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Cancer and Anticancer Therapy-Induced Modifications on Metabolism Mediated by Carnitine System

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An efficient regulation of fuel metabolism in response to internal and environmental stimuli is a vital task that requires an intact carnitine system. The carnitine system, comprehensive of carnitine, its derivatives, and proteins involved in its transformation and transport, is indispensable for glucose and lipid metabolism in cells. Two major functions have been identified for the carnitine system: (1) to facilitate entry of long-chain fatty acids into mitochondria for their utilization in energy-generating processes; (2) to facilitate removal from mitochondria of short-chain and medium-chain fatty acids that accumulate as a result of normal and abnormal metabolism. In cancer patients, abnormalities of tumor tissue as well as nontumor tissue metabolism have been observed. Such abnormalities are supposed to contribute to deterioration of clinical status of patients, or might induce cancerogenesis by themselves. The carnitine system appears abnormally expressed both in tumor tissue, in such a way as to greatly reduce fatty acid beta-oxidation, and in nontumor tissue. In this view, the study of the carnitine system represents a tool to understand the molecular basis underlying the metabolism in normal and cancer cells. Some important anticancer drugs contribute to dysfunction of the carnitine system in nontumor tissues, which is reversed by carnitine treatment, without affecting anticancer therapeutic efficacy. In conclusion, a more complex approach to mechanisms that underlie tumor growth, which takes into account the altered metabolic pathways in cancer disease, could represent a challenge for the future of cancer research. J. Cell. Physiol. 182: 339–350, 2000.

There has been increasing interest in the cellular metabolic pathway abnormalities that either might be induced by cell transformation or might induce cancerogenesis by themselves. The conclusive evidence of many studies demonstrates that cancer can present an altered metabolism characterized by: high rate of glycolysis (Fujibayashi et al., 1997; Mathupala et al., 1997; Rodriguez-Enriquez and Moreno-Sanchez, 1998) associated with an increased rate of glucose transport (Dang et al., 1997; Reske et al., 1997); increased gluconeogenesis (Lundholm et al., 1982); reduced pyruvate oxidation with increased production of lactic acid (Mazurek et al., 1997a); increased glutaminolytic enzyme activities (Wasa et al., 1996; Fischer et al., 1998); reduced fatty acid oxidation (Prip Buus et al., 1992; Ockner et al., 1993); increased glycerol and fatty acid turnover (Shaw and Wolfe, 1987); decreased glycerol 3-phosphate shuttle and malate-aspartate shuttle activities (Mazurek et al., 1997b, 1998); modified protein and amino acid metabolism (Heber et al., 1982; Jeevanandam et al., 1984; Souba, 1993); and increased pentose phosphate pathway enzyme activities (Boros et al., 1998).

Although advances in the knowledge of metabolism have put to rest a number of controversial issues, some burning questions remain for the comprehension of the metabolic abnormalities in cancer disease, two of which are: (1) Is there any difference as to how fatty acid groups gain access to the beta-oxidation machinery of normal and cancer cells? (2) Could the anticancer therapy, by itself, modify the intracellular lipid trafficking? The fatty acid transport mechanism has come to cover an ever-expanding role in fuel homeostasis, but it has not yet begun to disclose its guarded secrets in the case of neoplastic cells.

Since the carnitine system, which consists of carnitine, carnitine esters, several specific intracellular enzymes, and membrane transporters, plays an important role in the cell trafficking of short-, medium-, and long-chain fatty acids, it is of particular interest to analyze the possible modifications induced, either directly or indirectly, by cancer on this system.

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Indeed, the carnitine system is involved in the following functions (Bremer, 1997; Rebouche and Seim, 1998): (1) utilization of substrates for energy production at the mitochondrial level; (2) lipid oxidation at the peroxisomal level, not related to energy production; (3) acylation and deacylation of proteins, such as very low density lipoprotein, at the endoplasmic reticulum level; (4) membrane phospholipid turnover; and (5) maintenance of cell osmotic balance.

CARNITINE SYSTEM ENZYME NETWORK

As mentioned earlier, the carnitine system is primarily involved in the transport of long-chain acyl fatty acids across the mitochondrial membrane. This transport involves three enzymes located in the outer and inner mitochondrial membranes (McGarry and Brown, 1997) (Fig. 1). The enzyme carnitine palmitoyltransferase I (CPT I), located in the outer mitochondrial membrane, catalyzes the transfer of acyl groups from acyl-CoA to carnitine to synthesize acylcarnitine and to produce free CoA (Declercq et al., 1987; Murthy and Pande, 1987). The enzyme acylcarnitine/carnitine translocase (CT), located within the inner mitochondrial membrane, exchanges cytoplasmic acylcarnitine for mitochondrial free carnitine (antiport reaction) (Pande, 1975; Indiveri et al., 1990, 1994). The presence of a specific mitochondrial membrane phospholipid, the cardiolipin, is required for CT activity (Noël and Pande, 1986). Finally, the enzyme carnitine palmitoyltransferase II (CPT II), located on the matrix side of the inner mitochondrial membrane, catalyzes a reaction that is the reverse of that of CPT I, reconverting acylcarnitine to acyl-CoA, conveyed to beta-oxidation, while free carnitine is produced (Woeltje et al., 1987).

CPT I and CPT II enzymes are enriched within the mitochondrial contact sites that represent defined areas where the outer and inner boundary membranes come to within 4 nm of each other (Fraser and Zammit, 1998). Since CPT I and CPT II are closely in touch at contact sites, the possibility arises that this submitochondrial distribution of the two enzymes is important for lipid traffic between the cytosolic and intramitochondrial compartment, suggesting that acylcarnitines formed by CPT I are preferentially channeled to CPT II. The activity of CPT I, overtly expressed in mitochondria, has been observed to be extremely influenced by membrane fluidity, suggesting that the kinetic characteristics of CPT I are sensitive to changes in lipid composition of microdomains in which CPT I resides (Zammit et al., 1998).

