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REVIEW

Cachexia: a problem of energetic inefficiency

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Abstract An alteration of energy balance is the immediate cause of the so-called cachexia. Although alterations of energy intake are often associated with cachexia, it has lately became clear that an increased energy expenditure is the main cause of wasting associated with different types of pathological conditions, such as cancer, infections or chronic heart failure among others. Different types of molecular mechanisms contribute to energy expenditure and, therefore, involuntary body weight loss; among them, adenosine triphosphate (ATP) consumption by sarcoplasmic reticulum Ca^{2+} pumps could represent a key mechanism. In other cases, an increase in energy inefficiency will further contribute to energy imbalance.

Keywords Cachexia · SERCA · Muscle wasting · UCPs · Futile cycles

1 Energy balance and body weight

Cachexia is a term originating from the Greek *kakos* and *hexis* meaning 'bad condition'. The cachectic state is observed in many pathological conditions such as cancer, severe chronic obstructive pulmonary disease (COPD), sepsis or chronic heart failure (CHF). A recent definition states: 'Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and an increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity' [1]. From this definition, it is thus paramount clear that the main characteristic of cachexia is weight loss.

From an energy point of view, an increased weight loss may be related to a decrease in thermodynamic efficiency. Variable thermodynamic efficiency in metabolic systems is related not only to differences in weight but also may confer metabolic advantages or drawbacks. However, the underlying mechanisms are as yet unknown, although plausible ones at the metabolic level may be put forward [2]. The Gibbs free energy, ΔG, represents the maximum useful work that can be performed by any system at constant temperature and pressure; this parameter combines the first and second law of thermodynamics in biological systems. Therefore, both entropy and efficiency must be taken into account to understand energy utilization in biological and biochemical systems [2]. However, the actual process, as a rule, generates less useful work than permitted by the theoretically available ΔG due to inefficiency in energy uptake. Interestingly, in cancer-bearing states, there seems to be a clear increase in entropy, which would lower the value of ΔG; any change in this parameter brings 'the system' further away from equilibrium and, therefore, energy efficiency decreases due to heat release (revised by [2]).

2 Genomic alterations

Teschendorff and Severini, based on the observation that frequent genomic alterations underlie a more aggressive

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cancer phenotype, studied if such an effect could be detectable as an increase in the randomness of local gene expression patterns [3]. Their results demonstrate that a metastatic cancer phenotype is characterized by an increase in the degree of randomness of the local information flux patterns [3]. Current theories on cancer development focus on 'unlucky' mutations affecting oncogenes or tumour suppressor genes. Hauptmann interprets cancer as an adaptive phenomenon—a response to cellular stress induced by an energetic overload, which would ultimately lead to an increase in cellular entropy [4]. One of these adaptive mechanisms is aneuploid polyploidization, a phenomenon frequently described in malignant tumours. This inherent property of the genome to multiply with limited sequence variability may be involved just to make new proteins, which are more appropriate to manage the harmful situation of energetic overload. Another important mechanism to prevent increasing entropy is the change in chirality of proteins and carbohydrates because the use of enantiomers with higher intrinsic energy ultimately reduces entropy of the cell. These chiral alterations in turn affect the molecular structures of proteins and DNA, resulting in abnormal function of the former and disturbances of replication, transcription and repair of the latter. Moreover, the altered proteins may, as a secondary step, induce structural changes of the DNA. Because changes in chirality affect the structure of a cell randomly, one can expect alterations of multiple genes or proteins. Therefore, cancer could be seen as a reaction of a cell to entrap energy which reduces entropy, or, in other words, cancer may best be regarded as entropic devolution [4].

