J Mol Med (2003) 81:435–442
DOI 10.1007/s00109-003-0447-6

ORIGINAL ARTICLE

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Downregulation of carnitine acyltransferases and organic cation transporter OCTN2 in mononuclear cells in healthy elderly and patients with myelodysplastic syndromes

Received: 30 July 2002 / Accepted: 14 April 2003 / Published online: 12 June 2003
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Abstract Changes in key enzymes of oxidative metabolism at the mitochondrial level are known to be associated with the aging process, apoptosis, and many diseases. Considering the risk of acquiring a myelodysplastic syndrome (MDS) with age, the aim of this study was to quantify mRNA synthesis of the carnitine palmitoyltransferases (CPT1 and CPT2), carnitine acetyltransferase (CRAT), human specific microsomal CPT, and OCTN2 (organic cation transporter) in mononuclear cells of healthy humans of different age groups and MDS patients. Using quantitative reverse transcriptase real-time PCR we compared mRNA synthesis of the above mentioned enzymes in mononuclear cells from peripheral blood of 23 healthy persons (mean age 45 years), 9 blood and 22 bone marrow samples of 31 MDS patients with varying proportions of apoptotic cells (mean age 78 years), and blood samples of 30 age-matched controls. In addition, plasma carnitine levels were determined. Compared to younger adults, there was a 50% downregulation of CPT1 in elderly persons and in MDS patients. Reduction in CRAT, CPT 2, and OCTN2 was more than 85%. Reduction in microsomal CPT was more pronounced in MDS patients than in age-matched controls (96% vs. 43%). In MDS bone marrow cells there was a negative correlation of CPT1 and CRAT with the relative proportion of apoptotic cells. Plasma carnitine values were similar in all groups. The described reduction in transcription of different genes in blood cells which is well known in different tissues may reflect a systemic signaling process, associated with aging, apoptosis, and MDS.

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Keywords Carnitine acyltransferases · mRNA quantification · Blood cells · Aging · Myelodysplastic syndromes

Abbreviations *CACT:* Carnitine acylcarnitine translocase · *CoA:* Coenzyme A · *CPT:* Carnitine palmitoyltransferase · *CRAT:* Carnitine acetyltransferase · *MDS:* Myelodysplastic syndromes · *MNC:* Mononuclear cells · *PDH:* Pyruvate dehydrogenase · *RTQPCR:* Quantitative reverse transcriptase real-time polymerase chain reaction

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders occurring mainly in elderly persons and are characterized by ineffective erythropoiesis associated with morphological evidence of marrow cell dysplasia resulting in refractory cytopenia despite normal and hypercellular bone marrow. Disturbed regulation of apoptosis is a prominent phenomenon in the pathogenesis of MDS [1]. Although disease progression is accompanied by a decrease in expression of Fas/Apo-1 (CD95) [2] and an increase in antiapoptotic Bcl-2 [3], heterogeneity in patterns of protein expression indicates that factors additional to those of the Bcl-2 family members play a role in deregulated apoptosis in MDS.

However, it has been less recognized that Bcl-2 is located in the mitochondrial membrane in close association with carnitine palmitoyltransferase (CPT) 1, and L-carnitine is an additional factor in the regulation of apoptotic processes (Fig. 1) both at the mitochondrial level and at the level of ceramide synthesis and signaling [4]. CPT1 spans the outer mitochondrial membrane and catalyzes the transfer of fatty acid acyl groups from coenzyme A (CoA) to carnitine which is the rate-limiting step in mitochondrial fatty acid β-oxidation. Acylcarnitine thus formed traverses the inner membrane via carnitine acylcarnitine translocase (CACT). CPT2 catalyzes the transfer of acyl groups from carnitine back to CoA. Furthermore, carnitine acetyltransferase (CRAT) is a mitochondrial matrix enzyme catalyzing the transfer of short, medium and branched chain fatty acids from the corresponding acyl CoAs to carnitine and enabling the removal of these groups from the mitochondrial matrix. The equilibration of acetyl coenzyme and acetylcarnitine by CRAT is an important factor for pyruvate utilization since the activity of pyruvate dehydrogenase (PDH) is coregulated by the concentrations of acetyl-CoA and NADH. In muscle about 90% of pyruvate is shuttled out via PDH in mitochondria [5].

