and H^+ transfer, suggesting possibility of electrical connection between the remote chemical and biological processes (Nielsen *et al.* 2010). It can be assumed that for the mitochondrial network, as a conglomerate of all Mt within an organism, Quorum sensing interaction may be intrinsic and may be carries out via intercellular H^+ transfer. Perhaps, during inhibition of the nervous system function responsible for coordination of metabolism and communication among cells, this function is taken on by the congregated mitochondrial network. Possibly, an analogy exists between mitochondrial reticulum and film-forming bacteria in which something similar to primitive homeostasis and primitive "circulatory system" and metabolic cooperation are observed, ensuring resistance of these microbial communities to the damaging effects which is orders of magnitude greater (Shapiro 1998; Bassler & Losick 2006). Studies of functional activity of isolated Mt (β -oxidation of fatty acids) demonstrated dependency of activity of the process on the concentration of Mt (Vaartjes & Bergh 1978), which may explain increase in the number of Mt under hypoxic and anoxic conditions.

Thus, an analysis of existing evidence leads to conclusion that, in order to implement the mechanisms of cryptobiosis, coordinated and synchronized suppression of metabolic activity of the Mt and the cell is necessary. Violations of synchrony and coordination during suppression or activation of metabolic processes in the cell may result in pathogenesis.

Cancer cell and "arrest" of Mt

Cancer cell (according to Warburg) is a cell with mitochondrial dysfunction which exists at the expense of glycolysis (Warburg 1956), since the original cancer cells develop in a hypoxic microenvironment (Gatenby & Gillies 2004; Marotta *et al.* 2011). Active glycolysis suppresses Mt (Warburg 1956; Bayley & Devilee 2010) and prevents apoptosis (Plas & Thompson 2002). The property of Mt suppression is possessed by some glycolytic enzymes, while oncoproteins produced by tumor cells stimulate increased synthesis of these enzymes (Kim & Dang 2005). There are speculations regarding the origin of cancer as an adaptation to hypoxia resulting from cell's transition to glycolytic metabolic pathway and remodeling of mitochondrial functions (Gatenby & Gillies 2004; Bonnet *et al.* 2007). Hyperpolarization of Mt membranes (Bonnet *et al.* 2007) observed in cancer cells may indicate disruption in proton conductivity and lead to "isolation" of Mt (Potapova 2004). Indeed, changes in cell membranes lead to disruption of intercellular contacts noted in cancer cells and are accompanied by significant reduction in cell membrane potential (Jamakosmanović & Loewenstein 1968; Pointis *et al.* 2010). Moreover, disruption of contacts (connexins) may be different; the level of gap-junction defects varies depending on the stage of progress of cancerous tumor (Cronier *et al.* 2009). At the metastatic stage, intercellular contacts are absent (Bodenstine *et al.* 2011). If intercellular contacts in cancer cells are restored, tumor growth is inhibited (Leithe *et al.* 2006). It is noted that application of bacteria to cancer cells may restore connexins permeability (Saccheri *et al.* 2010). Probably, Mt are able to perceive structurally

similar bacterial signaling molecules and respond to them by activation of metabolism (Basu *et al.* 2008). Thus, hypoxia and subsequent local lactic acidosis may, with prolonged exposure, "reprogram" cells by inhibiting oxidative processes in Mt and blocking apoptosis (Lemasters *et al.* 1998; Gatenby & Gillies 2004). Inhibition of mitochondrial oxidative metabolism must be constantly maintained in the tumor, which may be accomplished by increase in synthesis of oncoproteins and cytokines in a growing mass (Viola & Bronte 2007). If oxidative processes in the Mt were activated, generated ROS would stimulate apoptosis in the cancer cells (Strathmann *et al.* 2010). Experiments with Mt extracted from the cells of animals during hibernation are described above. With increases in temperature and supplies with energy substrates, Mt have not increased their metabolism (Brustovetsky *et al.* 1993b), although sensitivity of the cells to changes in Ca^{2+} concentration is so high that even a single spike of (Ca^{2+} m) causes a complex sequence of changes aimed at activation of mitochondrial oxidative metabolism (Robb-Gaspers *et al.* 1998). Probably, this particular property and this sensitivity ensure the ability of animals in hibernation to respond to the most subtle awakening signals from the environment. However, in order to implement such a mechanism, it is necessary to maintain intercellular contacts. It seems that in the case of cancerous transformation within a cell, we are dealing with disruption of onset of the hypometabolic state when Mt have already passed all phases of activity reduction, have been transferred into a metabolic pathway corresponding to the hypobiotic state, and restructuring of cellular membranes preventing intercellular interactions have been carried out, but glycolysis in the cytosol has not been terminated or reactivated. Accordingly, two effective methods of influence on the cancer

cell can be expected: activation ("arousal") of Mt, leading the cell to apoptosis (Bonnet *et al.* 2007), or inhibition of the metabolic activity – glycolysis ("sleep") of a cell, transforming it into the same hypometabolic state which Mt are in (Allegrucci *et al.* 2011). Either method requires the use of specific signaling substances.

Apoptosis and the "survival instinct" of Mt

In apoptosis under hypoxic conditions, it seems, there are changes which are opposite to those in a cancer cell. Short-term initial blockade of the electron transport chain in Mt is replaced by its activation. However, due to glycolysis, decrease in pH and increase in (Ca^{2+} i) are observed in a cell (Lipton 1999). These changes should accompany phase transitions of cell membranes, disruption of their elasticity and permeability, changes in the colloidal properties of the cytoplasm, which, in turn, serve as a barrier to locomotor activity and metabolite exchange in Mt. For Mt, stressful conditions are created. Perhaps, such a situation stimulates activation of bacterial defense mechanisms in Mt, leading Mt to "sporogenesis", release of specific substances which dissolve the outer membrane, and to cell apoptosis.