On the other hand, CT is not only present in mitochondrial contact sites in association with CPTs but is also uniformly distributed within the inner mitochondrial membrane (Fraser and Zammit, 1999). The wide distribution of CT suggests a specific role of this enzyme in the flux of carnitine from and into mitochondria for the maintenance of the ratio between cytosolic and mitochondrial free carnitine levels.

The CT uniport modality of transport is also involved in the export of short-chain acylcarnitine, such as acetylcarnitine, out of mitochondria (Indiveri et al., 1991). The presence of another enzyme, the carnitine acetyltransferase (CAT) located on the matrix side of the inner mitochondrial membrane, is important for the synthesis of short-chain acylcarnitine and for the production of free CoA (Edwards et al., 1974; Bremer, 1983).

Intracellular organelles, other than mitochondria, may contain CPTs, CT, and CAT, the activities of which are demonstrated in the membranes of peroxisomes, endoplasmic reticulum, and nucleus (Bremer, 1997; Murphy and Pande, 1997) (Fig. 2). Whether these enzymes are the same proteins present in mitochondria has not yet been clarified.

Other components of the carnitine system are the plasma membrane carnitine transporters. Very recently, a Na^+-dependent, high-affinity human carnitine transporter has been identified and named organic cation transporter 2 (OCTN2) because of its similarity (75.8%) to the OCTN1, the low-affinity Na^+-independent carnitine transporter (Tamai et al., 1998). In adult tissues, OCTN2 is strongly expressed in kidney, skeletal muscle, placenta, heart, prostate, and thyroid; and weakly expressed in pancreas, liver, lung, brain, small intestine, uterus, thymus, adrenal gland, trachea, and spinal cord. The human OCTN1 participates, at least in part, in proton/organic cation antiport at the renal apical plasma membrane level (Tamai et al., 1998).

Carnitine system in cell metabolism

The role of the carnitine system in cell metabolism is mainly known in mitochondria where the interaction between fatty acid and glucose metabolism is fundamental for cell energy production (Bremer, 1997). Two key points in the interplay between fatty acids and glucose utilization are involved (Peluso et al., 1999). The first key point concerns the enzyme pyruvate dehydrogenase (PDH) located in the inner mitochondrial membrane. PDH catalyzes the conversion of pyruvate to acetyl-CoA, which enters the Krebs cycle. The extent of PDH activity is dependent on the fatty acid–produced increase in acetyl-CoA, that is, mitochondrial increase in the acetyl-CoA/CoA ratio, which inhibits PDH reaction. The mitochondrial acetyl-CoA/CoA ratio is modulated by the carnitine system by the removal of acetyl moieties by CAT-forming acetylcarnitine, which can be exported from mitochondria to cytosol by the uniport transport operated by CT (Indiveri et al., 1991). Removal of intramitochondrial acetyl-CoA leads to the release of PDH inhibition and consequent pyruvate utilization. Hence, carnitine, CAT, and CT work as a buffer system to maintain the acetyl-CoA/CoA ratio.

The other key point concerns the malonyl-CoA–CPT I interaction. Malonyl-CoA is the physiological inhibitor of CPT I activity, and is synthesized in the cytosol through a reaction catalyzed by acetyl-CoA carboxylase (ACC) (Murthy and Pande, 1990). ACC activation by insulin is a crucial component of the malonyl-CoA–CPT I partnership (McGarry, 1995).

The carnitine system has been investigated to an even deeper level than the mitochondrial, that is, the peroxisomal level. Today, it is clear that CPT I, CT, and CPT II are implicated in the transport of long-chain fatty acid into peroxisomes for beta-oxidation (Buechler and Lowenstein, 1990; Fraser and Zammit, 1999). Moreover, there is direct evidence that the transfer of short-chain acyl-CoA (propionyl-, acetyl-) produced by peroxisomal beta-oxidation, and branched-chain acyl-CoA produced by peroxisomal branched-chain amino acid oxidation to mitochondria depends on

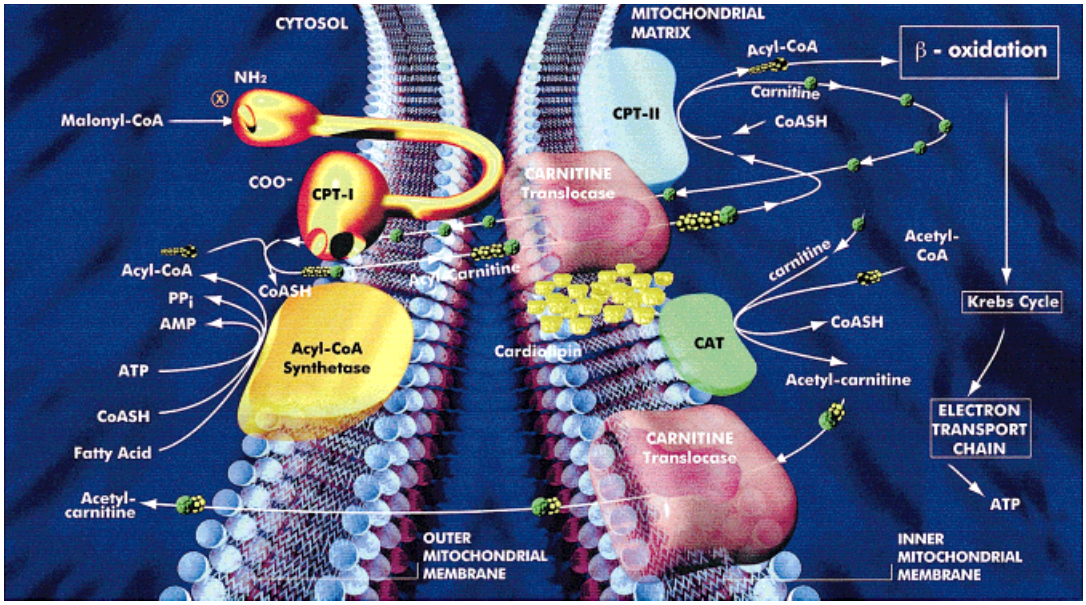

Fig. 1. Mitochondrial carnitine system. CPT I (carnitine palmitoyltransferase I); CPT II (carnitine palmitoyltransferase II); CAT (carnitine acetyltransferase); CoASH (Coenzyme A).

