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Cytidine Triphosphate (CTP) Synthetase Activity During Cell Cycle Progression in Normal and Malignant T-lymphocytic Cells

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The role of cytidine triphosphate (CTP) synthetase (EC 6.3.4.2.) in the pyrimidine ribonucleotide metabolism of MOLT-3 human T-ALL cell line cells and normal human T lymphocytes during the cell cycle traverse was studied. Highly pure G1-phase samples and samples enriched in S-phase cells were obtained by counterflow centrifugation. The activity of CTP synthetase *in situ*, measured in pulse-chase experiments, was similar in the G1-phase and S-phase MOLT-3 cells. In contrast, in S-phase T lymphocytes, an increased activity of CTP synthetase was observed compared with G1-phase T lymphocytes. Nevertheless, the MOLT-3 samples showed an increased activity of CTP synthetase in comparison with either G1-phase or S-phase enriched samples of normal T lymphocytes. Therefore, the increased activity of CTP synthetase of MOLT-3 cells is a cell cycle-independent feature, whereas among normal T lymphocytes, the increase in activity of CTP synthetase that arises after a growth stimulus is more prominent in the S-phase.

Key words: cell cycle, pyrimidine ribonucleotides, lymphoblastic leukemia, transformation, CTP synthetase
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INTRODUCTION

HUMAN LEUKAEMIA cells do not differ in growth rate from normal bone marrow blasts, but they do lack the normal restraint to re-enter the cell division cycle after mitosis and usually fail to differentiate [1]. In recent years, many aspects of the (onco-) genetic background of this deregulation have been unravelled, and many proteins that are normally involved in the regulation of the cell cycle have been identified [2, 3]. However, whether specific metabolic alterations are related to this uncontrolled drift for renewal is still largely unknown.

In general, cycling cells have an increased synthesis rate of RNA compared with resting cells. This increase is more pronounced in S-phase cells than in G1-phase cells [4]. Beyond this, S-phase cells by definition synthesise DNA as well. Therefore, cycling cells and especially S-phase cells can be assumed to synthesise increased amounts of ribonucleotides and deoxyribonucleotides to support the synthesis of the nucleic acids. Indeed, blood cells from patients suffering from leukaemia, which comprise an increased fraction of such cycling and therewith S-phase cells, do contain larger amounts of ribonucleotides [5–7] and deoxyribonucleotides [8–10] in comparison with resting normal peripheral blood lymphocytes. For ribonucleotides, the most pronounced increases observed are that of the pyrimidines, and since the relative increase in cytidine triphosphate (CTP) is largest, these leukaemic cells show a decreased ratio of uracil over cytosine ribonucleotides [5–7]. The enzyme CTP synthetase (EC 6.3.4.2.) is rate-limiting in the synthesis of CTP via the *de novo* pathway or the uridine salvage route, and maintains a certain uracil-to-cytosine ribonucleotide ratio due to feedback inhibition by its product CTP [11]. Therefore, one can expect an increased activity of CTP synthetase in the S-phase of the cell cycle to support the increased syntheses of nucleic acids.

Recently, we developed a system to study the *in situ* activity of CTP synthetase by analysis of the fluxes through the pyrimidine ribonucleotide pathways using [^{14}C]uridine. We found that the activity of CTP synthetase in MOLT-3 cells was increased compared with the activity observed in proliferating normal human T lymphocytes [12]. Using our pulse-chase approach, we have investigated the role of CTP synthetase in the synthesis of CTP in various cell-cycle phases of malignant and normal human proliferating T lymphoblastic cells.

METHODS

Cells

MOLT-3 T-ALL leukaemia cell-line cells and growth-induced normal human T lymphocytes were cultured, counted and the viability was determined as previously described [12].

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Fractions of either type of cells enriched in G1-phase or S-phase cells were obtained by counterflow centrifugation and analysed by flow cytometry as previously described [13].