Conclusions

On the basis of common metabolic changes that occur during the transition into hypometabolic state and in response to critical stress, presence in each cell of a specific mechanism ensuring transition of the cell into an autonomic state under conditions critical for survival can be assumed. However, in order to activate the tolerant survival strategy at the cellular level, a specific alteration is necessary, ensuring decline of functional activity of Mt as well as of the cell in general. Probably, this strategy has a genetically determined basis in the form of coordinated expression of a gene network specific

for implementation of the tolerant strategy. Existence of specific signaling substances functioning in a manner of a "switch" between the states of the gene network (Kolpakov *et al.* 1998) is necessary for such coordination. Most likely, such substances ("shunters"), due to routinely being in demand, are continuously present in cells of animals capable of hibernation and other types of hypobiosis. Search for these substances and their investigation is an extremely important area of research in biology and medicine. Perhaps, such substances can be formed in the cells of non-hibernating animals in critical life-threatening conditions or during training preconditioning. However, in order to implement the tolerant strategy for surviving in adverse conditions by non-hibernating animals, prior preparation and restructuring on the cellular level as well as on the level of the whole organism is required. Such adjustments can often be mistaken for pathologic manifestations and require multifaceted investigation.

If a hypothesis of simultaneous symbiotic and competitive relationship between the Mt and the cell is accepted, four possible types of a cell's state can be suggested.

Normal functional activity of the cell – distribution of functions, reciprocal control, active metabolism and energy exchange among the cell, Mt and extracellular medium. This state is possible under conditions of controlled membrane permeability, colloidal state of the cytoplasm, and intact motor and communicational activity of Mt.

Apoptosis – under stressful for Mt conditions, "ancient" bacterial mechanisms are recruited, facilitating Mt transition into a "spore-like" state, and, perhaps, reverse reactivation within the cells that engulf them.

Cancer cell – transition of Mt into hypometabolic state caused by prolonged hypoxic conditions. Violation of intercellular and inter-mitochondrial contacts in the background of preserved or restored active cellular glycolysis.

Hibernation (Cryptobiosis) – providing a cell with energy substrates for long-term autonomy and subsequent metabolic activation, synchronous decrease in metabolism of the cell and Mt, specific adjustments of cell membranes retaining permeability to H^+.

Of course, the above listed states are not absolute; they are flexible and, under certain conditions, reversible.

REFERENCES

Alexandrov, Y.I., Anokhin, K.V., Bezdenezhnykh, B.N., Garin, N.S., Grechenko, T.N., Latanov, A.V., Palihova, T.A., Savel'ev, S.V., Sokolov, E.N., Tushmalova, N.A., Filipov, V.A. & Chernorizov, A.M. (2008) *Neuron. Signal Processing. Plasticity. Modeling.* TSU, Tyumen.

Allegrucci, C., Rushton, M.D., Dixon, J.E., Sottile, V., Shah, M., Kumari, R., Watson, S., Alberio, R. & Johnson, A.D. (2011) Epigenetic Reprogramming of Breast Cancer Cells with Oocyte Extracts. *Molecular Cancer*, **10**, 7–8.

Anoshkina, I. (2005) *The Role of Monoaminergic Brain Systems in the Mechanisms of Behavior Regulation of Ground Squirrels (Citellus Undulatus)*. Dis. Cand. Biol. Science, Pushchino.

Appenzeller, O. & Oribe, E. (1997) *The Autonomic Nervous System: An Introduction to Basic and Clinical Concepts*. Elsevier Health Sciences.

Aubert, A., Costalat, R., Magistretti, P.J. & Pellerin, L. (2005) Brain Lactate Kinetics: Modeling Evidence for Neuronal Lactate Uptake Upon Activation. *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 16448–16453.

Azzam, N.A., Hallenbeck, J.M. & Kachar, B. (2000) Membrane Changes During Hibernation. *Nature*, **407**, 317–318.

Backer, D.D., Biston, P., Devriendt, J., Madl, C., Chochrad, D., Aldecoa, C., Brasseur, A., Defrance, P., Gottignies, P. & Vincent, J.-L. (2010) Comparison of Dopamine and Norepinephrine in the Treatment of Shock. *The New England Journal of Medicine*, **362**, 779–789.

Baker, P.F., Hodgkin, A.L. & Ridgway, E.B. (1971) Depolarization and Calcium Entry in Squid Giant Axons. *The Journal of Physiology*, **218**, 709–755.

Barger, J.L., Brand, M.D., Barnes, B.M. & Boyer, B.B. (2003) Tissue-specific Depression of Mitochondrial Proton Leak and Substrate Oxidation in Hibernating Arctic Ground Squirrels. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, **284**, R1306–1313.

Bari, L.D., Atlante, A., Valenti, D. & Passarella, S. (2004) Partial Reconstruction of in Vitro Gluconeogenesis Arising from Mitochondrial L-lactate Uptake/metabolism and Oxaloacetate Export via Novel L-lactate Translocators. *The Biochemical Journal*, **380**, 231–242.

Bassler, B.L. & Losick, R. (2006) Bacterially Speaking. *Cell*, **125**, 237–246.

Basu, S., Mukherjee, S. & Adhya, S. (2008) Proton-guided Movements of tRNA Within the Leishmania Mitochondrial RNA Import Complex. *Nucleic Acids Research*, **36**, 1599–1609.

Baulieu, E.-E. (1990) *Hormones□: From Molecules to Disease*. Hermann□;;Chapman and Hall, Paris□;New York.

Bayley, J.-P. & Devilee, P. (2010) Warburg Tumours and the Mechanisms of Mitochondrial Tumour Suppressor Genes. Barking up the Right Tree? *Current Opinion in Genetics & Development*, **20**, 324–329.

Belenichev, I.F., Cherniy, V.I. & Kolesnik, Y.M. (2009) *Rational Neuroprotection*. Publisher Zaslavsky A., Donetsk.

Benedict, C.R. & Grahame-Smith, D.G. (1978) Plasma Noradrenaline and Adrenaline Concentrations and Dopamine-beta-hydroxylase Activity in Patients with Shock Due to Septicaemia, Trauma and Haemorrhage. *The Quarterly Journal of Medicine*, **47**, 1–20.

