Changes in Mobility Account for Camptothecin-induced Subnuclear Relocation of Topoisomerase I*

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DNA topoisomerase I is a nucleolar protein, which relocates to the nucleoplasm in response to drugs stabilizing topoisomerase I-DNA intermediates (e.g. camptothecin). Here we demonstrate that this phenomenon is solely caused by the drug’s impact on the interplay between mobility and localization of topoisomerase I in a living cell nucleus. We show by photobleaching of cells expressing biofluorescent topoisomerase I-chimeras that the enzyme moves continuously between nucleoli and nucleoplasm. Complex kinetics of fluorescence recovery after photobleaching indicates that two enzyme fractions with different mobility coexist in nucleoli and nucleoplasm. However, the whole complement of topoisomerase I is in continuous flux between these compartments and nucleolar accumulation can plausibly explained by the enzyme’s 2-fold lesser overall mobility in nucleoli versus nucleoplasm. Upon addition of camptothecin, topoisomerase I relocates within 30 s from the nucleoli to radial nucleoplasmic structures. At these sites, the enzyme becomes retarded in a dose-dependent manner. Inside nucleoli the mobility of topoisomerase I is much less affected by camptothecin. Thus, the enzyme’s distribution equilibrium is shifted toward the nucleoplasm, which causes nucleolar delocalization.

In general, topoisomerase I is an entirely mobile nuclear component, unlikely to require specific signaling for movements between nuclear compartments.

DNA topoisomerase I changes the pitch of DNA helices by cutting one DNA strand and allowing passage of the complementary strand through the transient nick (1). One important role for this mechanism is the release of torsional stress created by DNA transcription. Thus, topoisomerase I activity is in principle required in the nucleoplasm for mRNA synthesis (2) and in the nucleolus for rRNA synthesis (3). However, the latter is considered the major working place of the enzyme, which has been recognized as a predominantly nucleolar protein (3, 4). Camptothecin and other agents stabilizing covalent topoisomerase I-DNA intermediates cause relocation of topoisomerase I from the nucleoli to the nucleoplasm (5). This was also observed with inhibitors of RNA synthesis prompting the conclusion that the phenomenon might be related to reduced activity of rRNA biosynthesis in the nucleolus (6). Alternatively, it has been proposed that camptothecin-induced conjugation of topoisomerase I with small ubiquitin-like modifiers might serve as a signal triggering translocation of topoisomerase I from the nucleoli to the nucleoplasm (7).

Until now the dynamic properties of topoisomerase I in the nucleus or between nuclear compartments have not been assessed directly. Thus, it is not clear whether the enzyme is mobile or not, whether it resides in the nucleolus in a static manner and moves into the nucleoplasm in response to specific signals (as suggested in ref. 7) or whether it shuttles continuously between nucleolus and nucleoplasm. Consequently, it is also unclear as to what is the molecular event that leads to nucleolar delocalization of topoisomerase I upon exposure to camptothecins. We addressed these questions by determining the mobility of topoisomerase I in substructures of the living cell nucleus using high resolution confocal fluorescent microscopy and photobleaching techniques.

**EXPERIMENTAL PROCEDURES**

GFP*-topoisomerase I was stably expressed in the human embryonal kidney cell line 293 (German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany) using a bicistronic expression vector (8). The first cistron was hybrid genes of GFP and either human topoisomerase I or the active site mutant topoisomerase I<sup>18528</sup>-723. The second cistron contained the selection marker puromycin-N-acetyltransferase. Cells were grown in Dulbecco’s modified Eagle’s medium with Glutamax-I (Invitrogen, Karlsruhe, Germany) and transfected using LipofectAMINE (Invitrogen). Stably transfected cell lines were selected and maintained with 0.35 μg/ml puromycin. Immunoblotting and immunohistochemistry followed published protocols (9). Epifluorescent images were acquired with a Zeiss Axiovert 100 inverted microscope equipped with a heated live-cell chamber system (Bioptechs Inc., Butler, PA) for inspection of living cell specimen. For confocal imaging, FRAP, and FLIP, we used a Zeiss LSM 510 inverted confocal laser scanning microscope equipped with a CO<sub>2</sub>-controlled on-stage heating chamber and a heated 63×/1.4 NA oil-immersion objective. Culturing of cells at 37 °C under the microscope was crucial for obtaining consistent data of localization and mobility of topoisomerase I, whereas erratic results were obtained when native cell specimen were analyzed at ambient temperature. For FRAP measurements, fluorescent images of a single optical section were taken at 1.6-s time intervals before (n = 5) and after bleaching of a circular area at 20 milliwatt nominal laser power with three iterations. Imaging scans were acquired with the laser power attenuated to 0.1–1% of the bleaching intensity. The same laser settings were used for FLIP experiments, where the cells were repeatedly bleached and imaged at intervals of 15 s. For quantitative analysis of FRAP, fluorescence intensities of the bleached region and the entire...
cell nucleus were measured at each time point. Data were corrected for extracellular background intensity and for the overall loss in total intensity as a result of the bleach pulse itself and of the imaging scans. FLIP measurements were corrected only for the loss of fluorescence intensity caused by the imaging scans, which was determined in neighboring cell nuclei not subjected to bleaching. The relative intensity of the bleached area \( I_{\text{bl}} \) was calculated according to Ref. 10, and the computer software Prism (GraphPad Software Inc., San Diego, CA) was used for nonlinear regression analysis and plotting of the data. Kinetic models assuming the coexistence of one, two, or three individual enzyme fractions with different mobility were tested. In all cases, best fits (according to \( R^2 \)-value and F-test significance) were obtained assuming the coexistence of two enzyme fractions with different mobility. Values of maximal recovery derived from nonlinear regression were used to calculate the proportion of the two enzyme fractions with different mobility, whereas a third, immobile enzyme fraction was calculated by adding up the individual fractions to 100%.