In addition to the mitochondrial transport system there are analogous fatty acid transport systems in microsomes and peroxisomes. Microsomal carnitine acyltransferases are found both in rough and smooth endoplasmic reticulum. The human-specific microsomal CPT1 is also known as “glucose-regulated protein-58” (GRP58), phosphoinosite-specific phospholipase C, hormone-induced protein 70, and endoplasmic reticulum protein 61 (ERp61) [6]. Furthermore, intramitochondrial carnitine and CRAT can react with short- and medium-chain acyl-CoAs to produce acylcarnitines which can be shuttled out of mitochondria. In this way pyruvate dehydrogenase kinase 4 of the PDH complex is coregulated since acetyl-CoA and NADH-H^+ are the main physiological inhibitors of pyruvate utilization. In muscle about 90% of pyruvate is shuttled via PDH in mitochondria [5].

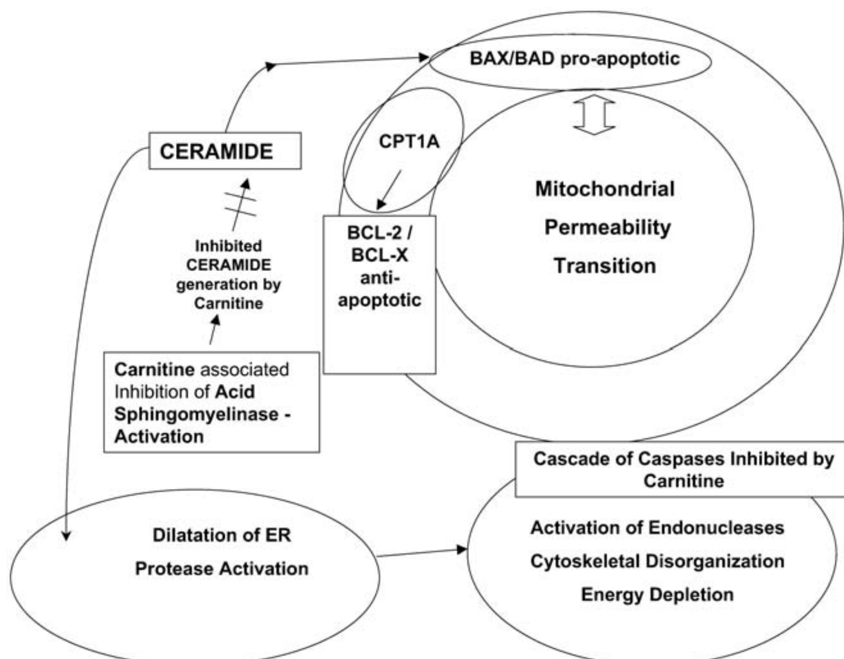

Fig. 1 Schematic diagram showing the role of carnitine in regulation of apoptosis. Association of CPT1 with antiapoptotic Bcl-2 [4] counteracts proapoptotic Bax/Bad which induces mitochondrial permeability transition pore opening and as a consequence release of cytochrome c into the cytoplasm where it participates in caspase activation, which is inhibited by carnitine [23]. Furthermore, carnitine counteracts synthesis of ceramide by inhibiting the key enzyme of ceramide synthesis, acid sphingomyelinase [24]. Activation of proapoptotic Bax/Bad by ceramide [25] is thus inhibited

Table 1 Genomic localization of human carnitine acyltransferase genes and OCTN2

Gene	Protein	Chromosome	Leukemia-associated gene or aberration
Mitochondrial carnitine acyltransferases			
CPT1A	L-CPT I	11q13.1-2	BCL1 (cyclin D_1, involved in B-cell malignancies, 11q13)
CPT1B	M-CPT I	22q13.3-3-ter	E1A (transcription factor binding protein, involved in therapy related acute leukemia, 22q13)
CRAT	CrAT	9q34.1	c-ABL (tyrosine kinase involved in BCR/ABL rearrangement positive leukemias, 9q34)
CPT2	CPT II	1p32	TAL1 (T-cell acute leukemia associated transcription factor, 1p32)
Organic cation transporter: OCTN2	OCTN 2	5q31	5q-deletion (involved in myelodysplastic syndrome and acute myelogenous leukemia)
Microsomal carnitine palmitoyltransferase: GRP58	Glucose-regulated protein-58	15q15	–