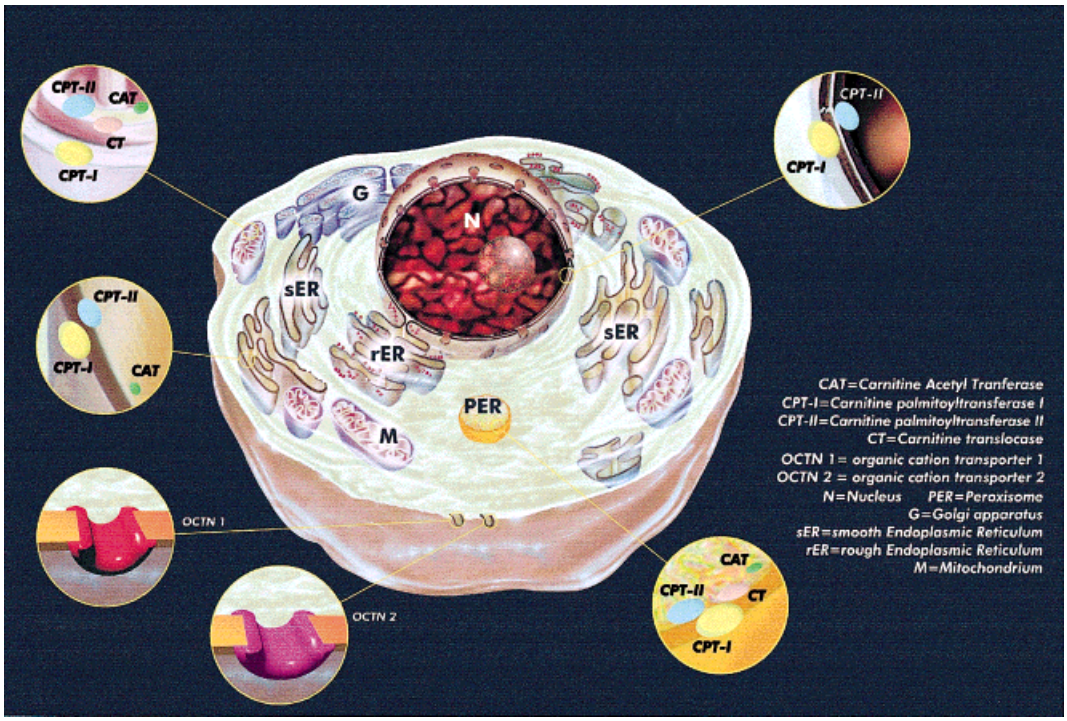

Fig. 2. Cellular carnitine system enzyme network.

the carnitine system (shuttle of shortened acylcarnitines to mitochondria to further and complete oxidation) (Jakobs and Wanders, 1995). Once more, the CT uniport modality of transport is involved in the transport of short-chain acylcarnitines into mitochondria.

At the endoplasmic reticulum level, CPTs are demonstrated to participate in the reesterification of triglycerides in the liver. In fact, cytosolic triacylglycerol is not secreted directly into the blood, but a breakdown by lipolysis and reesterification are needed. This takes place as part of the transit into the lumen of endoplasmic reticulum before secretion as VLDL (very low density lipoproteins) by the Golgi apparatus (Broadway and Saggerson, 1995).

Regulation of carnitine system enzyme activity

In the last decade, molecular biology techniques applied to the study of carnitine system, including fine chromosome mapping, genomic DNA sequencing, qualitative and quantitative determination of gene expression, and promoter characterization, have provided new tools for understanding this intriguing system.

Mitochondrial CPT I is a protein of approximately 88 kDa tightly associated with the outer membrane. It contains both the malonyl-CoA inhibitor-binding domain, exposed on the cytosolic face, and the active catalytic domain (Esser et al., 1993; Fraser et al., 1996). Moreover, two membrane spans are connected by a loop in the intermembrane space (Swanson et al., 1998).

The site of the enzyme, to which malonyl-CoA binds, corresponds to the N-terminal amino acid domain (Shi et al., 1998) projecting into the cytosol, and a single amino acid substitution seems to abolish malonyl-CoA inhibition and high-affinity binding (Shi et al., 1999). The larger C-terminal domain dictates the degree of sensitivity to malonyl-CoA as well as the response to carnitine at the active site (Swanson et al., 1998). Thus, two distinct sites for the control of CPT I activity, malonyl-CoA binding site and active catalytic site, are located in different positions of the protein and protude on the cytoplasmic face of the mitochondrial outer membrane (Cook et al., 1994; Fraser et al., 1997).

CPT I exists as at least two different enzymes, one isoform being highly expressed in the liver (L-CPT I) and the other in the skeletal muscle (M-CPT I). Two important kinetic parameters differentiate the liver and muscle enzymes: L-CPT I shows a higher affinity for carnitine (lower K_m) and a lower sensitivity to malonyl-CoA inhibition (higher IC_{50}) than M-CPT I (McGarry, 1995). It has been proposed that the different sensitivities to malonyl-CoA inhibition between the two isoforms could depend not only on their N-termini primary sequence, but also on the structure of their C-terminal domain (Swanson et al., 1998).

The L-CPT I isoform is expressed in liver, kidney, lung, spleen, intestine, pancreas, ovary, brain, and to a lesser extent in heart; the M-CPT I isoform is expressed in skeletal muscle, heart, brown and white adipose tissue, and testes (McGarry and Brown, 1997). The heart provides a paradigm of complexity of the carnitine system. In fact, it contains both M-CPT I (96–97%) and L-CPT I (3–4%) isoforms (Weis et al., 1994), suggesting that in this organ the enzymes of the carnitine system can follow different kinetics, a feature that allows for appropriate modulations in the utilization of glucose and lipid.