Bickler, P.E. & Buck, L.T. (2007) Hypoxia Tolerance in Reptiles, Amphibians, and Fishes: Life with Variable Oxygen Availability. *Annual Review of Physiology*, **69**, 145–170.

Bishop, T., St-Pierre, J. & Brand, M.D. (2002) Primary Causes of Decreased Mitochondrial Oxygen Consumption During Metabolic Depression in Snail Cells. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, **282**, R372–382.

Blanco, M.B. & Rahalinarivo, V. (2010) First Direct Evidence of Hibernation in an Eastern Dwarf Lemur Species (Cheirogaleus Crossleyi) from the High-altitude Forest of Tsinjoarivo, Central-eastern Madagascar. *Naturwissenschaften*, **97**, 945–950.

Blicher, A., Wodzinska, K., Fidorra, M., Winterhalter, M. & Heimburg, T. (2009) The Temperature Dependence of Lipid Membrane Permeability, Its Quantized Nature, and the Influence of Anesthetics. *Biophysical Journal*, **96**, 4581–4591.

Bodenstine, T.M., Vaidya, K.S., Ismail, A., Beck, B.H., Cook, L.M., Diers, A.R., Landar, A. & Welch, D.R. (2011) Homotypic Gap Junctional Communication Associated with Metastasis Suppression Increases with PKA Activity and Is Unaffected by PI3K Inhibition. *Cancer Research*, **70**, 1–10.

Bonnet, S., Archer, S.L., Allalunis-Turner, J., Haromy, A., Beaulieu, C., Thompson, R., Lee, C.T., Lopaschuk, G.D., Puttagunta, L., Bonnet, S., Harry, G., Hashimoto, K., Porter, C.J., Andrade, M.A., Thebaud, B. & Michelakis, E.D. (2007) A mitochondria-K+ Channel Axis Is Suppressed in Cancer and Its Normalization Promotes Apoptosis and Inhibits Cancer Growth. *Cancer Cell*, **11**, 37–51.

Boumezbeur, F., Petersen, K.F., Cline, G.W., Mason, G.F., Behar, K.L., Shulman, G.I. & Rothman, D.L. (2010) The Contribution of Blood Lactate to Brain Energy Metabolism in Humans Measured by Dynamic 13C Nuclear Magnetic Resonance Spectroscopy. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **30**, 13983–13991.

Boutilier, R.G. & St-Pierre, J. (2002) Adaptive Plasticity of Skeletal Muscle Energetics in Hibernating Frogs: Mitochondrial Proton Leak During Metabolic Depression. *The Journal of Experimental Biology*, **205**, 2287–2296.

Boyle, D.W., Meschia, G. & Wilkening, R.B. (1992) Metabolic Adaptation of Fetal Hindlimb to Severe, Nonlethal Hypoxia. *The American Journal of Physiology*, **263**, R1130–1135.

Bröker, L.E., Kruyt, F.A.E. & Giaccone, G. (2005) Cell Death Independent of Caspases: A Review. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, **11**, 3155–3162.

Brooks, G.A., Dubouchaud, H., Brown, M., Sicurello, J.P. & Butz, C.E. (1999) Role of Mitochondrial Lactate Dehydrogenase and Lactate Oxidation in the Intracellular Lactate Shuttle. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 1129–1134.

Brooks, G.A. & Hashimoto, T. (2007) Investigation of the Lactate Shuttle in Skeletal Muscle Mitochondria. *The Journal of Physiology*, **584**, 705–706.

Brough, D., Schell, M.J. & Irvine, R.F. (2005) Agonist-induced Regulation of Mitochondrial and Endoplasmic Reticulum Motility. *Biochemical Journal*, **392**, 291–297.

Brustovetsky, N.N., Egorova, M.V. & Gnutov, D.Y. (1993a) The Mechanism of Calcium-dependent Activation of Respiration of Liver Mitochondria from Hibernating Ground Squirrels, Citellus Undulatus. *Comparative Biochemistry and Physiology. B, Comparative Biochemistry*, **106**, 423–426.

Brustovetsky, N., Egorova, M., Iljasova, E. & Bakeeva, L. (1993b) Relationship Between Structure and Function of Liver Mitochondria from Hibernating and Active Ground Squirrels, Citellus Undulatus. *Comparative Biochemistry and Physiology Part B:*

Biochemistry and Molecular Biology, **106**, 125–130.

Buja, L.M., Burton, K.P., Hagler, H.K. & Willerson, J.T. (1983) Quantitative X-ray Microanalysis of the Elemental Composition of Individual Myocytes in Hypoxic Rabbit Myocardium. *Circulation*, **68**, 872–882.

Carey, H.V., Andrews, M.T. & Martin, S.L. (2003) Mammalian Hibernation: Cellular and Molecular Responses to Depressed Metabolism and Low Temperature. *Physiological Reviews*, **83**, 1153–1181.

Chatham, J.C., Rosiers, C.D. & Forder, J.R. (2001) Evidence of Separate Pathways for Lactate Uptake and Release by the Perfused Rat Heart. *American Journal of Physiology. Endocrinology and Metabolism*, **281**, E794–802.

Chedid, A., Jao, W. & Port, J. (1980) Megamitochondria in Hepatic and Renal Disease. *The American Journal of Gastroenterology*, **73**, 319–324.

Chesler, M. (2003) Regulation and Modulation of pH in the Brain. *Physiological Reviews*, **83**, 1183–1221.

Cleaver, J.E. (1992) Replication of Nuclear and Mitochondrial DNA in X-ray-damaged Cells: Evidence for a Nuclear-specific Mechanism That Down-regulates Replication. *Radiation Research*, **131**, 338–344.

Cramp, R.L., Kayes, S.M., Meyer, E.A. & Franklin, C.E. (2009) Ups and Downs of Intestinal Function with Prolonged Fasting During Aestivation in the Burrowing Frog, Cyclorana Alboguttata. *The Journal of Experimental Biology*, **212**, 3656–3663.