Ritchie et al. compared isoform expression entropy in normal and cancer tissues from the same anatomical site for different classes of transcript variations: alternative splicing, polyadenylation and transcription initiation [5]. Alternative splicing showed highly significant entropy gains for 13 of the 27 cancers studied [5]. This entropy gain is characterized by a flattening in the expression profile of normal isoforms and is correlated to the level of estimated cellular proliferation in the cancer tissue. Interestingly, the genes that present the highest entropy gain are enriched in splicing factors. Using a breast cancer gene expression data set and a model network of protein interactions, constrained weighted networks were derived, defined by a stochastic information flux matrix reflecting expression correlations between interacting proteins. Based on this stochastic matrix, they proposed and computed an entropy measure that quantifies the degree of randomness in the local pattern of information flux around single genes. By comparing the local entropies in the non-metastatic versus metastatic breast cancer networks, they showed that breast cancers that metastasize are characterized by a small yet significant increase in the degree of randomness of local expression patterns. These results demonstrate that a metastatic cancer phenotype is characterized by an increase in the randomness of the local information flux patterns [5].

3 Altered intestinal absorption of nutrients

Some of the changes in energy efficiency can be attributed to altered nutrient absorption. A decrease in this parameter represents a decrease in the efficiency of energy intake, one of the key components of the energy balance. In cancer, lipid and carbohydrate alterations in intestinal absorption have been reported in both humans [6] and experimental animals [7, 8]. Malabsorption is generally attributed to the consequences of oncologic treatments reducing the gastrointestinal absorption. Chemotherapy is, in part, responsible for the intestinal alterations [9, 10]. In the case of CHF, the illness leads to increased sympathetic activity, which contributes to a redistribution of blood flow away from the splanchnic circulation. Thus, in CHF patients, a decrease in intestinal mucosal pH has been observed, indicating intestinal ischemia [11]. In addition, experimental studies have demonstrated that loss of gastrointestinal tract integrity plays a major role in the amplification of systemic inflammation in cachexia. Specifically, translocation of endotoxin across a damaged gastrointestinal tract and into the circulation promotes local and systemic cytokine release. Thus, lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, can enter the circulation through the gut wall if barrier function is impaired in various diseases, such as burn injury, sepsis, liver cirrhosis and cancer. In the circulation of cachectic patients, LPS may activate monocytes and macrophages to release pro-inflammatory mediators, thus leading to an inflammatory state, which generates more energetic inefficiency due to the fact that cytokines are able to activate, for instance, mitochondrial-uncoupling proteins [12].

4 Hypermetabolism in cachexia

At present, it is widely held that elevated resting energy expenditure (REE) is a major determinant in the development of malnutrition in cachectic patients [13]. Resting energy metabolism represents the combustion of fuel sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs and for the mechanical processes involved in keeping the body alive. It is appropriate, therefore, to presume that abnormalities in carbohydrate, lipid and protein metabolism are major biochemical bases of elevated REE [14–16]. Other components of energy expenditure are either not altered or decreased. This seems to be the case for diet-induced thermogenesis [17] and energy expenditure associated with exercise.

5 Molecular mechanisms leading to energetic inefficiency

As a result of taking into consideration both the first and second laws of thermodynamics, one concludes that decreased

efficiency has precisely the same result as reduced caloric intake. Reducing efficiency may be simply related to mitochondrial energy uncoupling. However, adenosine triphosphate (ATP) is produced in different cellular compartments. From this point of view, glycolysis results in a net production of two ATPs per molecule of glucose in the cell cytoplasm. However, 36 additional molecules of ATP are produced from glucose as a result of the mitochondrial tricarboxylic acid (TCA) cycle and electron transport. According to Mitchell's chemiosmotic theory, mitochondrial ATP synthesis involves the formation of a proton gradient across the inner mitochondrial membrane. The proton concentration gradient provides the energy that is converted into ATP as the gradient is dissipated through ATP synthase; this enzyme allows for protons to pass through the inner mitochondrial membrane, therefore converting the proton gradient concentration energy into ATP in the mitochondrion [2]. ATP constitutes an 'energy coin' for performing work within cells. This process of energy capture is crucial for permitting work to be performed by living systems [18].