Measurement of cytidine triphosphate synthetase activity in situ *using* [^{14}C]*uridine*

After elutriation, the collected cell fractions were exposed to standard culture conditions for 1 h. Subsequently, samples were subjected to a pulse-chase study of the pyrimidine ribonucleotide metabolism with emphasis on the role of CTP synthetase as previously described [12]. Briefly, 2–4 μM of [^{14}C]uridine was added to cell samples, and after 1 h (pulse), the nucleotides were extracted from part of the cells using perchloric acid. The remaining cells were centrifuged and resuspended in fresh medium at 37°C. Another extract was made 4 h after application of [^{14}C]uridine (chase). Extracts were analysed for content of nucleotides and of incorporated [^{14}C]uridine by HPLC and on-line radiodetection [14]. The amounts of [^{14}C]uridine incorporated into the nucleic acids were analysed in the pellets obtained by the acid extraction of the cells [12]. The differences between the data were analysed with the two-sided students *t*-test.

RESULTS

Counterflow centrifugation of cells and cell cycle analyses

By counterflow centrifugation, various cell samples were obtained with differences in mean cell size, as assessed by the Coulter Channelyser (Table 1). The difference between the largest and smallest cells was greater for T lymphocytes (median values 45 versus 15) than for MOLT-3 cells (51 versus 35). This finding was confirmed by microscopic analysis of cell diameters in cytospin preparations from elutriated cell fractions. Based on the differences in cell size, specific samples were selected for pulse-chase studies and analyses of cell cycle distribution. The results of the cell-cycle analyses of fractions are given in Table 1. The MOLT-3 fraction with median size value 35 contained more than 85% G1-phase cells. The MOLT-3 fraction with median size value 51 contained not more than 5% G1-phase cells, 70–75% S-phase cells and 20–25% G2/M cells including 10% mitotic cells (as judged by the microscopical analyses of cytospinned cells). The fraction of T lymphocytes with median size value 15 contained over 90% G1-phase cells. These small T lymphocytes were actively proceeding through the G_1-phase because a high cytoplasm to nucleus ratio was measured in these cells, a parameter that characteristically increases as soon as human lymphocytic G_0 cells are stimulated to proliferate. The fraction of T lymphocytes with median size value 38 contained 45–55% S-phase cells. With the fractions mentioned, studies on the ribonucleotide contents and studies on the pyrimidine ribonucleotide metabolism using [^{14}C]uridine were performed with emphasis on the activity of CTP synthetase.

Nucleotide contents and ratios

The amounts of ribonucleotides and their ratios for the various cell fractions are given in Table 1. In S-phase T lymphocytes, the adenine-to-guanine and the uracil-to-cytosine ribonucleotide ratios were decreased compared with those of G1-phase T lymphocytes ($P < 0.001$). In contrast, similar adenine-to-guanine and uracil-to-cytosine nucleotide ratios were observed in the G1- and S-phase enriched MOLT-3 cell samples. Moreover, the ratios in these samples were equal to that of non-elutriated MOLT-3 cells, whereas in both G1- and S-phase T lymphocytes the adenine-to-guanine ratio was decreased in comparison with non-elutriated proliferating T lymphocytes ($P < 0.001$) (results not shown, see ref. [12]). A slight inconsistency between the adenine/guanine ratios of non-elutriated cells and their elutriated fractions is not uncommon as it has also been described for HL-60 cells [5].

Incorporation of [^{14}C]*uridine into nucleotides and nucleic acids*

During the 1-h pulse, much more [^{14}C]uridine was incorporated into the nucleotide pools of both G1- and S-phase MOLT-3 cells in comparison with either G1- or S-phase T lymphocytes (Table 2). In S-phase T lymphocytes the rate of incorporation into the pyrimidine ribonucleotides per million cells was 4-fold greater, compared with that for G1-phase T lymphocytes. After correction for the protein mass of these cells, the synthesis rate was still 1.5 times greater ($P < 0.01$) in the S-phase T lymphocytes (Tables 1 and 2). In contrast, in MOLT-3 cells, the

Table 1. Cell size, cell cycle distribution, nucleotide contents and nucleotide ratios of various fractions of various types of human lymphocytic cells