Recently, by screening of human cDNA libraries, the two CPT I isoforms have been identified as derived from different genes and not as the product of alternative splicing of mRNA: M-CPT I gene resides on chromosome 22q13.3, whereas L-CPT I resides on chromosome 11q13 (Yamazaki et al., 1996; Britton et al., 1997). Moreover, the screening of a human cardiac cDNA library has revealed the expression of two novel CPT I isoforms, generated by alternative splicing of the mRNA for M-CPT I, that show internal deletions within their N-termini (Yu et al., 1998). It is proposed that the expression of products of alternative mRNA splicing may be responsible for tissue-specific CPT I activity and kinetic variations, in response to changes in metabolic requirements.

Mitochondria, endoplasmic reticulum, and peroxisomes express CPT I in proportions of 65, 25, and 10%, respectively, of total cellular CPT I activity. In all three membrane fractions, a single protein with an identical molecular mass of approximately 88 kDa has been identified, but Western blot analysis revealed that the N-terminal domain of the endoplasmic reticulum protein differs from the protein present in the mitochondria and peroxisomes (Fraser et al., 1999).

A single isoform for CPT II is present in almost all tissues (Gellera et al., 1994), loosely associated with the inside of the inner mitochondrial membrane (Woeltje et al., 1987). The initial full-length peptide contains a NH_2-terminal leader sequence that is cleaved upon mitochondrial import to yield a mature protein with a molecular size of approximately 71 kDa (Brown et al., 1991). CPT II is malonyl-CoA insensitive but, given the strict similarity with CPT I, it seems likely that the active sites of the two enzymes share some common kinetic features (McGarry and Brown, 1997). In particular, the binding of acyl-CoA or CoA must precede that of carnitine (Nic a' Bhaird et al., 1993), and the involvement of histidine residues appears to be important for catalytic activity (Nic a' Bhaird and Ramsay, 1995). Human CPT II gene has been identified and assigned to chromosome 1p32 (Gellera et al., 1994).

CT is an enzyme of an apparent molecular mass of 32.5 kDa. It is composed of three repeated sequence motifs, each folded into two transmembrane α-helices linked by an extensive hydrophilic loop outside the lipid bilayer, whereas shorter stretches of hydrophilic amino acids connect the three repeats (Iacobazzi et al., 1998). Both N- and C-terminal regions are exposed to the cytosolic side (Indiveri et al., 1997). All these features of the secondary structure of CT protein point to its asymmetric nature, which is also suggested by functional studies revealing different substrate binding sites on the inner and outer sides of reconstituted mitochondrial membrane (Indiveri et al., 1994). Western blot analysis has revealed that mitochondrial CT is present in peroxisomes but not in endoplasmic reticulum, suggesting that acylcarnitine transport into peroxisomes is CT mediated, whereas the transport across the endoplasmic reticulum may occur by a pore mechanism (Fraser and Zammit, 1999). CT gene has been cloned (Huizing et al., 1997) and assigned to human chromosome 3p21.31 (Viggiano et al., 1997).

Human CAT is a monomer of approximately 61 kDa, enriched in mitochondria and peroxisomes, and also present in endoplasmic reticulum (Chung et al., 1991). Mitochondrial and peroxisomal CAT enzymes have been proposed to originate from alternative splicing of a single CAT gene (Corti et al., 1994a), localized on human chromosome 9q34.1 (Corti et al., 1994b)

Regulation of carnitine system enzyme expression

The levels of mRNA encoding L-CPT I are subjected to changes in response to physiological stimuli. In rats, the expression of L-CPT I gene is very low before birth, increases fivefold during the first day of extrauterine life, and is high during the entire suckling period. L-CPT I expression continues to be elevated if the

animals are weaned to a high-fat diet, whereas it is markedly decreased in the liver of rats weaned to a high-carbohydrate diet (Thumelin et al., 1994). These data suggest that expression of CPT I is regulated by glucagon/insulin ratio and by the abundance of long-chain fatty acids (Kispal et al., 1987; Park et al., 1995; Park and Cook, 1998). Since cAMP in cultured hepatocytes is able to increase CPT I gene transcription (Chatelain et al., 1996), it can be hypothesized that the rapid increase in hepatic CPT I mRNA level that accompanies the fetal/neonatal transition in the rat may also be due to the elevation of the liver content of cAMP. On the contrary, the levels of mRNA encoding CPT II are already high in the liver early in fetal life and remain at this level, without oscillations, throughout the entire period of life (Thumelin et al., 1994).

It appears that CPT I and CPT II promoters should be different, since CPT II is not subjected to hormonal control. One main difference in humans is that CPT I promoter, of both liver and muscle isoforms, is a TATA-less promoter (Steffen et al., 1999), whereas CPT II promoter contains a TATA box (Montermini et al., 1994). Moreover, CPT I gene is highly regulated by multiple transcription factors such as the member of Sp family (Sp1, Sp3), nuclear factor Y, and other nuclear proteins (Park et al., 1998).