Energetic inefficiency in all metabolic processes is guaranteed by the second law of thermodynamics [2]. However, differences in inefficiency do exist between different organisms. If efficiency can vary (as in the example of oxidative uncoupling), then the statement 'a calorie is just a calorie' no longer applies. There is a family of proteins—the so-called uncoupling proteins—that are partially responsible for the differences in efficiency. However, their role in humans is still not fully understood [19, 20]. In fact, these proteins may have different roles, in addition to providing differences in energetic efficiency between different cell types.

5.1 Oxidative phosphorylation uncoupling: UCPs

Oxidation of carbohydrates, lipids and, to some extent, proteins in the cytosol and the mitochondria—through oxidative phosphorylation [21]—leads to energy which is finally stored in the form of ATP. However, in homeothermic animals, the energy that is derived from metabolic fuels is also dissipated as heat, in a process that is facilitated by different mechanisms [22]. Among these mechanisms, proton leak, natural uncouplers (such as fatty acids) and uncoupling proteins are found in the mitochondria which serve in the maintenance of body temperature, participating of adaptive non-shivering thermogenesis [23, 24]. This process is called uncoupled respiration and is performed by uncoupling proteins (UCPs) [24, 25]. These proteins belong to the mitochondrial anion carrier protein family, which has approximately 30 members. UCP2 and UCP3, were discovered two decades ago. UCP3 is highly expressed in skeletal muscle, brown adipose tissue (BAT) and in small quantity in the heart, while UCP2 is expressed in many cell types of the immune system, the brain and in pancreatic β cells [26]. While the overall and relative physiologic importance of these proteins remains incompletely understood in human tissues [20], UCP1 has been shown in mice [27] to result in modest degrees of uncoupling in brown fat (BAT). Elevation of fatty acid concentration has been associated with the induction of UCP3 and even with pathologic reductions of myocardial efficiency in rat heart [28]. Although the involvement of UCP other than UCP1 in thermogenesis has been questioned, several recent evidences indicate the contrary [29–31]. In fact, ectopic expression of UCP2 cDNA in mammalian cells in culture or in recombinant yeast creates a drop in membrane potential—without inhibiting the respiratory rate—and increases heat production [32], consistent with UCP2-induced uncoupling of mitochondrial respiration. Similarly, transfection studies overexpressing UCP3 cDNA and construction of UCP3-recombinant yeast [33] have established that under these conditions, UCP3 also lead to a drop in membrane potential consistent with an uncoupling activity. However, several investigators indicate that UCP1 is the only verified uncoupling protein [34]. Therefore, the role of UCP2 and UCP3 in oxidative phosphorylation uncoupling remains controversial.

Mitochondrial ATP synthesis is an essential biochemical process for any living cell [21]. We have shown that this process is severely impaired in skeletal muscle during cancer cachexia [35]. If we take into account that skeletal muscle represents up to 40 % of total body weight, any impairment in ATP synthesis in this tissue will severely affect the efficiency of the subject submitted to tumour burden [36–38]. In addition, chemotherapy may also affect mitochondrial ATP synthesis. Indeed, there are known endogenous and pharmacologic agents, which result in uncoupling the formation of ATP from the dissipation of the gradient. Thus, for instance, tamoxifen—the widely prescribed drug in the prevention and therapy of breast cancer and a well-known modulator of oestrogen receptor that also inhibits the proliferation of different cell types that lack this receptor—promotes extensive permeability to protons due to destructive effects in the structural integrity of the mitochondrial inner membrane [39]. These multiple effects of tamoxifen on mitochondrial bioenergetic functions, causing changes in the respiration, phosphorylation efficiency and membrane structure, may explain the cell death induced by this drug in different cell types, its anticancer activity in oestrogen receptor-negative cells and its side effects. Just as an example, if we take into consideration the overall efficiency of glucose metabolism, and supposing a decrease in efficiency from 38.5 to 30 %, the result would be the production of only 30 mol of ATP instead of the usual 38. In terms of glucose requirements, if an individual requires 3 mol of glucose to generate 100 mol of ATP and supposing the above-referred decrease in energetic efficiency, by eating just the 3 mol of glucose the individual would produce less ATP, therefore our individual metabolism would activate the

oxidation of body stores to make up the additional ATP needed for homeostasis. This would result in weight loss exactly as it did for reduced caloric intake [2]. In spite of this, a recent study supports that ATP production efficiency is not altered in skeletal muscle mitochondria in a model of cancer cachexia [40]. Therefore, again, one cannot be fully conclusive concerning a persistent alteration of mitochondrial ATP synthesis during cancer cachexia.