Crockett, E.L. (2008) The Cold but Not Hard Fats in Ectotherms: Consequences of Lipid Restructuring on Susceptibility of Biological Membranes to Peroxidation, a Review. *Journal of Comparative Physiology. B, Biochemical, Systemic, and Environmental Physiology*, **178**, 795–809.

Cronier, L., Crespin, S., Strale, P.-O., Defamie, N. & Mesnil, M. (2009) Gap Junctions and Cancer: New Functions for an Old Story. *Antioxidants & Redox Signaling*, **11**, 323–338.

Csordás, G., Várnai, P., Golenár, T., Roy, S., Purkins, G., Schneider, T.G., Balla, T. & Hajnyczky, G. (2010) Imaging Interorganelle Contacts and Local Calcium Dynamics at the ER-mitochondrial Interface. *Molecular Cell*, **39**, 121–132.

Cukierman, S. (2006) Et Tu, Grotthuss! and Other Unfinished Stories. *Biochimica Et Biophysica Acta*, **1757**, 876–885.

Dalton, S., Hughes, B.P. & Barritt, G.J. (1984) Effects of Lysophospholipids on Ca^{2+} Transport in Rat Liver Mitochondria Incubated at Physiological Ca^{2+} Concentrations in the Presence of Mg^{2+}, Phosphate and ATP at 37 Degrees C. *The Biochemical Journal*, **224**, 423–430.

Decoursey, T.E. (2003) Voltage-gated Proton Channels and Other Proton Transfer Pathways. *Physiological Reviews*, **83**, 475–579.

Desborough, J.P. (2000) The Stress Response to Trauma and Surgery. *British Journal of Anaesthesia*, **85**, 109–117.

Devi, B.G., Habeebullah, C.M. & Gupta, P.D. (1992) Glycogen Metabolism During Human Liver Development. *Biochemistry International*, **28**, 229–237.

Distelhorst, C.W. & Shore, G.C. (2004) Bcl-2 and Calcium: Controversy Beneath the Surface. *Oncogene*, **23**, 2875–2880.

Drew, K.L., Rice, M.E., Kuhn, T.B. & Smith, M.A. (2001) Neuroprotective Adaptations in Hibernation: Therapeutic Implications for Ischemia-reperfusion, Traumatic Brain Injury and Neurodegenerative Diseases. *Free Radical Biology & Medicine*, **31**, 563–573.

Duchen, M.R. (2000) Mitochondria and Calcium: From Cell Signalling to Cell Death. *The Journal of Physiology*, **529 Pt 1**, 57–68.

Dunser, M.W. & Hasibeder, W.R. (2009) Sympathetic Overstimulation During Critical Illness: Adverse Effects of Adrenergic Stress. *Journal of Intensive Care Medicine*, **24**, 293–316.

Dyall, S.D., Brown, M.T. & Johnson, P.J. (2004) Ancient Invasions: From Endosymbionts to Organelles. *Science (New York, N.Y.)*, **304**, 253–257.

Ereciska, M., Nelson, D., Dagani, F., Deas, J. & Silver, I.A. (1993) Relations Between Intracellular Ions and Energy Metabolism Under Acidotic Conditions: A Study with Nigericin in Synaptosomes, Neurons, and C6 Glioma Cells. *Journal of Neurochemistry*, **61**, 1356–1368.

Fajardo-Cavazos, P. & Nicholson, W. (2006) Bacillus Endospores Isolated from Granite: Close Molecular Relationships to Globally Distributed Bacillus Spp. from Endolithic and Extreme Environments. *Applied and Environmental Microbiology*, **72**, 2856–2863.

Feofilova, E.P. (2003) [Deceleration of Vital Activity as a Universal Biochemical Mechanism Ensuring Adaptation of Microorganisms to Stress Factors: A Review]. *Prikladnaia Biokhimiia I Mikrobiologiia*, **39**, 5–24.

Filippin, L., Magalhães, P.J., Benedetto, G.D., Colella, M. & Pozzan, T. (2003) Stable Interactions Between Mitochondria and Endoplasmic Reticulum Allow Rapid Accumulation of Calcium in a Subpopulation of Mitochondria. *The Journal of Biological Chemistry*, **278**, 39224–39234.

Frerichs, K.U., Smith, C.B., Brenner, M., DeGracia, D.J., Krause, G.S., Marrone, L., Dever, T.E. & Hallenbeck, J.M. (1998) Suppression of Protein Synthesis in Brain During Hibernation Involves Inhibition of Protein Initiation and Elongation. *Proceedings of the National Academy of Sciences of the United States of America*, **95**, 14511–14516.

Gatenby, R.A. & Gillies, R.J. (2004) Why Do Cancers Have High Aerobic Glycolysis? *Nat Rev Cancer*, **4**, 891–899.

Goldovsky, A.M. (1981) *Anabiosis*. Science, L.

Goyal, G., Fell, B., Sarin, A., Youle, R.J. & Sriram, V. (2007) Role of Mitochondrial Remodeling in Programmed Cell Death in Drosophila Melanogaster. *Developmental Cell*, **12**, 807–816.

Gupte, V.G. (1968) Glycogen Rhythm in the Embryonic Liver of the Goat. *Histochemistry and Cell Biology*, **15**, 79-83.

Gusev, M.V. & Mineeva, L.A. (1985) *Microbiology*. Univ Press, M.

Hackenbrock, C.R. (1966) Ultrastructural Bases for Metabolically Linked Mechanical Activity in Mitochondria. I. Reversible Ultrastructural Changes with Change in Metabolic Steady State in Isolated Liver Mitochondria. *J Cell Biol*, **30**, 269–297.

Hajnóczky, G., Saotome, M., Csordás, G., Weaver, D. & Yi, M. (2007) Calcium Signalling and Mitochondrial Motility. *Novartis Foundation Symposium*, **287**, 105–121.