	G1-phase T lymphocytes (n = 5)	S-phase T lymphocytes (n = 5)	G1-phase MOLT-3 cells (n = 5)	S-phase MOLT-3 cells (n = 5)
Median cell size	15	45	35	51
Cell-cycle distribution	> 90% G1 < 10% S	< 45% G1 55% S	> 85% G1 < 15% S	< 5% G1 > 70% S
AMP + ADP + ATP	1377 ± 167	3307 ± 418	3814 ± 1364	4968 ± 1998
GMP + GDP + GTP	376 ± 45	1138 ± 162	894 ± 150	1189 ± 245
UDP + UTP	250 ± 47	712 ± 109	904 ± 271	1190 ± 427
CRP + CTP	111 ± 18	432 ± 63	393 ± 84	526 ± 154
UDP sugars	94 ± 19	345 ± 78	565 ± 188	729 ± 268
Total nucleotides	2210 ± 267	5961 ± 780	6581 ± 1947	8634 ± 2911
Picomol nucleotides/μg protein	19 ± 1	53 ± 5	56 ± 4	58 ± 9
Purine : pyrimidine	4.9 ± 0.5	3.9 ± 0.2	3.6 ± 0.4	3.6 ± 0.5
Adenine : guanine	3.7 ± 0.1	2.9 ± 0.2	4.2 ± 1.1	4.1 ± 1.2
Uracil : cytosine	2.4 ± 0.3	1.7 ± 0.1	2.3 ± 0.4	2.2 ± 0.4

Concentration in pmol/10^6 cells; mean ± standard deviation. The cell size is given in arbitrary units.

Table 2. Incorporation of radiolabelled pyrimidine nucleosides into pyrimidine nucleotide pools and nucleic acids of various lymphocytic cells

	1-h pulse, presteady state		3-h chase, steady state	
	Nucleotides	Nucleic acids	Nucleotides	Nucleic acids
G1-phase T lymphocytes	25 ± 3	6 ± 1	14 ± 1	10 ± 2
S-phase T lymphocytes	98 ± 19	48 ± 12	52 ± 14	64 ± 20
G1-phase MOLT-3 cells	189 ± 21	113 ± 16	105 ± 23	191 ± 15
S-phase MOLT-3 cells	223 ± 19	124 ± 8	136 ± 14	252 ± 58

The values represent pmol radiolabelled nucleotides (including UDP sugars) or radiolabelled nucleic acids per 10^6 cells, and are the mean of three independent experiments with standard deviation for each cell type. Because MOLT-3 cells are tetraploid cells, this in part explains the increased incorporation of [^{14}C]uridine compared with the normal T lymphocytes.

rate of incorporation of [^{14}C]uridine into nucleotides was similar in both the G1- and S-phase (Table 2).

As Table 2 further shows, the G1- and S-phase MOLT-3 cells also incorporated more [^{14}C]uridine into the nucleic acids compared with either G1-phase or S-phase T lymphocytes. This is probably, in part, a reflection of the tetraploid state of the MOLT-3 cells. The amount incorporated into the nucleic acids in S-phase MOLT-3 cells was equivalent to the amount incorporated in G1-phase MOLT-3 cells (Table 2). In contrast, in the S-phase T lymphocytes more [^{14}C]uridine was incorporated into the nucleic acids than in the G1-phase T lymphocytes.

Thus, the fluxes of [^{14}C]uridine through the nucleotide pools into the nucleic acids were enhanced in T lymphocytes during their transition from the G1- to the S-phase of the cell cycle, whereas in MOLT-3 cells no such increase was observed. The amounts of [^{14}C]uridine that were present in the nucleotide pools and nucleic acids during the steady-state phase (3 h chase, see ref. [12]), confirmed the observations we made after the 1-h pulse (Table 2).

The synthesis of CTP

As soon as the distribution of [^{14}C]uridine has reached a steady-state situation, the contributions of CTP synthetase and the cytidine salvage reactions to the synthesis of CTP are reflected by the ratio of the percentages of newly synthesised CTP and UTP, i.e. [^{14}C]CTP/CTP over [^{14}C]UTP/UTP (C*/U*) as described in ref. [12]. If all CTP is synthesised from UTP, this ratio will be one, and if all CTP is synthesised via salvage of cytidine, this ratio will be zero. The presteady-state (1-h pulse) and steady-state (3-h chase after the 1-h pulse) C*/U* ratios for the cell samples are given in Table 3. In G1- and S-phase MOLT-3 cells, similar C*/U* ratios were observed, both after the pulse and at 3 h after the onset of the chase. In both situations, the values for G1- and S-phase T lymphocytes were lower compared with the MOLT-3 cells. Comparison between the T-lymphocytic samples showed that, at the end of the pulse, in the S-phase-enriched fractions, the ratio was higher, suggesting an increased activity of CTP synthetase in S-phase T lymphocytes as compared with G1-phase T lymphocytes. 3 h after the onset of the chase, the C*/U* ratio in both samples had increased. The S-phase-enriched fractions had a small but still significantly ($P < 0.01$) higher value than the G1-phase T lymphocytes. The convergence to more similar ratios was probably related to the progression of part of the G1-phase T lymphocytes towards the S-phase during the pulse-chase experiments. Such a shift was demonstrated by the flow-cytometric analyses (results not shown). However, the values never approached the high steady-state C*/U* values observed in the MOLT-3 cells (Table 3).