Cellular carnitine uptake depends on the function of the organic cation transporter OCTN2. Mutations of this gene are the most common cause of secondary carnitine deficiency in humans [7]. As the transcription and function of such carriers is also known to be affected by the aging process [8], the regulation of this protein might play a critical role in maintenance of intracellular carnitine concentration and thus in the function of both mitochondrial and extramitochondrial carnitine acyltransferases. The chromosomal locations of genes which encode mitochondrial carnitine acyltransferases (CPT1A on 11q13, CPT1B on 22q13, CRAT on 9q34, and CPT2 on 1p32) and of OCTN2 on 5q31 are in the vicinity of regions where leukemia- and lymphoma-associated breakpoints and rearrangements are known to occur (Table 1), but this does not necessarily implicate that these genes play a role in hematological malignancies, many of which are diagnosed in the elderly.

The aim of this study was to determine whether the reduction in the transcriptional rate of carnitine acyltransferases is age-dependent or is characteristic of patients with MDS. Furthermore, MDS bone marrow samples of different subtypes were characterized according to a higher or lower proportion of apoptotic cells. Consequently the transcription of CPT1, CPT2, CRAT, microsomal CPT and OCTN2 was determined in mononuclear cells (MNC) of from different types of MDS and compared to MNC of middle-aged adults and healthy elderly.

Methods

Characteristics of healthy donors and patients

The mean age of adult volunteers was 45.6 years in women (range 33- 58, median 45) and 41.5 years in men (range 26–57, median 40). Elderly persons with normal hematological parameters were residents of two geriatric units. The mean age of elderly women was 87.5 years (range 78–95, median 87) and that of elderly men 88.3 years (range 82–93, median 90). The study examined blood samples which were donated in the course of a routine health check up after informed consent. MNC from 23 adults (10 men, 13 women), 41 elderly persons (3 men, 39 women), and 31 MDS

Table 2 Patients' characteristics (*AML* acute myoblastic leukemia, *FAB* French-American-British Cooperative Group,*MDS* myelodysplastic syndromes,*RA* refractory anemia,*RARS* refractory anemia with ringed sideroblasts, *RAEB* refractory anemia with excess of blasts,*RAEB-T* refractory anemia with excess of blasts in transformation,*RCMD* refractory cytopenia with multilineage dysplasia, *RCMDRS* refractory cytopenia with multilineage dysplasia with ringed sideroblasts, *WHO* World Health Organization)

Patient no.	Age (years)	Sex	Classification	
			FAB	WHO
Marrow				
1	76	F	RA	5q-
2	87	F	RA	RCMD
3	91	F	RA	RCMD
4	87	F	RA	RA
5	80	M	RARS	RARS
6	79	M	RARS	RARS
7	82	F	RARS	RCMDRS
8	79	M	RARS	RCMDRS
9	80	M	RARS	RCMDRS
10	82	M	RARS	RCMDRS
11	72	F	RARS	RCMDRS
12	87	F	RARS	RCMDRS
13	67	M	RARS	RCMDRS
14	88	M	RARS	RCMDRS
15	90	F	RARS	RCMDRS
16	73	F	RAEB	RAEB I
17	67	M	RAEB	RAEB I
18	73	M	RAEB	RAEB I
19	61	M	RAEB	RAEB I
20	80	F	RAEB	RAEB I
21	87	M	RAEB-T	No MDS (AML)
22	75	M	RAEBT	No MDS (AML)
Blood				
1	77	M	RA	RA
2	76	M	RA	RA
3	84	F	RA	RCMD
4	85	F	RA	RCMD
5	80	F	RARS	RCMDRS
6	76	F	RARS	RCMDRS
7	80	M	RARS	RCMDRS
8	72	F	RARS	RCMDRS
9	75	F	RAEB	RAEB I

Table 3 Primers and PCR conditions (mCPT microsomal CPT)