Hardaway, R.M. (2006) Traumatic Shock. *Military Medicine*, **171**, 278–279.

Hazel, J.R. (1995) Thermal Adaptation in Biological Membranes: Is Homeoviscous Adaptation the Explanation? *Annual Review of Physiology*, **57**, 19–42.

Hazel, J.R. & Williams, E.E. (1990) The Role of Alterations in Membrane Lipid Composition in Enabling Physiological Adaptation of Organisms to Their Physical Environment. *Progress in Lipid Research*, **29**, 167–227.

Heimburg, T. & Jackson, A.D. (2007) The Thermodynamics of General Anesthesia. *Biophysical Journal*, **92**, 3159–3165.

Hochachka, P.W. & Somero, G.N. (2002) *Biochemical Adaptation: Mechanism and Process in Physiological Evolution*, 1st ed. Oxford University Press, USA.

Hoppins, S., Horner, J., Song, C., McCaffery, J.M. & Nunnari, J. (2009) Mitochondrial Outer and Inner Membrane Fusion Requires a Modified Carrier Protein. *J Cell Biol*, **184**, 569–581.

Isaacson, J.S., Solís , J.M. & Nicoll, R.A. (1993) Local and Diffuse Synaptic Actions of GABA in the Hippocampus. *Neuron*, **10**, 165–175.

Jackson, D.C. (2002) Hibernating Without Oxygen: Physiological Adaptations of the Painted Turtle. *The Journal of Physiology*, **543**, 731–737.

Jamakosmanović, A. & Loewenstein, W.R. (1968) Intercellular Communication and Tissue Growth. 3. Thyroid Cancer. *J Cell Biol*, **38**, 556–561.

James, R., Branton, D., Wisnieski, B. & Keith, A. (1972) Composition, Structure and Phase Transition in Yeast Fatty Acid Auxotroph Membranes: Spin Labels and Freeze-fracture. *Journal of Supramolecular Structure*, **1**, 38–49.

Kandel, E., Schwartz, J. & Jessell, T. (2000) *Principles of Neural Science*, 4th ed. McGraw-Hill Medical.

Kayes, S.M., Cramp, R.L., Hudson, N.J. & Franklin, C.E. (2009) Surviving the Drought: Burrowing Frogs Save Energy by Increasing Mitochondrial Coupling. *J Exp Biol*, **212**, 2248–2253.

Kelly, D.A. & Storey, K.B. (1988) Organ-specific Control of Glycolysis in Anoxic Turtles. *The American Journal of Physiology*, **255**, R774–779.

Kim, J.-W. & Dang, C.V. (2005) Multifaceted Roles of Glycolytic Enzymes. *Trends in Biochemical Sciences*, **30**, 142–150.

Kirk, D.L. (2005) *Volvox: A Search for the Molecular and Genetic Origins of Multicellularity and Cellular Differentiation*. Cambridge University Press.

Kolpakov, F.A., Ananko, E.A., Kolesov, G.B. & Kolchanov, N.A. (1998) GeneNet: A Gene Network Database and Its Automated Visualization. *Bioinformatics (Oxford, England)*, **14**, 529–537.

Kroemer, G., Dallaporta, B. & Resche-Rigon, M. (1998) The Mitochondrial Death/life Regulator in Apoptosis and Necrosis. *Annual Review of Physiology*, **60**, 619–642.

Kulinsky, V.I. & Olhovsky, I.A. (1992) Two Adaptive Strategies in Adverse Conditions - Resistant and Tolerant. The Role of Hormones and Receptors. *Achievents in modern biology*, **5-6**, 697–714.

Kurland, C.G. & Andersson, S.G. (2000) Origin and Evolution of the Mitochondrial Proteome. *Microbiology and Molecular Biology Reviews: MMBR*, **64**, 786–820.

Kurz, F.T., Aon, M.A., O'Rourke, B. & Armoundas, A.A. (2010) Spatio-temporal Oscillations of Individual Mitochondria in Cardiac Myocytes Reveal Modulation of Synchronized Mitochondrial Clusters. *Proceedings of the National Academy of Sciences of the United States of America*, **107**, 14315–14320.

Leithe, E., Sirnes, S., Omori, Y. & Rivedal, E. (2006) Downregulation of Gap Junctions in Cancer Cells. *Critical Reviews in Oncogenesis*, **12**, 225–256.

Lemasters, J.J., Nieminen, A.L., Qian, T., Trost, L.C., Elmore, S.P., Nishimura, Y., Crowe, R.A., Cascio, W.E., Bradham, C.A., Brenner, D.A. & Herman, B. (1998) The Mitochondrial Permeability Transition in Cell Death: A Common Mechanism in Necrosis, Apoptosis and Autophagy. *Biochimica Et Biophysica Acta*, **1366**, 177–196.

Lewis, A.M. (2000) Trauma Triad of Death. Emergency! *Nursing*, **30**, 62–64.

Lipton, P. (1999) Ischemic Cell Death in Brain Neurons. *Physiological Reviews*, **79**, 1431–1568.

Lokotko, V.O. (1949) *Relationship of Cardiac and Respiratory Function in Cold-blooded and Warm-blooded Animals During Changes in Their Body Temperature*. TomskGU, Tomsk.

Lyamzaev, K.G., Nepryakhina, O.K., Saprunova, V.B., Bakeeva, L.E., Pletjushkina, O.Y., Chernyak, B.V. & Skulachev, V.P. (2008) Novel Mechanism of Elimination of Malfunctioning Mitochondria (mitoptosis): Formation of Mitoptotic Bodies and Extrusion of Mitochondrial Material from the Cell. *Biochim Biophys Acta*, **1777**, 817–825.

Lyons, J. & Raison, J. (1970) A Temperature-induced Transition in Mitochondrial Oxidation: Contrasts Between Cold and Warm-blooded Animals. *Comparative Biochemistry and Physiology*, **37**, 405–411.