In experimental cancer cachexia, however, the expression of both the UCP2 and UCP3 genes is significantly increased in skeletal muscle of tumour-bearing animals [41] (Fig. 1), suggesting that these proteins could certainly have a role in the increased metabolic rate observed in this type of syndrome. In fact, BAT thermogenesis, measured as GDP binding (UCP1), was also reported to be increased in tumour-bearing animals [42]. Similar results have been obtained by Tisdale's group [43] using the MAC16 adenocarcinoma—a highly cachectic mouse tumour—reporting increases in BAT UCP1 gene expression and in skeletal muscle UCP2 and UCP3 mRNA contents. In children with leukaemia, an increased GDP binding was also reported in BAT [44]. In cancer patients, UCP3 gene expression has also been shown to be increased in skeletal muscle [45]. Interestingly, cancer cachexia also results in the UCP2 gene in the brain, suggesting a potential role for the brain as a thermogenic organ [46]. In these cachectic conditions, cytokines—tumour necrosis factor alpha (TNF) in particular—seem to be responsible for the increased UCP2 and UCP3 gene expression in skeletal muscle. Thus, systemic administration of TNF to rats results in an increase in both UCP2 and UCP3 gene expression in skeletal muscle [12]. This does not seem to be the result of a direct effect of the cytokine but rather seems to be associated with the hyperlipemia induced by TNF administration [47]. In fact, Masaki et al. have demonstrated that TNF regulates the in vivo expression of the UCP family differentially and tissue dependently [48]. A very recent data from our laboratory clearly indicate that uncoupling of oxidative phosphorylation is present in skeletal muscle of tumour-bearing animals [49]. Therefore, this phenomenon contributes, during the cachectic syndrome, to the generation of energetic inefficiency and, ultimately, to body weight loss.

5.2 SERCA

The endoplasmic reticulum has emerged as an organelle that plays a major role in cell signalling pathways, cellular response to stress and cellular activation of apoptosis. In the skeletal muscle, the sarcoplasmic reticulum (SR) functions as a dynamic Ca^{2+} governor that provides automatic feedback control for altering and maintaining myoplasmic and SR Ca^{2+} levels [50, 51]. One of the proteins involved in Ca^{2+} transport is the sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) [52]. In the skeletal muscle, SERCA1 has the capacity to interconvert different forms of energy. Thus, SERCA1 activity may be coupled to Ca^{2+} translocation from the cytosol to the sarcoplasmic reticulum, a process that requires a considerable amount of energy since it represents a dynamic process against a concentration gradient. Some of the energy associated with the activity of the pump is released as heat [53]. Interestingly, the pump may also function in an uncoupled way, releasing just heat without translocating Ca^{2+} [53, 54]. In fact, the rate of uncoupled ATPase activity is much higher than the coupled one. It is for this reason that SERCA1, in addition to being involved in Ca^{2+} translocation, has also been related to non-shivering thermogenesis [55]. Conversely, SERCA2, most of the hydrolytic ATP-derived energy, is coupled to Ca^{2+} transport to the lumen of the sarcoplasmic reticulum [53]. Recently, we have shown that in skeletal muscle of cachectic tumour-bearing animals, SERCA gene expression and protein content are increased (Fig. 2) suggesting an active role of the calcium pump in generating metabolic inefficiency and thus contributing to body weight loss [56]. In addition, chemotherapy treatment may decrease the energetic efficiency of