PCR primer	Sequence	PCR product size (bp)	Annealing		Extension		Acquisition	
			Temp. (°C)	Time (s)	Temp. (°C)	Time (s)	Temp. (°C)	Time (s)
β-Actin	S: 5′-gccATccTAAAAgccAc 3′ A: 5′-TcAAcTggTcTcAAgTcAgTg-3′	289	64	5	72	34	83	1
CPT1A	S: 5′-ccTTccAAcTcATTcAg –3′ A: 5′-ccAggATccTcTgcATcTg- 3′	298	62	5	72	34	87	1
CPT1B	S: 5′-ggTgAAcAgcAAcTATTATgTc–3′ A: 5′–ATccTcTggAAgTgcATc–3′	348	62	6	72	34	87	1
CPT 2	S. 5′-gggAAgggAAgggAgAcgAg–3′ A: 5′-ccAAgAcAcTgcgTcAggAc–3′	173	63	5	72	34	92	1
CRAT	S: 5′-gAAgcccTTcTccTT-3′ R: 5′-cTc ccc TAc Acc Tcc TgA g-3′	175	64	5	72	34	91	1
mCPT	S: 5′-cccTcAcATgAcAgAAgAc–3′ A: 5′-cTccTgcATgAcAAAcTTc-3′	270	64	5	72	34	83	1
OCTN2	S: 5′-TccAAgTcAcAcAAggATg–3′ A: 5′-TcccTAgAggAAggTggTg–3′	246	62	5	72	34	86	1
FAS	S: 5′-ggcATcTggAcccTccTAc-3′ A: 5′-ccT cTTTgcAcTTggTgTTg-3′	367	62	5	72	34	87	1

patients (15 men, 16 women) as well as plasma samples from 110 adults (25 men, 85 women), 44 elderly (3 men, 41 women), and 9 MDS patients (2 men, 7 women) were analyzed. The mean age of MDS patients was 78 years (range 67–87, median 79), 15 men with a mean age of 78 years (range 67–87, median 80), and 16 women with a mean age of 78 years (range 67–87, median 79). Blood samples of MDS patients were from 9 patients (2 men, 7 women) receiving supportive therapy, and bone marrow samples were from 22 untreated patients (10 men, 12 women) obtained at the time of diagnosis. Patients' characteristics are shown in Table 2. To evaluate a possible association of gene expression profiles and cell types, lymph node derived B-lymphocytes and peripheral blood stem cells (enriched for $CD34^+$ cells) and bone marrow, each from three different younger adults were used as additional controls.

Cell separation for collection of CD34+ cells

Peripheral blood stem cell donors were treated with 10 µg/kg per day of glycosylated granulocyte colony-stimulating factor (Lenograstin, Aventis, Milan, Italy) for 4–6 days, after informed consent. The progenitor cell content in peripheral blood and apheresis components was monitored by flow cytometric enumeration of $CD34^+$ cells. Peripheral blood stem cell collection was started when the threshold of 20 million $CD34^+$ cells/l peripheral blood was reached [9]. Low-density mononuclear cells were isolated by centrifugation over Ficoll/Hypaque (Nycomed Pharma, Oslo, Norway) gradients to obtain MNC. After washing the cells were subjected to plastic adherence for 60 min at 37°C. $CD34^+$ cells were isolated from the nonadherent fraction using Midi-MACS high-gradient separation column (Miltenyi Biotech, Bergisch Gladbach, Germany) according to the manufacturer's instruction.

Analysis of mRNA expression

All analyses were made from 4 ml peripheral blood or bone marrow collected in EDTA tubes. After separation of plasma for L-carnitine determination mononuclear cells were enriched by density gradient centrifugation using Ficoll/Hypaque separation medium (density according to fraction index: 1.077) and washed several times in phosphate-buffered solution. Aliquots of 1–10 million cells were frozen in 4 M guanidine isothiocyanate for preparation of mRNA and cDNA for subsequent quantitative reverse transcriptase real-time polymerase chain reaction (RTQPCR).

Isolation of mRNA and preparation of cDNA were carried out according to standard procedures. RTQPCR was carried out using a LightCycler System (Roche) which allows amplification and detection (by fluorescence) in the same tube, using a kinetic approach. The method of quantitative PCR has been described in detail elsewhere [10, 11, 12]. Dilutions of 200–2 ng cDNA were used in each assay. The transcription rate was evaluated by calculating the number of copies of the analyzed gene per 100 copies of β-actin which showed the lowest standard deviations per amount of cDNA and therefore was used as an internal standard. Details of primers and reaction conditions are shown in Table 3.

Statistical comparison between the groups used analysis of variance followed by Dunnet's *t* test for multiple comparison.