The expression of several genes involved in lipid metabolism, in particular those involved in peroxisomal and mitochondrial beta-oxidation, is mediated by lipid-activated receptors, collectively referred to as peroxisome proliferator-activated receptors (PPARs). PPARs (PPARα, PPARβ, and PPARγ subtypes) are transducer proteins belonging to a superfamily of nuclear receptors that includes the retinoic acid receptors (RARs), the thyroid hormone receptors (TRs), and steroid hormone receptors (SRs) (Lemberger et al., 1996). PPARs bind to DNA as heterodimers with retinoid X receptors (RXRs) (Keller et al., 1993; Mangelsdorf and Evans, 1995). In particular, PPARs depend strictly on RXRs for DNA-binding because it is inactive as a monomer or homodimer. Activated PPARs, heterodimerized with RXR, alter the transcription of target genes after binding to DNA at the level of specific response elements (PPREs), consisting of a direct repeat of the nuclear receptor hexameric DNA core-recognition motif spaced by one nucleotide. The different PPARs can be considered key messengers responsible for the transduction of nutritional, pharmacological, and metabolic stimuli into changes in the expression of genes, more specifically those genes involved in lipid metabolism (Schoonjans et al., 1996a). PPARα plays an importat role in fatty acid oxidation, as demonstrated by the number of PPAR target genes identified so far. Among them, fatty acid transport protein and long-chain acyl-CoA synthetase, which respectively facilitate the transport of FAs across the cell membrane and activate fatty acids into acyl-CoA thioesters (preventing their efflux), are under transcriptional control of PPARα (Schoonjans et al., 1995; Martin et al., 1997). Again, lipoprotein lipase gene transcription is controlled by PPARs (Schoonjans et al., 1996b) as well as mitochondrial medium-chain acyl-CoA dehydrogenase (Gulick et al., 1994), the enzymes involved in peroxisomal beta-oxidation pathway (Lemberger et al., 1996), and microsomal CYP4A, a cytochrome P450 fatty acid ω-hydroxylase (Belury et al., 1998).

Several studies have demonstrated that fatty acids and peroxisomal proliferator compounds, such as clofibrate (a ligand for PPARα), stimulate transcription of L-CPT I gene (Feller et al., 1987; Gerondaes et al., 1988; Brady and Brady, 1989; Brady et al., 1991). Thus, the gene encoding CPT I probably represents a PPARα target gene.

A recent finding is that the human M-CPT I gene is also a target gene for the action of PPARs, since a PPAR-responsive element upstream of the first exon of the gene has been localized (Mascaro et al., 1998). Concomitantly, other authors have demonstrated that the M-CPT I gene promoter contains a fatty acid response element localized to a hexameric repeat sequence upstream of the initiator codon that, in cotransfection experiments with expression vectors, demonstrated to be a PPARα response element (Brandt et al., 1998). These results indicate that long-chain fatty acids regulate the transcription of the gene for M-CPT I, a pivotal enzyme in the mitochondrial fatty acid uptake pathway in cardiac myocytes, as well as in skeletal muscle and brown adipose tissue in which fatty acids are a major source of energy; and that this mechanism is mediated by PPARs. Interestingly, the expression of PPARα in liver is under positive and negative control of glucocorticoids and insulin, respectively. The PPAR gene-regulating unit seems to contain hormone-response elements for dexamethasone and insulin, which make possible a significant enhancement or inhibition of the physiological actions of fatty acids in liver (Steineger et al., 1994).

The L-CPT I gene also seems to be regulated by thyroid hormone. In livers of hypothyroid rats, the L-CPT I mRNA level is 40-fold lower compared with that of the hyperthyroid animals (Mynatt et al., 1994). These data suggest that L-CPT I is regulated at the transcriptional level by thyroid hormone, although no thyroid hormone responsive elements have been identified within the first intron or in the proximal promoter (Mangelsdorf and Evans, 1995). It is possible that response elements are located further upstream in the promoter of the gene. Interestingly, it must be kept in mind that nuclear T_3 receptors form heterodimers with RXRs, RARs, vitamin D receptors, and PPARs (Keller et al., 1993; Mangelsdorf and Evans, 1995).

Moreover, since cytokines such as IL-1α and tumor necrosis factor α (TNFα) are implicated in the modulation of fat metabolism after injury and sepsis, it is not surprising that both factors are able to increase hepatic mitochondrial fatty acid oxidation via an increased CPT gene transcription and translation (Barke et al., 1991).

ANTICANCER DRUGS AND THE ROLE OF CARNITINE SYSTEM

Carnitine system in cancer

A possible role of the carnitine system in inducing or worsening the dysmetabolic syndrome associated with cancer has been hypothesized (Calvani et al., 1999). The carnitine system has been studied in different experimental and clinical models of cancer. Although much information is still lacking, a landscape appears in which the carnitine system is variously modified. Abnormalities in the modulation and expression of the components of the system are differently present in various models of tumors under investigation.

TABLE 1. Biochemical changes in Walker 256 carcinosarcoma-bearing rats[1]

Tumor		
Lack of enzyme 3-ketoacid CoA transferase		
Incapability to use ketone bodies as energy substrates		
= CPT I and CPT II activity		
+ different CPT I enzyme isoform		
− different CPT II enzyme isoform		
Liver	Muscle	Pancreas
= CPT I activity	↓ Glutamine content	↓ Insulin secretion
↓ CPT II activity	↑ Branched-chain amino acid oxidation	
− Different CPT I enzyme isoform		
+ Different CPT II enzyme isoform		
↓ Fatty acid oxidation	Plasma	
↑ Fatty acid esterification	↑ Triglycerides	
↑ Free fatty acids	↓ Ketone bodies	
↑ Triglycerides	↑ Free fatty acids	
↓ Ketogenesis		
↓ Ketone bodies	Lymphocytes	
↓ Glycogenolysis	↑ CPT I activity	
↑ Gluconeogenesis	↑ CPT II activity	

[1]= not modified with respect to normal rats; ↑ increased; ↓ decreased; + presence; − no presence.

TABLE 2. Carnitine system in Walker 256 carcinosarcoma-bearing rats[1]

Endocellular metabolic pathways	Tumor	Liver	Lymphocytes
CPT I activity	=	=	↑
CPT II activity	=	↓	↑
CPT I different isoform	+	=	No data
CPT II different isoform	=	+	No data
CT	No data	No data	No data

[1]= not modified; ↑ increased; ↓ decreased; + presence.

TABLE 3. CPT I and CPT II activity in Walker 256 carcinosarcoma-bearing rats after various treatments[1]

	Liver		Tumor	
	CPT I activity	CPT II activity	CPT I activity	CPT II activity
None	=	↓	=	=
Indomethacin	↑	↑	=	=
Insulin			=	↑
Soya oil			↓	=
Almond oil			=	=
Macadamia oil			=	=
Cod liver oil			=	=

[1]= not modified; ↑ increased; ↓ decreased.