DISCUSSION

Both in the G1- and S-phase leukaemic MOLT-3 cells, the fluxes through CTP synthetase were increased compared with either G1- and S-phase growth-stimulated normal T lymphocytes (Tables 2 and 3). The contribution of CTP synthetase to newly synthesised CTP was similar in G1-phase and S-phase MOLT-3 cells. In contrast, an increasing proportion of CTP was synthesised via CTP synthetase as the growth-stimulated normal T lymphocytes entered the S-phase of the cell cycle (Table 3). Previously, we showed that even after growth arrest and induction of differentiation in MOLT-3 cells most CTP was still synthesised from UTP and not by salvage of cytidine [12]. The combined results of both studies form strong evidence that

Table 3. Activity of CTP synthetase

	1-h pulse, presteady state	3-h chase, steady state
G1-phase T lymphocytes	0.05*	0.22 ± 0.02
S-phase T lymphocytes	0.17 ± 0.04	0.27 ± 0.03
G1-phase MOLT-3 cells	0.28 ± 0.06	0.75 ± 0.17
S-phase MOLT-3 cells	0.31 ± 0.07	0.75 ± 0.18

* Only in one of three experiments was sufficient [^{14}C]CTP detected to calculate the quotient, in the other two this resulted in a quotient of zero. The ratio of [^{14}C]CTP/CTP over [^{14}C]UTP/UTP, reflecting the contribution of CTP synthetase to newly synthesised CTP. Data are the mean of three independent experiments ± standard deviation.

the increased activity of CTP synthetase in MOLT-3 cells is not related to an increased cell cycle traverse or altered cell cycle distribution, or to an enhanced synthesis of nucleotides or nucleic acids, but is related to the transformed character of the MOLT-3 cells. Previous results using HL-60 cells suggested a transformation-associated, cell cycle independent increase in the activity of CTP synthetase in malignant myeloid leukaemia cells compared with their normal counterpart cells (human neutrophils) [5]. In contrast, for normal human T lymphocytes, the increase in ribonucleotide contents with the decreased purine-to-pyrimidine, adenine-to-guanine and uracil-to-cytosine ratios compared with peripheral blood lymphocytes (Table 1), the incorporation of [^{14}C]uridine into nucleotides and nucleic acids (Table 2) and the increase in the activity of CTP synthetase (Table 3) are more pronounced in the S-phase T lymphocytes than in the G1-phase T lymphocytes. This demonstrates that in normal T lymphocytes, these phenomena are related to cell cycle progression. The S-phase T lymphocytes have a uracil-to-cytosine ribonucleotide ratio which is even lower than that of MOLT-3 cells (Table 1). Nevertheless, the contribution of CTP synthetase to the synthesis of CTP is quite limited in the S-phase T lymphocytes, compared with the MOLT-3 cells (Table 3). This implies that in the proliferating T lymphocytes most CTP must be synthesised through the salvage of cytidine [15].

A decreased ratio of uracil-to-cytosine ribonucleotides compared with resting peripheral blood lymphocytes due to increased CTP pools is a feature discovered in all human ALL patients cells as well as in other malignant human blood cell disorders studied for this aspect [5–7]. CTP synthetase is probably the most important enzyme maintaining the uracil-to-cytosine ribonucleotide ratio in intact cells [11]. Furthermore, studies on the activity of CTP synthetase with an *in vitro* assay have shown increased activities in human ALL patients cells compared with resting human peripheral blood lymphocytes [16]. Moreover, with the MOLT-3 cells as a model for human ALL, we have shown that the activity of the enzyme CTP synthetase is increased in intact human ALL cells compared with proliferating normal human lymphocytes [12]. Our present study shows that the activity of CTP synthetase in leukaemic MOLT-3 cells is increased throughout various phases of the cell cycle. In patients' ALL cells, no correlation has been observed between the uracil-to-cytosine ribonucleotide ratio and the percentage of S-phase cells [6]. The assumption that in patients' ALL cells the activity of CTP synthetase is not subject to cell-cycle dependent regulations, as in MOLT-3 cells, could explain this phenomenon. In conclusion, the enzyme CTP synthetase might form an attractive target to selectively kill human ALL patients' cells irrespective of the distribution of the cells over the various cell cycle phases.