Analysis of apoptosis

From all MDS bone marrow samples analyzed in this study the percentage of apoptotic cells was determined by screening at least 1000 cells for evaluation of typical nuclear fragmentation patterns. In addition, staining for phosphatidyl serine movement to the outer leaflet of the plasma membrane was performed from eight bone marrow samples using a commercially available annexin V–fluorescein isothiocyanate system (Roche Diagnostics) and counterstaining with propidium iodide. From the same samples we also analyzed mRNA expression of Fas/CD95 using RTQPCR.

Results

Expression of mitochondrial carnitine acyltransferases

Transcript levels of CPT1A, CPT1B, CPT 2, and CRAT are shown in Fig. 2. None of the genes analyzed showed differences in expression rate between men and women, and there were also no notable differences between blood and bone marrow samples. Results from controls

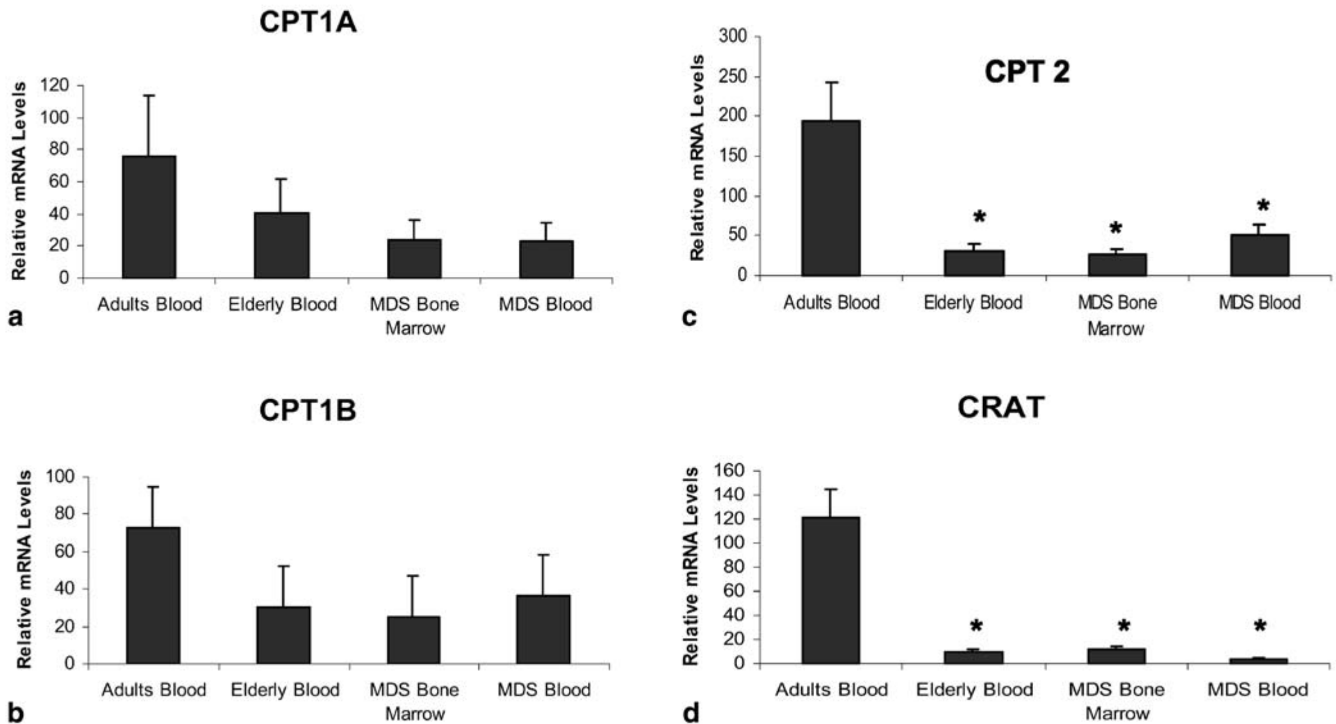

Fig. 2 Gene expression rates of mitochondrial carnitine acyltransferases CPT1A (**a**), CPT1B (**b**), CPT 2 (**c**), and CRAT (**d**) all decrease in MNC from elderly persons and MNC from blood or bone marrow of MDS patients vs. adults. *$P<0.05$ vs. adults