Walker 256 carcinosarcoma-bearing rat is an experimental model of tumor in which metabolic changes in tumor and nontumor tissue have been more thoroughly studied (Table 1). In particular, although no data are available about carnitine synthesis and transport in this model of cancer, the expression and activity of CPTs are modified in tumor and nontumor tissue, both in basal conditions and after pharmacological treatment (insulin or indomethacin) and fat diets (Tables 2 and 3) (Evans and Williamson, 1988; Siddiqui and Williams, 1989; Colquhoun and Curi, 1995; Seelaender et al., 1996, 1998; Colquhoun et al., 1998).

In other experimental models of cancer, both in vitro (rat FAO hepatoma cells) (Prip Buus et al., 1992) and in vivo (methylcholantrene-induced sarcoma, Yoshida sarcoma, Morris hepatoma 7777 and 7800), carnitine system status has also been studied, although less extensively (Table 4) (Fields et al., 1981; De la Morena et al., 1988; Noguchi et al., 1993).

No data are currently available regarding carnitine synthesis in cancer patients, although carnitine transport seems to be altered. In fact, sodium ion–dependent, high-affinity human carnitine transporter OCTN2 is strongly expressed in cancer cells (Tamai et al., 1998), such as Melanoma G361, Lung Carcinoma A549, Colorectal Carcinoma SW480, Chronic Myelogenous Leukemia KS62, and Cervix Carcinoma HeLa S3.

Moreover, little information is available about the intracellular carnitine system enzymatic network in human cancers, both in tumor tissue and in nontumor tissue. Nevertheless, experimental results confirm that the carnitine system is affected in different forms of human cancer in a specific manner. In particular, the ratio between free carnitine and carnitine ester concentrations appears modified in tumor patients compared with healthy controls (De la Morena et al., 1983; Willson et al., 1983; Sachan and Dodson, 1987; Dodson et al., 1989; Rössle et al., 1989; Yazdanpanah et al., 1997) (Table 5). This suggests that a dysmetabolic syndrome, extended to the whole organism, may be occurring.

Anticancer drugs and carnitine system

Anticancer drugs can be classified based on their biochemical activities or their origins. These classes include alkylating agents, antimetabolites, natural products, miscellaneous agents, and hormones. Chemotherapeutic effects of anticancer drugs are accomplished through mechanisms occurring at different sites, but are generally aimed toward cytotoxicity. The incapability of anticancer drugs to discriminate between normal and cancer cells represents a limit for their use. Furthermore, anticancer drugs may cause side effects through mechanisms other than anticancer, that can severely compromise the life of patients and, in some cases, can represent a cause of death. For example, it has been described that anticancer therapy can worsen the dysmetabolic syndrome described to occur in cancer patients.

Very little is known about the modulation of the carnitine system by anticancer compounds, but in the last few years more and more experimental and clinical findings have suggested an interference of some anticancer drugs on the carnitine network. Prototypes of anticancer drugs that affect the carnitine system are ifosfamide, cisplatin, taxol, and adriamycin.

TABLE 4. Carnitine system status in experimental models of cancer[1]

In vitro		
Rat FAO hepatoma cells	= CPT I activity ↑ CPT I levels, malonyl-CoA inhibition, lipogenesis ↓ fatty acids oxidation, ketone bodies production	
In vivo		
Animal model	Nontumor tissue	Tumor tissue
Methylcholantrene sarcoma in rat	= Liver CPT activity ↓ Liver lipogenesis	
Yoshida sarcoma in rat	↓ Free carnitine in heart, muscle, liver, serum ↑ Acetylcarnitine in muscle, liver; ↓ in serum ↑ Acylcarnitine in heart, muscle, liver ↑ Free fatty acids in tissues and serum	
Morris hepatoma 7777 and 7800 in Buffalo rat	↓ Liver fatty acid oxidation	↓ CPT activity or absent

[1]= not modified; ↑ increased; ↓ decreased.

TABLE 5. Carnitine system in human cancers[1]

Population	FC	LCAC	SCAC	TC	CPT levels
Pediatric patients with various forms of cancer	= Plasma	= Urine	= Urine	= Plasma	
54 patients with various forms of cancer	= Plasma	= Plasma		= Plasma	
10 patients with esophageal carcinoma	↑ Plasma	↓ Muscle	= Muscle	↑ Plasma	
21 patients with metastatic disease	↓ Plasma ↑ Urine	↓ Plasma ↑ Urine ↓ Renal clearance ↓ Renal absorption	↓ Plasma ↑ Urine ↑ Renal clearance	↓ Plasma ↑ Urine	
6 patients with colon cancer		↑ Tumor tissue	↑ Tumor tissue	↑ Tumor tissue	↑ Tumor tissue
52 women with early breast cancer	↓ Plasma				

[1]FC = free carnitine; LCAC = long-chain acylcarnitine; SCAC = short-chain acylcarnitine; TC = total carnitine; = not modified; ↑ increased; ↓ decreased.

Ifosfamide. The most important pharmacological actions of ifosfamide, and other alkylating agents, are those that disturb the fundamental mechanisms related to cell proliferation. The ability of these drugs to interfere with DNA integrity and function in rapidly proliferating cells provides the basis for their therapeutic applications as well as of their toxic properties.

The alkylating agents differ in their patterns of antitumor activity and in the sites and severity of their side effects. They have in common a propensity to cause dose-limiting toxicity to bone marrow elements and, to a lesser extent, intestinal mucosa. Severe urinary tract toxicity limits the use of ifosfamide, as well.