Magarinos, A.M., McEwen, B.S., Saboureau, M. & Pevet, P. (2006) Rapid and Reversible Changes in Intrahippocampal Connectivity During the Course of Hibernation in European Hamsters. *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 18775–18780.

Malan, A., Rodeau, J.L. & Daull, F. (1985) Intracellular pH in Hibernation and Respiratory Acidosis in the European Hamster. *Journal of Comparative Physiology. B, Biochemical, Systemic, and Environmental Physiology*, **156**, 251–258.

Malan, A. national de la santé et de la recherche médicale I. (1989) Living in the Cold. *2nd International Symposium : proceedings of the Second Symposium on Living in the Cold* p. John Libbey Eurotext, Le Hohwald France.

Malatesta, M., Zancanaro, C., Baldelli, B. & Gazzanelli, G. (2002) Quantitative Ultrastructural Changes of Hepatocyte Constituents in Euthermic, Hibernating and

Arousing Dormice (Muscardinus Avellanarius). *Tissue & Cell*, **34**, 397–405.

Margolis, R.N. (1983) Regulation of Hepatic Glycogen Metabolism in Pre- and Postnatal Rats. *Endocrinology*, **113**, 893–902.

Markovitch, O., Chen, H., Izvekov, S., Paesani, F., Voth, G.A. & Agmon, N. (2008) Special Pair Dance and Partner Selection: Elementary Steps in Proton Transport in Liquid Water. *The Journal of Physical Chemistry. B*, **112**, 9456–9466.

Marotta, D., Karar, J., Jenkins, W.T., Kumanova, M., Jenkins, K.W., Tobias, J.W., Baldwin, D., Hatzigeorgiou, A., Alexiou, P., Evans, S.M., Alarcon, R., Maity, A., Koch, C. & Koumenis, C. (2011) In Vivo Profiling of Hypoxic Gene Expression in Gliomas Using the Hypoxia Marker EF5 and Laser-capture Microdissection. *Cancer Research*, **71**, 779–789.

Mazurkiewicz, G. & Bagnenko, S.F. (2004) *Shock*. Politehnica, Saint-Petersburg.

Mironov, S.L. (2006) Spontaneous and Evoked Neuronal Activities Regulate Movements of Single Neuronal Mitochondria. *Synapse (New York, N.Y.)*, **59**, 403–411.

Mulkidjanian, A.Y., Cherepanov, D.A., Heberle, J. & Junge, W. (2005) Proton Transfer Dynamics at Membrane/water Interface and Mechanism of Biological Energy Conversion. *Biochemistry. BiokhimiiHY̆a*, **70**, 251–256.

Nicotera, P., McConkey, D.J., Jones, D.P. & Orrenius, S. (1989) ATP Stimulates Ca^{2+} Uptake and Increases the Free Ca^{2+} Concentration in Isolated Rat Liver Nuclei. *Proceedings of the National Academy of Sciences of the United States of America*, **86**, 453–457.

Nielsen, L.P., Risgaard-Petersen, N., Fossing, H., Christensen, P.B. & Sayama, M. (2010) Electric Currents Couple Spatially Separated Biogeochemical Processes in Marine Sediment. *Nature*, **463**, 1071–1074.

Nilsson, G.E. (1990) Long-term Anoxia in Crucian Carp: Changes in the Levels of Amino Acid and Monoamine Neurotransmitters in the Brain, Catecholamines in Chromaffin Tissue, and Liver Glycogen. *The Journal of Experimental Biology*, **150**, 295–320.

Oehler, S., Bourtzis, K. & International, C.A.B. (2011) First International Wolbachia Conference – Wolbachia 2000.

Orbeli, L.A. (1949) *Issues in Higher Nervous Function*. AN USSR, Moscow-Leningrad.

Osenniy, A.S. & Kuryndina, N.K. (1975) Studies on Identification of Longitudinal Electric Current in the Nerve of a Frog. *Biofizika*, **20**, 78 – 81.

Padilla, P.A., Nystul, T.G., Zager, R.A., Johnson, A.C.M. & Roth, M.B. (2002) Dephosphorylation of Cell Cycle-regulated Proteins Correlates with Anoxia-induced Suspended Animation in Caenorhabditis Elegans. *Molecular Biology of the Cell*, **13**, 1473–1483.

Patrushev, M., Kasymov, V., Patrusheva, V., Ushakova, T., Gogvadze, V. & Gaziev, A. (2004) Mitochondrial Permeability Transition Triggers the Release of mtDNA Fragments. *Cellular and Molecular Life Sciences: CMLS*, **61**, 3100–3103.

Petronilli, V., Miotto, G., Canton, M., Brini, M., Colonna, R., Bernardi, P. & Lisa, F.D. (1999) Transient and Long-lasting Openings of the

Mitochondrial Permeability Transition Pore Can Be Monitored Directly in Intact Cells by Changes in Mitochondrial Calcein Fluorescence. *Biophysical Journal*, **76**, 725–734.

Philp, A., Macdonald, A.L. & Watt, P.W. (2005) Lactate – a Signal Coordinating Cell and Systemic Function. *The Journal of Experimental Biology*, **208**, 4561–4575.

Plas, D.R. & Thompson, C.B. (2002) Cell Metabolism in the Regulation of Programmed Cell Death. *Trends in Endocrinology and Metabolism: TEM*, **13**, 75–78.

Plattner, H., Salpeter, M.M., Saltzgaber, J. & Schatz, G. (1970) Promitochondria of Anaerobically Grown Yeast, IV. Conversion into Respiring Mitochondria. *Proceedings of the National Academy of Sciences of the United States of America*, **66**, 1252–1259.

Podrabsky, J.E., Lopez, J.P., Fan, T.W.M., Higashi, R. & Somero, G.N. (2007) Extreme Anoxia Tolerance in Embryos of the Annual Killifish Austrofundulus Limnaeus: Insights from a Metabolomics Analysis. *The Journal of Experimental Biology*, **210**, 2253–2266.