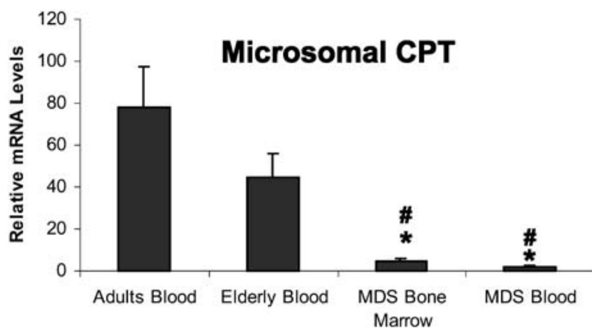

Fig. 3 Gene expression rate of microsomal carnitine palmitoyltransferase [also known as glucose-regulated protein-58 (GRP58), phosphoinosite-specific phospholipase C, hormone-induced protein 70, and endoplasmic reticulum protein-61 (Erp61)] decreases in MNC from elderly persons and MDS patients vs. adults and also in MNC from blood or bone marrow of MDS patients vs. elderly. *$P<0.05$ vs. adults, $^{\#}P<0.05$ vs. elderly

($CD34^+$ stem cells from blood or bone marrow and lymph node derived B-lymphocytes) did not indicate a cell type associated mRNA expression profile of the above genes. The mean expression rate of CPT1A which encodes the so-called liver isoform of CPT1 in MNC from adults was 76% of β-actin. CPT1A expression was significantly lower in MNC from peripheral blood of elderly persons and from bone marrow and peripheral blood of MDS patients than in healthy adults, with mean transcription rates of 41%, 24%, and 23% of β-actin, respectively (Fig. 2a). The mean expression rate of CPT1B, which encodes the muscle isoform of CPT1 in MNC from adults, was 73% of β-actin. CPT1B expression was also significantly lower in elderly persons and in both bone marrow and peripheral blood of MDS patients, with mean transcription rates of 30%, 25%, and 36% of β-actin, respectively (Fig. 2b). The mean expression rate of CPT2 in MNC from adults was 195% of β-actin. CPT2 expression was significantly lower in elderly persons and in both bone marrow and peripheral blood of MDS patients, with mean transcription rates of 31%, 27%, and 51% of β-actin (Fig. 2c). The mean expression rate of CRAT in MNC from adults was 121% of β-actin. CRAT expression was significantly lower in elderly persons and in bone marrow and peripheral blood of MDS patients, with mean transcription rates of 10%, 12% and 4% of β-actin (Fig. 2d).

Expression of the microsomal carnitine palmitoyltransferase microsomal CPT1

Transcript levels of the microsomal CPT1 are shown in Fig. 3. The mean expression rate of microsomal CPT1 in MNC from adults was 78% of β-actin. MCPT1 expression was decreased but not significantly lower in healthy elderly adults, with a mean transcription rate of 45% of β-actin, but significantly downregulated in MNC from MDS patients (5% in bone marrow and 2% of β-actin in blood).

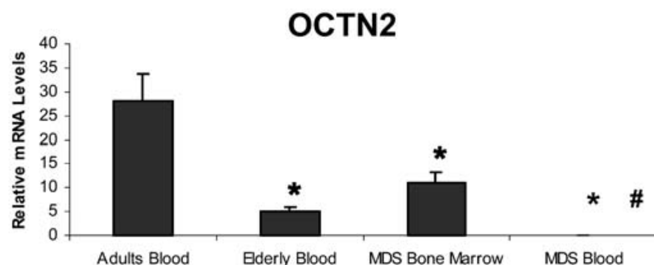

Fig. 4 Gene expression rate of organic cation transporter OCTN2 decreases in MNC from elderly persons and bone marrow from MDS patients vs. adults; in MNC from peripheral blood of MDS patients mRNA of this gene was below the detection limit. $^*P<0.05$ vs. adults, $^\#P<0.05$ vs. elderly