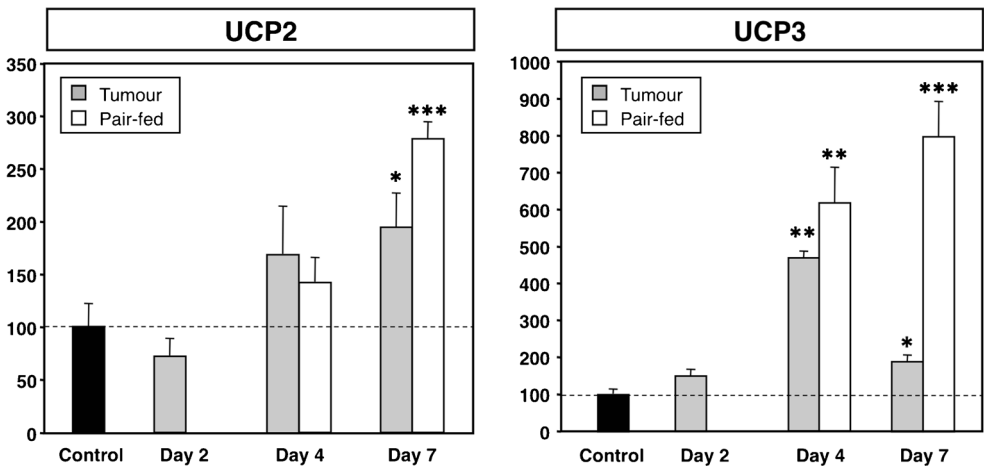

Fig. 1 Uncoupling proteins in skeletal muscle during weight loss associated with cancer. UCP2 and UCP3 could participate in the disruption of the electrochemical proton gradient that drives oxidative phosphorylation, therefore uncoupling this process and generating energetic inefficiency (adapted from Sanchís et al. [41])

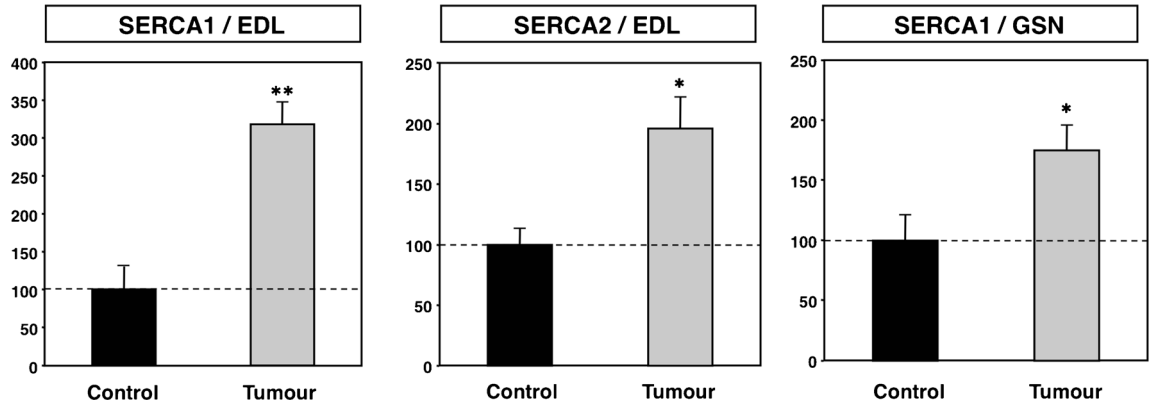

Fig. 2 SERCA pump in skeletal muscle during weight loss. SERCA activity may be coupled to Ca^{2+} translocation from the cytosol to the sarcoplasmic reticulum, a process that requires a considerable amount of energy since it represents a dynamic process against a concentration gradient. Some of the energy associated with the activity of the pump is released as heat. Interestingly, the pump may also function in an uncoupled way, releasing just heat without translocating Ca^{2+} (adapted from Fontes-Oliveira et al. [56]). *GSN* gastrocnemius muscle; *EDL* extensor digitorum longus muscle; *SERCA* sarcoendoplasmic reticulum Ca^{2+}-ATPase

SERCA pumps, thus further contributing to energy imbalance and weight loss in cancer patients [57].