Currently, the reason why transformed cells build up increased pyrimidine ribonucleotide pools with a decreased uracil-to-cytosine ratio is not clear. This might be the result of a genetic reprogramming, that provides some selective advantage to these cells. Both the amounts of UTP and CTP allosterically control the *de novo* pyrimidine nucleotide biosynthesis. Moreover, UTP and CTP act as feedback regulators of the uridine/-cytidine kinase (EC 2.7.1.48), the rate-limiting enzyme in pyrimidine ribonucleoside salvage reactions. Cells can, therefore, save energy by inhibiting the pyrimidine *de novo* synthesis pathway while favouring the less energy-consuming salvage of pyrimidine ribonucleosides. It has been reported that the *de novo* pyrimidine synthesis activity of human lymphocytic cells is very low compared with the salvage activity [15, 17]. Synthesis of CTP via salvage of cytidine is the least energy-consuming pathway (3 * ATP). Normal T lymphocytes apparently favour the salvage of cytidine [12]. However, of the pyrimidine ribonucleosides, uridine has the highest concentration in human blood plasma, (2–8 μM), far higher than cytidine (0–0.5 μM) [18–20]. In leukaemia patients, the blood plasma concentration of uridine is even further increased compared with the level in blood plasma of healthy subjects [19]. We hypothesise that, among human leukaemia cells, those with metabolic adaptations that favour the salvage of uridine can proliferate more rapidly, despite the loss of some energy (4 * ATP to synthesise CTP from uridine).

Whether restoration of the decreased uracil-to-cytosine ribonucleotide ratio to the values which are observed in normal human peripheral blood cells is able to interfere with cell-cycle traverse and/or to induce leukaemic cells to enter a growth-arrested (G0) and perhaps a more differentiated state, is being studied in our laboratory.

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Feature Articles

Offering Choice of Treatment to Patients With Cancers. A review based on a symposium held at the 10th Annual Conference of The British Psychosocial Oncology Group, December 1993

M.A. Richards, A.J. Ramirez, L.F. Degner, L.J. Fallowfield, E.J. Maher and J. Neuberger

INTRODUCTION

MARKED cultural changes have occurred in Europe and the U.S.A. over the past 30 years, with an increasing concern for individual autonomy and the rights of the consumer. Changes in medical practice have occurred which reflect these broader changes in society. Increasing emphasis is now placed on the provision of information to patients and on their participation in decision making about their management. Until the 1960s, it was rare even in the U.S.A. for patients to be told they had cancer [1]. By 1979 the reverse was true [2]. In Europe the pace of change has been variable, with use of the word "cancer" being considerably higher in Scandinavian than in Latin countries [3]. However, there is a widespread trend towards more open disclosure [3].

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Involving patients in the decision making process (often abbreviated to "offering choice") could have both advantages and disadvantages for them. Proponents of offering choice may hope that this will lead to higher levels of patient satisfaction with care and improved acceptance of treatment [4]. It might also lessen psychological morbidity and improve quality of life. Against this, offering choice could place an undue burden of responsibility on patients [5]. Revealing uncertainty about the "best treatment" could lead to a loss of confidence in the doctor. Provision of the complex information required to make a valid choice may lead to confusion and could challenge a psychological response of denial/avoidance. Choice of a treatment which subsequently proves unsuccessful might induce feelings of self blame and regret in the patient.

In order to establish what constitutes good practice in this area, data and arguments presented at the 10th annual conference of the British Psychosocial Oncology Group have been summarised in this article, alongside evidence from published reports. In a symposium on "offering choice", there were presentations on patients' preferences for participation in decision making (Professor Lesley Degner) and on related clinical and psychosocial issues (Dr Jane Maher and Dr Lesley Fallowfield). Ethical issues surrounding "offering choice" were set in the context of four basic principles of medical ethics—beneficence, non-