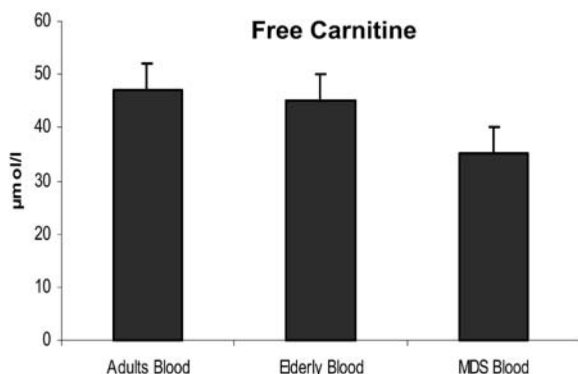

Fig. 5 Plasma carnitine levels in healthy elderly persons (*n*=129) are similar to those in adults (*n*=14; 45 vs. 47 µmol/l) and lower in MDS (*n*=16; 35 µmol/l), but differences are not significant

Expression of organic cation transporter OCTN2 and carnitine levels in plasma

Transcript levels of OCTN2 are shown in Fig. 4. The mean expression rate of OCTN2 in MNC from adults was 28% of β-actin. OCTN2 expression was significantly lower in MNC from elderly persons (5%) and bone marrow of MDS patients, with a mean transcription rate of 11% of β-actin. In MNC from peripheral blood of MDS patients the transcripts were below the detection limit. Plasma carnitine levels in healthy elderly persons were similar to those in adults (45 vs. 47 µmol/l) and lower in MDS (35 µmol/l) but differences were still not significant (Fig. 5).

Transcription rates in MDS bone marrow in relation to apoptosis

The percentage of apoptotic cells as evaluated by morphological analysis in all 23 MDS bone marrow samples and in addition by annexin V–propidium iodide staining in eight cases was higher in refractory anemia with ringed sideroblasts and refractory anemia than in refractory anemia with excess of blasts or refractory anemia with excess of blasts in transformation (less than 2%

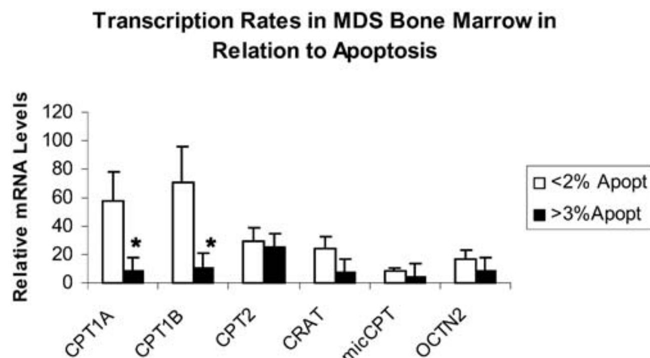

Fig. 6 Gene expression rates of mitochondrial carnitine acyltransferases CPT1A, CPT1B, CPT2, and CRAT as well as microsomal CPT and OCTN2 are all downregulated in MDS bone marrow cells with a relatively higher proportion of apoptotic cells (15 samples: 11 refractory anemia with ringed sideroblasts, 4 refractory anemia) than those with a lower rate of apoptosis (7 samples: 5 refractory anemia with excess of blasts, 2 refractory anemia with excess of blasts in transformation). $^*P<0.05$ vs. samples with fewer than 2% apoptotic cells

apoptotic cells). Mean relative mRNA expression level of the apoptosis-associated Fas (CD95) as determined by RTQPCR was 0.5% of β-actin in those bone marrow samples with a low rate of apoptotic cells and 7% of β-actin in samples with more than 3% apoptotic cells. As shown in Fig. 6, all samples with a higher percentage of apoptotic cells had lower gene expression levels which were most pronounced in CPT1A with 8 vs. 58, CPT1B with 11 vs. 71, and CRAT with 7 vs. 24 copies/100 copies β-actin.

Discussion

The data presented here show that the transcription rate of CPT1A, CPT1B, and CPT2 is decreased in the MNC of elderly persons and MDS patients. There is also a remarkable downregulation of CRAT, the microsomal CPT and OCTN2 in MNC of elderly persons and MDS patients, possibly indicating a predisposition to age-associated diseases. The present results support the necessity of age-matched controls, particularly when examining diseases such as MDS [13], which are known for their predominance in the elderly population. It is well known that aging is associated with a decrease in levels of thyroid and steroid hormones. These hormones play a general role in transcriptional regulation of carnitine acyltransferases, although the transcription of each enzyme is regulated individually.