5.3 Other ATPases

In addition to SERCA, other membrane ATPases may be involved in energy inefficiency during cachexia. Thus, it has been described that some tumorigenic cells show inefficient Na^+-K^+ ATPases [58]. These particular enzyme complexes work by pumping Na^+ out of the cells at a certain energetic cost in order to fulfil the demands of the active transport. In the Ehrlich ascites tumour cells, a phosphorylation of the beta subunit of the Na^+-K^+ ATPases by a membrane-bound kinase leads to a lower ratio of Na^+ transported/ATP hydrolysed. Interestingly, the efficiency is enhanced by quercetin, a natural antioxidant compound present in grapes among other fruits. There are many more ATPases that could be affected in a similar way and, therefore, alter the energetic efficiency of a subject, in particular during cachexia (revised in [2]). Bearing this in mind, future investigations on this topic are granted.

5.4 Metabolic futile cycles

Substrate—also called 'futile'—cycles refer to a dynamic process that generates energetic inefficiency. Thus, increased cycling of metabolic intermediates utilizes ATP and generates heat (Fig. 3). The simplest examples are the numerous kinase–phosphatase pairs that regulate many metabolic pathways. Other futile cycles, although sometimes not placed in the category of substrate cycling, are involved in the breakdown and re-synthesis of proteins, lipids and carbohydrates in cycles that use ATP without apparent net metabolic gain. These cyclic mechanisms, however, far from being useless, permit the precise regulation of metabolism and are one of the uses of ATP. Protein turnover (protein synthesis and degradation), in particular, provides for error correction or removal of 'old' or damaged proteins [2].

To understand the importance of cycling in generating inefficiency, if the energy yield of glucose is taken into consideration, 1 mol of the sugar—completely oxidized to CO_2 and water—generates 38 mol of ATP with an overall efficiency of about 40 % However, if glucose is first incorporated into glycogen, followed by hydrolysis of the glucose and subsequent oxidation, 2 mol of ATP is lost per mole in this cycle

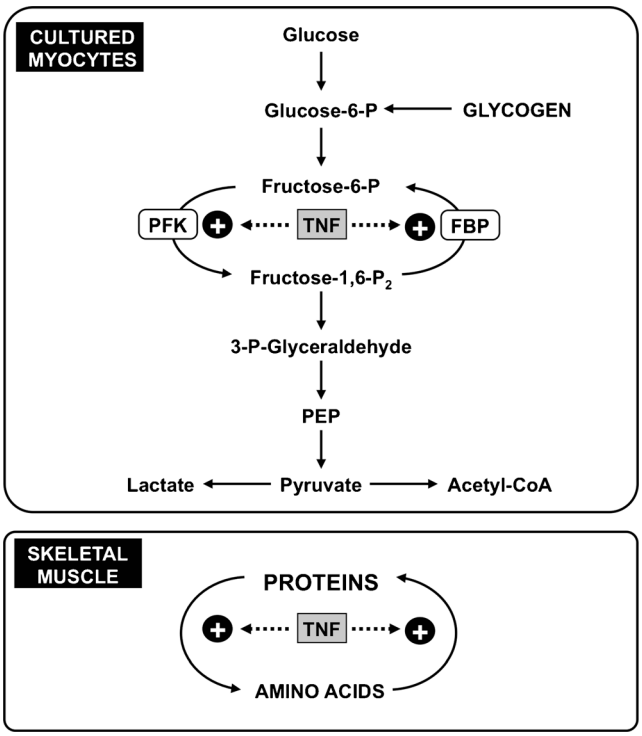

Fig. 3 Examples of cellular futile cycles and their modulation by the inflammatory response that accompanies catabolic conditions. Several cytokines have been implicated in the activation of cellular futile cycling involving different metabolic pathways