Pointis, G., Gilleron, J., Carette, D. & Segretain, D. (2010) Physiological and Physiopathological Aspects of Connexins and Communicating Gap Junctions in Spermatogenesis. *Philos Trans R Soc Lond B Biol Sci*, **365**, 1607–1620.

Pokrovsky, V.M. & Korotko, G.F. (1998) *Human Physiology*. Medicine.

Polianchikova, O.L., Cherniakhovskii, O.B., Kuznetsova, V.A. & Abramova, I.V. (2009) [Clinical Significance of the Determination of Blood Lactate in Perinatology]. *Klin Lab Diagn*, 7–9.

Politoff, A.L., Socolar, S.J. & Loewenstein, W.R. (1969) Permeability of a Cell Membrane Junction. Dependence on Energy Metabolism. *The Journal of General Physiology*, **53**, 498–515.

Pollack, G.H. (2001) *Cells, Gels and the Engines of Life*, 1st ed. Ebner and Sons Publishers.

Pollack, G.H. & Chin, W.-C. (2008) *Phase Transitions in Cell Biology*, 1st ed. Springer.

Pories, W.J., Harris, P.D., Hinshaw, J.R., Davis, T.P. & Schwartz, S.I. (1962) Blood Sludging: An Experimental Critique of Its Occurrence and Its Supposed Effects. *Ann Surg*, **155**, 33–41.

Potapova, T.V. (2004) Intercellular Interactions in Hyphae of Neurospora Crassa: Twenty Years Later. *Biologicheskie Membrany*, **21**, 304–312.

Quistorff, B., Secher, N.H. & Lieshout, J.J.V. (2008) Lactate Fuels the Human Brain During Exercise. *The FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, **22**, 3443–3449.

Qvisth, V., Hagström-Toft, E., Enoksson, S. & Bolinder, J. (2008) Catecholamine Regulation of Local Lactate Production in Vivo in Skeletal Muscle and Adipose Tissue: Role of β-Adrenoreceptor Subtypes. *The Journal of Clinical Endocrinology and Metabolism*, **93**, 240–246.

Raison, J.K., Lyons, J.M., Mehlhorn, R.J. & Keith, A.D. (1971) Temperature-induced Phase Changes in Mitochondrial Membranes Detected by Spin Labeling. *Journal of Biological Chemistry*, **246**, 4036 –4040.

Randall, G.C. & L'Ecuyer, C. (1976) Tissue Glycogen and Blood Glucose and Fructose Levels in the Pig Fetus During the Second Half of Gestation. *Biology of the Neonate*, **28**, 74–82.

Rawicz, W., Olbrich, K.C., McIntosh, T., Needham, D. & Evans, E. (2000) Effect of Chain Length and Unsaturation on Elasticity of Lipid Bilayers. *Biophysical Journal*, **79**, 328–339.

Robb-Gaspers, L.D., Burnett, P., Rutter, G.A., Denton, R.M., Rizzuto, R. & Thomas, A.P. (1998) Integrating Cytosolic Calcium Signals into Mitochondrial Metabolic Responses. *The EMBO Journal*, **17**, 4987–5000.

Roots, C. (2006) *Hibernation*. Greenwood.

Rosati, E., Sabatini, R., Rampino, G., Falco, F.D., Ianni, M.D., Falzetti, F., Fettucciari, K., Bartoli, A., Screpanti, I. & Marconi, P. (2010) Novel Targets for Endoplasmic Reticulum Stress-induced Apoptosis in B-CLL. *Blood*, **116**, 2713–2723.

Roth, E. & Oehler, R. (2010) Hypothesis: Muscular Glutamine Deficiency in Sepsis–a Necessary Step for a Hibernation-like State? *Nutrition*, **26**, 571–574.

Saccheri, F., Pozzi, C., Avogadri, F., Barozzi, S., Faretta, M., Fusi, P. & Rescigno, M. (2010) Bacteria-Induced Gap Junctions in Tumors Favor Antigen Cross-Presentation and Antitumor Immunity. *Science Translational Medicine*, **2**, 44ra57–44ra57.

Saprunova, V.B. (2008) *Ultrastructure of Mitochondria Under Conditions of Oxidative Stress*. Diss.dokt.biol.nauk, M.

Savina, M.V. (1992) *Adaptive Mechanisms of Tissue Respiration in Evolution of Vertebrates*. Nauka, S.-Peterburgskoe otd-nie, Saint-Petersburg.

Schäfer, A. & Reichert, A.S. (2009) Emerging Roles of Mitochondrial Membrane Dynamics in Health and Disease. *Biological Chemistry*, **390**, 707–715.

Selye, H. (1998) A Syndrome Produced by Diverse Nocuous Agents. 1936. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **10**, 230–231.

Serowy, S., Saparov, S.M., Antonenko, Y.N., Kozlovsky, W., Hagen, V. & Pohl, P. (2003) Structural Proton Diffusion Along Lipid Bilayers. *Biophysical Journal*, **84**, 1031–1037.

Shapiro, J.A. (1998) Thinking About Bacterial Populations as Multicellular Organisms. *Annual Review of Microbiology*, **52**, 81–104.

Simpson, I.A., Carruthers, A. & Vannucci, S.J. (2007) Supply and Demand in Cerebral Energy Metabolsm: The Role of Nutrient Transporters. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, **27**, 1766–1791.

Sinensky, M. (1974) Homeoviscous Adaptation–a Homeostatic Process That Regulates the Viscosity of Membrane Lipids in Escherichia Coli. *Proceedings of the National Academy of Sciences of the United States of America*, **71**, 522–525.

Siunov, A.V., Nikitin, D.V., Suzina, N.E., Dmitriev, V.V., Kuzmin, N.P. & Duda, V.I. (1999) Phylogenetic Status of Anaerobacter Polyendosporus, an Anaerobic, Polysporogenic Bacterium. *International Journal of Systematic Bacteriology*, **49 Pt 3**, 1119–1124.