CPT1A has a thyroid hormone responsive element and a CCAAT box in its transcriptional promoter which is frequently observed in glucocorticoid and thyroid responsive genes [14]. Thus downregulation of CPT1A might be partly associated with lower thyroid hormone levels in senescent organisms. A recent study showed that the age-related decline in thyroid stimulating hormone and free thyroxine may be related to an age-depen-

dent reduction of 5′-deiodinase activity rather than to important changes in nutritional markers [15]. Long chain fatty acids have been shown to activate both CPT1A and CPT1B transcription [16, 17, 18], and the fat-activated fatty acid response element in the promotor of these genes is activated through the peroxisome proliferator-activated receptor α.

Our data indicate that the degree of mRNA downregulation in healthy elderly and MDS patients is more pronounced for CRAT, CPT2, and OCTN2. Furthermore, the transcriptional rate of most carnitine acyltransferases is not in the least dependent on the intracellular carnitine levels and thus the efficiency of carnitine uptake [8, 19]. In MDS patients and elderly persons there was also remarkable downregulation of the organic cation transporter OCTN2 which is the most important factor for cellular carnitine uptake in addition to other transport proteins which need higher concentrations of carnitine [20]. Considering our results showing that plasma carnitine levels of MDS patients were in the same range as in healthy adults (Fig. 5), a dysregulation of carnitine uptake into the cell appears to provide an explanation for the downregulation of these enzymes in aged organisms as well as MDS patients [11]. However, it was not possible to analyze intracellular carnitine levels in MNC due to the limited amount of material available for the present study.

In contrast to the elderly, there is a marked reduction in microsomal CPT1 in MDS patients This may be related to the multiple activities of this enzyme including a phospholipase C activity which may have a striking effect on signal transduction from growth factor receptors involved in hematopoiesis. Different proteins with phospholipase C activity and endoplasmic reticulum proteins are known to show impaired expression in lymphocytes of elderly persons. Phospholipase C activity is involved in signal transduction of G protein mediated cytokine effects to phosphoinositole diphosphate. This may be related to disturbed patterns of cellular proliferation which appear to be associated with altered signal transduction patterns in MDS [21].

Despite age-associated differences mRNA synthesis rates in MNC were similar in peripheral blood and bone marrow. This indicates that expression rates of MCAs appear to be independent of cell type, which was confirmed by a pilot study showing similar ranges of mRNA levels for the genes analyzed in lymph node derived B-lymphocytes and $CD34^{+}$ blood stem cells. Differences were observed between the heterogeneous MDS subtypes when the relative percentage of apoptotic cells was considered. Subtypes with 5–30% blasts (refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation) which were associated with fewer than 2% apoptotic cells (e.g., [1]) had higher mRNA levels of CPT1A, CPT1B, and CRAT than subtypes with fewer than 5% blasts (refractory anemia, refractory anemia with ringed sideroblasts) and more than 3% apoptotic cells. As seen in Fig. 6, the levels of CPT1A, CPT1B, and CRAT of bone marrow samples from MDS patients with a lower rate of apoptosis were similar to those in blood cells and bone marrow cells of healthy younger adults. This may be due to the fact that in both cases there is a lower incidence of apoptosis than in blood samples of elderly persons, which are also known to have a higher percentage of apoptotic cells [22]. The close association of CPT1 and the antiapoptotic Bcl-2 within the mitochondrial membrane [4] could provide an explanation for this observation.

To our knowledge, this is the first report to describe differences between MNC of peripheral blood or bone marrow from MDS patients to those of middle-aged adults and elderly donors with respect to the transcription rate of CPT1, CPT2, CRAT, microsomal CPT, and OCTN2. Considering the heterogeneity of MDS, the accuracy of subtype diagnosis validated in different classifications and prognostic scores is still a topic of discussion [10]. Our findings provide a basis for future studies which aim to examine whether the repression of adult metabolic genes in MDS patients and elderly individuals is regulated by the induction of repressors or by a decrease in stimulation and to elucidate whether there are MDS-specific expression profiles in metabolically regulated genes. The reduced transcriptional rate of mitochondrial carnitine acyltransferases could be responsible for malnutrition in the elderly and particularly in patients with malignant diseases but possibly reflects also the higher rate of apoptosis in these individuals.

Acknowledgements This research was supported in part by the Herzfelder Stiftung, Jubiläumsfonds der Österreichischen Nationalbank, and Bürgermeisterfonds der Stadt Wien.

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