After treatment with ifosfamide, a dysfunction of the tricarboxylic acid (TCA) cycle is observed and it is not related to the anticancer properties of the molecule, but rather to the intrinsic toxicity of the compound. The metabolic pathway of ifosfamide leads to formation of chloroacetyl-CoA, with subsequent depression of the CoASH level, an indispensable activator in most of the energy-providing systems (TCA cycle, fatty acid oxidation). Carnitine is known to detoxify excess amounts of CoA-bound moieties with formation of acylcarnitines and a subsequent release of free CoA. Indeed, after treatment with ifosfamide, the presence of chloroacetyl-carnitine is detected in urine. In this way, accumulation of chloroacetaldehyde (a nonactive metabolite of the drug) responsible for the observed ifosfamide-induced neurological toxicity and nephrotoxicity, is thought to be prevented (Schlenzig et al., 1995; Visarius et al., 1999). On the other hand, this detoxification leads to an increased secretion of carnitine derivatives in the urine with subsequent secondary deficiency of the molecule.

Thiodiglycolic acid has been identified as a major metabolite of ifosfamide in humans. When administered to rats, thiodiglycolic acid inhibits the carnitine-dependent oxidation of palmitic acid by 55%, but does not affect either the oxidation of octanoic acid, which is carnitine independent, or the oxidation of succinic acid, a marker of Krebs-cycle activity. Additionally, thiodiglycolic acid inhibited oxidation of palmitic acid but not palmitoyl-L-carnitine in isolated rat liver mitochondria, indicating that it either sequesters carnitine or inhibits CPT I. Hence, a mitochondrial dysfunction induced by thiodiglycolic acid may contribute to the adverse effects associated with ifosfamide chemotherapy (Visarius et al., 1998).

Cisplatin. Cisplatin (*cis*-diamminedichloroplatinum) is a divalent, inorganic, water-soluble, platinum-containing complex that appears to enter cells by diffusion. Replacement of chloride by water yields a positively charged molecule that is probably responsible for formation of the activated species of the drug, able to react with nucleic acids, forming DNA adducts. A number of factors influence cisplatin sensitivity in cells, including the intracellular drug accumulation and intracellular levels of glutathione as well as other sulfhydryl compounds, such as metallothionein, capable of binding to and inactivating the drug. Cisplatin can lead to reduction in glomerular filtration and to tubular damage. Since carnitine is absorbed proximal to the tubular level, patients treated with cisplatin may run into an increased loss of carnitine through the kidney. In fact, it has been observed that during the course of therapy with cisplatin, total carnitine clearance increases by a factor of 8. The increased renal excretion of carnitine (likely due to inhibition of carnitine reabsorption) may be considered an early marker of tubular damage due to cisplatin (Berardi et al., 1996;

Heuberger et al., 1998). Also in this case, the loss of carnitine can induce a secondary deficiency of the molecule that can worsen the dysmetabolic status of the patients.

Taxol. This compound exhibits unique pharmacological actions as an inhibitor of mitosis, differing from vinca alkaloids and colchicine derivatives in that it promotes, rather than inhibits, microtubule formation. It binds specifically to the β-tubulin subunit of microtubules and appears to antagonize the disassembly of this key cytoskeletal protein, with the result that bundles of microtubules and aberrant structures derived from microtubules appear in taxol-treated cells. Arrest in mitosis follows. Cell killing is dependent on both drug concentrations and duration of cell exposure. Drugs that block the progression of cells through DNA synthesis and into mitosis antagonize the toxic effects of taxol. Taxol exerts its primary toxic effects on the bone marrow. Myalgias, sensory neuropathy, and mucositis have also been observed. In vitro studies on isolated hepatocytes have revealed that taxol is able to modulate CPT I activity. A number of reports have recently described the existence of specific interactions between CPT I activity and cytoskeletal elements (Bereiter-Hahn and Voth, 1994; Fontaine et al., 1995). The phosphatase inhibitor okadaic acid (OA), which has been shown to disrupt the cytoskeleton of hepatocytes (Holen et al., 1992), has been widely used to investigate the effects of taxol because of its opposite action with respect to taxol. OA is able to stimulate by up to 50% hepatic CPT I activity and palmitate oxidation (Guzman and Geelen, 1992). This observation led to the suggestion that, apart from modulation of rat-liver CPT I activity by malonyl-CoA, a phosphorylation–dephosphorylation mechanism might be involved in the short-term control of this enzyme. However, further research showed that the increase of CPT I activity observed in OA-treated hepatocytes was not due to direct phosphorylation of the CPT I enzyme, but may involve interactions between the mitochondrial outer membrane and extramitochondrial cell components (Guzman et al., 1994). The microtubule stabilizer taxol abolished the changes in CPT I activity induced by OA (Velasco et al., 1996).

Adriamycin. Adriamycin (Doxorubicin), an anthracycline antibiotic, is among the most important antitumor agents. Adriamycin can intercalate with DNA, affecting both DNA and RNA synthesis. DNA single- and double-strand breaks occur by activation of topoisomerase II or by generation of free radicals, which is also highly destructive to cells. The clinical value of adriamycin is limited by an unusual, often irreversible, dose-dependent cardiomyopathy.

A number of studies have demonstrated that the carnitine system is deeply influenced by adriamycin treatment (Table 6). Heart concentrations of free carnitine, and long- and short-chain acylcarnitines are reduced, whereas the concentration of long-chain acyl-CoA is increased (Kawasaki et al., 1996). Associated metabolic changes are decreased fatty acid oxidation (Abdel-aleem et al., 1997), creatine phosphate (Kawasaki et al., 1996), and ATP (Neri et al., 1986). Moreover, protein synthesis and oxygen consumption are decreased, and Ca^{2+} concentration is increased (Neri et al., 1986). Lipemia and proteinemia are increased (Bizzi et al., 1983). Moreover, these studies have shown that adriamycin-induced metabolic changes can be improved by carnitine treatment (Table 6).

TABLE 6. Adriamycin-induced myocardial metabolic changes and effects of L-carnitine treatment[1]

↓ CPT I activity ■	↓ Creatine phosphate ●
↓ CPT II activity ■	↓ Intracellular ATP content ●
↓ Free carnitine ●	↑ Lipemia ○
↓ Short-chain acylcarnitine ●	↑ Proteinemia ○
↓ Long-chain acylcarnitine ●	↓ Protein synthesis ○
↑ Long-chain acyl-CoA ●	↑ Calcium concentration ●
↓ Free fatty acid oxidation ●	↓ Oxygen uptake ●

[1]● = carnitine improvement; ○ = carnitine no effect; ■ = not reported; ↑ increased; ↓ decreased.