Skulachev, V.P., Bakeeva, L.E., Chernyak, B.V., Domnina, L.V., Minin, A.A., Pletjushkina, O.Y., Saprunova, V.B., Skulachev, I.V., Tsyplenkova, V.G., Vasiliev, J.M., Yaguzhinsky, L.S. & Zorov, D.B. (2004) Thread-grain Transition of Mitochondrial Reticulum as a Step of Mitoptosis and Apoptosis. *Molecular and Cellular Biochemistry*, **256 – 257**, 341 – 358.

Smith, D.E., Lewis, Y.S. & Svihla, G. (1954) Prolongation of Clotting Time in the Dormant Bat (Myotis Lucifugus). *Experientia*, **10**, 218 – 219.

Solodovnikova, I.M., Saprunova, V.B., Bakeeva, L.E. & Iaguzhinskii, L.S. (2006) [Dynamics of Mitochondrial Ultrastructure in Small Pieces of Cardiac Tissue Under Long-term Anoxic Incubation]. *Tsitologiia*, **48**, 848–855.

Stalker, A.L. (1970) The Microcirculation in Shock. *Journal of Clinical Pathology. Supplement (Royal College of Pathologists)*, **4**, 10–15.

van Steveninck, J. & Ledeboer, A.M. (1974) Phase Transitions in the Yeast Cell Membrane. The Influence of Temperature on the Reconstitution of Active Dry Yeast. *Biochimica Et Biophysica Acta*, **352**, 64–70.

Storey, K.B. & Storey, J.M. (2004) Metabolic Rate Depression in Animals: Transcriptional and Translational Controls. *Biological Reviews*, **79**, 207–233.

St-Pierre, J., Brand, M.D. & Boutilier, R.G. (2000) Mitochondria as ATP Consumers: Cellular Treason in Anoxia. *Proceedings of the National Academy of Sciences of the United States of America*, **97**, 8670–8674.

Strathmann, J., Klimo, K., Sauer, S.W., Okun, J.G., Prehn, J.H.M. & Gerhäuser, C. (2010) Xanthohumol-induced Transient Superoxide Anion Radical Formation Triggers Cancer Cells into Apoptosis via a Mitochondria-mediated Mechanism. *The FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, **24**, 2938–2950.

Sun, M.G., Williams, J., Munoz-Pinedo, C., Perkins, G.A., Brown, J.M., Ellisman, M.H., Green, D.R. & Frey, T.G. (2007) Correlated Three-dimensional Light and Electron Microscopy Reveals Transformation of Mitochondria During Apoptosis. *Nature Cell Biology*, **9**, 1057–1072.

Trzcionka, M., Withers, K.W., Klingenspor, M. & Jastroch, M. (2008) The Effects of Fasting and Cold Exposure on Metabolic Rate and Mitochondrial Proton Leak in Liver and Skeletal Muscle of an Amphibian, the Cane Toad Bufo Marinus. *The Journal of Experimental Biology*, **211**, 1911–1918.

Turdyev, A.A., Ivanov, V.I., Trifonov, I.A., Abbasova, I.A. & Usmanov, R.B. (1984) [Effect of a Tortoise Spleen Extract on the Functional State of Liver Mitochondria in Irradiated Mice]. *Radiobiologiia*, **24**, 834–838.

Vaartjes, W.J. & van den Bergh, S.G. (1978) The Oxidation of Long-chain Unsaturated Fatty Acids by Isolated Rat Liver Mitochondria as a Function of Substrate Concentration. *Biochimica Et Biophysica Acta*, **503**, 437–449.

Vartapetian, B.B., Andreeva, I.N., Generozova, I.P., Polyakova, L.I., Maslova, I.P., Dolgikh, Y.I. & Stepanova, A.Y. (2003) Functional Electron Microscopy in Studies of Plant Response and Adaptation to Anaerobic

Stress. *Annals of Botany*, **91 Spec No**, 155–172.

Vasington, F.D. & Murphy, J.V. (1962) Ca Ion Uptake by Rat Kidney Mitochondria and Its Dependence on Respiration and Phosphorylation. *The Journal of Biological Chemistry*, **237**, 2670–2677.

Viola, A. & Bronte, V. (2007) Metabolic Mechanisms of Cancer-induced Inhibition of Immune Responses. *Seminars in Cancer Biology*, **17**, 309–316.

Volkova, T.N. & Turdyev, A.A. (1987) Hepatocyte Ultrastructure of Testudo Horsfieldi Turtle in Ontogenesis. *Tashkent*, **4**, 53–54.

Walsh, C., Barrow, S., Voronina, S., Chvanov, M., Petersen, O.H. & Tepikin, A. (2009) Modulation of Calcium Signalling by Mitochondria. *Biochimica Et Biophysica Acta*, **1787**, 1374–1382.

Wang, S.Q., Lakatta, E.G., Cheng, H. & Zhou, Z.Q. (2002) Adaptive Mechanisms of Intracellular Calcium Homeostasis in Mammalian Hibernators. *The Journal of Experimental Biology*, **205**, 2957–2962.

Warburg, O. (1956) On the Origin of Cancer Cells. *Science (New York, N.Y.)*, **123**, 309–314.

Xue, L., Fletcher, G.C. & Tolkovsky, A.M. (2001) Mitochondria Are Selectively Eliminated from Eukaryotic Cells After Blockade of Caspases During Apoptosis. *Current Biology: CB*, **11**, 361–365.

Xü, Y.H., Gietzen, K., Galla, H.J. & Sackmann, E. (1983) Protein-mediated Lipid Transfer. The Effects of Lipid-phase Transition and of Charged Lipids. *The Biochemical Journal*, **213**, 21–24.

Yaguzhinsky, L.S. & Krasinskaya, I.P. (1987) Current State of the Problem of Conjugation of Electric Transport Chain and ATP Synthesis in Mitochondria. *Nauka*, 66 –76.

Yamada, K. (1968) Some Observations on the Fine Structure of Light and Dark Cells in the Gall Bladder Epithelium of the Mouse. *Z Zellforsch Mikrosk Anat.*, **84**, 463–472.