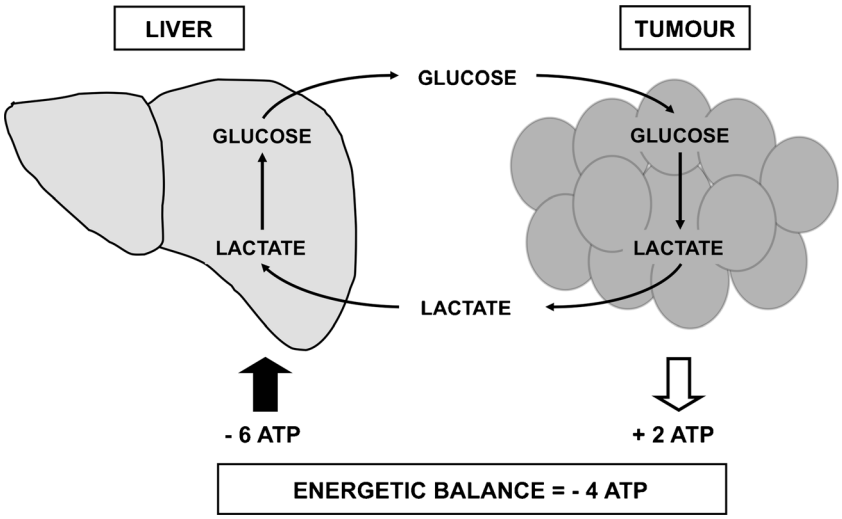

Fig. 4 Inter-organ futile cycling. The so-called Cori cycle is activated between the liver and the tumour in cancer and generates energetic inefficiency as can be seen from the ATP balance shown

with overall efficiency reduced to 37 %. In a similar manner, in the case of proteins, when an amino acid is directly oxidized to CO_2, the result is ATP synthesis with an overall efficiency of about 33 %. On the other hand, if the amino acid is first incorporated into a protein and later hydrolysed and oxidized, four additional ATPs per molecule are used for the synthesis of the peptide bond. The result is a decrease in the efficiency the process to about 27 %. Taking into account lipid cycles, smaller degrees of inefficiency are seen. However, in the case of multiple cycles, a cumulative effect may exist. For instance, it can be estimated that half of the fatty acids that constitute the triacylglycerols have been through at least one cycle [2]. We can therefore conclude that variations in energetic efficiency are not simply a thermodynamic issue but have an empiric component that depends on the requirements of metabolism [2].

The activity of futile cycles, such as the Cori cycle (glucose to lactate to glucose) or lactate recycling (Fig. 4), that takes place between the tumour and the host is certainly involved in generating energetic inefficiency. Indeed, the gluconeogenic utilization of the tumour-derived lactate is a very inefficient metabolic process consuming six molecules of ATP per cycle, but it is essential for compensating tumour acidosis (revised in [2]).

An activation of the inflammatory status (cytokine release due to catabolic conditions such as cancer or sepsis) leads to the activation of futile cycling. For instance, Zentella et al. have clearly shown that TNF action in cultured myocytes is linked with an important activation of a futile cycle [59]. Thus, the cytokine stimulates glucose utilization and lactate formation activating the substrate cycle between phosphofructokinase and fructose-1,6-bisphosphatase; there is a subsequent increase in lactate production. A similar situation is encountered in protein turnover in skeletal muscle [60] (Fig. 3).

6 Therapeutic implications and future research

Bearing in mind the previous considerations, it becomes clear that energy balance is an essential component of body weight control that, if altered, may lead to either gain or loss of body weight. In the particular case of the cachectic patient, the balance is clearly negative, leading to body wasting. An essential component of the energy balance is expenditure. This is modulated by the efficiency of the different biochemical processes involved in metabolism. Any decrease in efficiency will lead to less energetic potential to drive ATP synthesis and, therefore, an increase in energy intake will be necessary to compensate or else a negative energy balance will appear. Understanding the regulation of some of the commented processes (i.e. the SERCA pump) may lead to the design of pharmacological strategies to modulate the energy efficiency of a particular reaction(s) and therefore may serve to diminish the degree of muscle and body wasting associated with cachexia.

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Conflict of interest statement and statement of authorship Each author has participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including

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