The mitochondrial membrane could be the target responsible for adriamycin cardiotoxicity. The formation of a very stable complex between adriamycin and cardiolipin, a phospholipid specific to the inner mitochondrial membrane, has been shown to inhibit several mitochondrial membrane enzymes, whose activities depend on the presence of cardiolipin (Goormaghtigh et al., 1987; Demant, 1991; Robinson, 1993).

Indeed, cardiolipin is also essential for mitochondrial carnitine CT activity. This is supported by the finding that in intact mitochondria of rat liver and heart, the CT activity is markedly inhibited by micromolar concentrations of adriamycin, through binding to cardiolipin (Noël and Pande, 1986).

In rat heart, adriamycin has been observed to inhibit phosphatidylethanolamine N-methylation, resulting in decreased production of methylated intermediates, phosphatidyl-*N*-monomethylethanolamine, and phosphatidyl-*N,N*-dimethylethanolamine, as well as phosphatidylcholine (Iliskovic et al., 1997). Since these phospholipids are involved in cardiolipin synthesis, it is conceivable that adriamycin-induced phosphatidyletanolamine *N*-methyltransferase inhibition leads to a decrease in the cardiolipin content of the inner mitochondrial membrane. It could represent another route for decreasing CT activity.

Adriamycin has been found to directly inhibit rat heart and liver carnitine palmitoyltransferases of both mitochondrial outer (CPT I) and inner (CPT II) membranes. CPT I was more sensitive than CPT II to inhibition by adriamycin. Moreover, the cardiac mitochondrial carnitine palmitoyltransferases seemed to be more sensitive to the inhibitory effects of adriamycin than the liver enzyme (it is useful to keep in mind that CPT I is present in heart in two different isoforms), thus accounting for the toxic effects of the drug observed in heart but not in liver (Brady and Brady, 1987; Kashfi et al., 1990).

Enzymatic kinetic studies have revealed that adriamycin behaves as an uncompetitive inhibitor with respect to palmitoyl-CoA and as a noncompetitive inhibitor with respect to carnitine for both mitochondrial outer and inner membrane enzymes (Kashfi et al., 1990). Adriamycin causes a concentration- and time-dependent inhibition of CPT I–dependent long-chain fatty acid oxidation, whereas acute or chronic administration of carnitine completely abolished adriamycin inhibition. Interestingly, medium- and short-chain fatty acid oxidation, which are independent of CPT I, are also inhibited acutely by adriamycin and could be reversed by carnitine. These data suggest that adriamycin inhibits fatty acid oxidation, in part, secondarily

TABLE 7. L-Carnitine and adriamycin-induced cardiomyopathy[1]

Acute form	Delayed form
Manifested by ECG abnormalities	Manifested by congestive heart failure unresponsive to digitalis
▲ ST-T waves alterations	▲ Signs and symptoms
	Histological features
▲ Arrythmias	*Light microscopy*
	● Edema
	● Sarcoplasmic alterations
	● Myofibrillar fragmentation
	● Myocytes damage and loss
	Electron microscopy
	● Sarcoplasmic vacuolation
	● Mitochondrial degeneration
	● Myofibrillar lysis with formation of sarcoplasmic granular masses

[1]▲ = L-carnitine prevention or improvement in patients; ● = L-carnitine prevention or improvement in animal models.

to inhibition of CPT I and/or depletion of its substrate, carnitine, in cardiac tissue (Abdel-aleem et al., 1997).

A number of studies have demonstrated that carnitine treatment significantly prevents or decreases both acute and delayed forms of cardiomyopathy induced by adriamycin, in animal models (Payne, 1982; McFalls et al., 1986; Torresi et al., 1990; Vick et al., 1990) and in patients (Neri et al., 1983; Gulizia et al., 1984; Durante et al., 1985; De Leonardis et al., 1987; Anselmi et al., 1991, 1993) (Table 7).

The effects of L-carnitine treatment on delayed onset cardiomyopathy induced by adriamycin represent a good paradigm on which to discuss the nature of carnitine and its role in defending and repairing cell structure.

Strauss et al. (1998) define carnitine as a molecule capable of promoting heat shock protein synthesis in a neonatal rat experimental model of adriamycin-induced late onset cardiomyopathy. The heat shock protein 25 (HSP 25) parameter has been chosen because it has been demonstrated that HSP 25 expression plays a role in the protection of cells against injury, including toxic damage (adriamycin toxicity). Moreover, HSP 25 expression appears to be related to adriamycin-induced late onset cardiomyopathy in children (Lipshultz et al., 1991). The HSP-associated protection may be related to the induction of antioxidant enzymes (Yamashita et al., 1997). In heart, which has a low synthesis of HSPs in normal conditions, adriamycin induces a high expression of HSP 25 but more remarkable is the increase of HSP 25 expression with L-carnitine cotreatment. L-Carnitine treatment in animals not intoxicated with adriamycin does not induce HSP 25 gene expression; thus L-carnitine activity is exerted through defense mechanisms.

It is noteworthy to mention that the protective effects of carnitine on adriamycin toxicity are accomplished without either decreasing adriamycin antitumor activity or promoting tumor growth.

In vivo experimental models have demonstrated that: (1) L-carnitine pretreatment increased survival time and did not affect adriamycin inhibition of leukemic colony formation in mice (Alberts et al., 1978); and (2) L-carnitine administration did not promote tumor growth, either in mice bearing osteosarcoma or in mice with implanted mammary carcinoma (Senekowitsch et al., 1987).

Finally, in vitro studies have demonstrated that carnitine addition to three different human cell lines derived from pancreatic tumors had no effect on the number of cells incubated in the presence or absence of adriamycin (Culbreath et al., 1989; Carter et al., 1992).

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