**RESULTS**

Constitutive Expression of Active GFP-topoisomerase I in 293 Cells—This investigation is based on the constitutive expression of biofluorescent chimera of human topoisomerase I at physiological levels. To avoid overexpression, we used a vector conferring a balanced coexpression of a hybrid gene of topoisomerase I fused at its N terminus to GFP and the selection marker puromycin-N-acetyltransferase from a single bicistronic transcript (8). Significantly less clones emerged from transfection of human 293 cells with GFP-topoisomerase I than with GFP alone, attesting to a narrow tolerance margin for stable transgenic expression of human topoisomerase I. However, growth rate and morphology of cell lines supporting constitutive expression of GFP-topoisomerase I were similar to untransfected cells or cells expressing GFP alone. This suggested a quasi physiological expression of GFP-topoisomerase I, provided that the chimeric enzyme was active, not overexpressed, and colocalized with endogenous topoisomerase I. Control experiments addressing these requirements are summarized in Fig. 1.

When Western blots were probed with GFP antibodies (Fig. 1A, top), GFP-topoisomerase I was readily detected in transfected cells as a single protein band (Fig. 1A, lane 3) not apparent in untransfected cells (Fig. 1A, lane 1) or cells expressing GFP alone (not shown). Thus, rearrangements of the chimeric gene could be excluded, and green fluorescence of the cells could be unambiguously assigned to full-length GFP-topoisomerase I. When Western blots were probed with topoisomerase I antibodies (Fig. 1A, bottom), GFP-topoisomerase I appeared as an additional band of slower migration and similar intensity as compared with endogenous topoisomerase I. In untransfected 293 cells the additional band was absent. It is interesting to note that expression of GFP-topoisomerase I was accommodated by a slight reduction in expression of endogenous topoisomerase I (Fig. 1A, bottom, lane 3). Thus, the GFP-tagged species was not overexpressed, and the overall expression of topoisomerase I was the same as in untransfected cells.

The activity of GFP-topoisomerase I was tested by immuno-band depletion (11). Before immunoblotting, cells were treated with camptothecin, which stabilizes covalent topoisomerase II DNA intermediates inherent in the enzyme’s catalytic cycle. Since these intermediates are too large to enter the gel, the active fraction of the enzyme becomes depleted from the blots. Apparently, endogenous as well as GFP-linked topoisomerase I was effectively depleted within the same cell sample (Fig. 1A, lane 4). Moreover, the dose response to camptothecin was similar for GFP-tagged and endogenous topoisomerase I (Fig. 1B). In contrast, GFP-chimera of the active site mutant topoisomerase II*H18528 was not depleted at all by camptothecin (Fig. 1A, lanes 5 and 6), attesting to the specificity of the assay.

Considering finally that fusion to GFP might disrupt the cellular targeting of topoisomerase I, we compared within individual cells the fluorescent patterns of GFP-topoisomerase I (Fig. 1C, top) and topoisomerase I labeled with antibodies (Fig. 1C, middle). Untransfected cells (Fig. 1C, left) gave rise to antibody-derived signals only, whereas cells expressing GFP-topoisomerase I (Fig. 1C, right) also emitted GFP fluorescence. The patterns of GFP fluorescence and immunofluorescence were virtually the same, confirming colocalization of the GFP signal with endogenous topoisomerase I. Moreover, immuno-staining patterns of untransfected and transfected cells were similar (Fig. 1C, compare left and right), excluding that transgenic expression of GFP-topoisomerase I disrupted localization of the endogenous enzyme. Thus, the transgenic cell lines had fully integrated the GFP-chimera into their cellular pool of topoisomerase I and could be used to study the behavior of the enzyme.

Localization and Mobility of GFP-topoisomerase I in Living Cells—Fig. 2A shows time lapsed epifluorescence microscopy of a cell expressing GFP-topoisomerase I. Apparently, the cell lived under the microscope because it divided while observed. Monitoring begins in late G2 phase/early prophase (0 min), where GFP-topoisomerase I was concentrated in the nucleoli. As the cell moved into prophase (4 min), nucleoli disappeared, and a granular fluorescent pattern emerged indicating association of GFP-topoisomerase I with condensing chromatin from
Dynamics of Topoisomerase I in Living Cells

Figure 2. Localization and mobility of GFP-topoisomerase I. A, time-lapsed imaging of a cell proceeding from late G2 to early G1 phase. Cells expressing GFP-topoisomerase I were cultured at 37 °C under an inverted epifluorescence microscope. A cell in late G2 phase was selected and imaged at the indicated time points by phase contrast (top) and green fluorescence (bottom) until it reached G1 phase. B, FRAP analysis of living cells expressing GFP-topoisomerase I. Circular areas (Ø = 2 µm) of the nucleoplasm (top) or a nucleolus (bottom) of interphase nuclei were bleached. Consecutive images at 1.6-s time intervals were taken before and at the indicated time points after the bleach pulse. Areas to be bleached are indicated by a circle in the pre-bleach panels. Corresponding quantitative data of fluorescence recovery kinetics are plotted below. Fluorescence intensities in the bleached nucleoplasm (Δ) or nucleolar (○) region were measured and expressed as the relative recovery over time after the bleach pulse (at 0 s). Mean values from at least six individual cells and three independent experiments are shown. Standard deviations were in each case less than 5% of the mean values (not displayed). Hatched lines represent the results of nonlinear regression analyses of the data. The inset shows FRAP kinetics obtained with cells expressing unfused GFP (□) or GFP-histone H3 (○).

B, FLIP analysis of cells expressing GFP-topoisomerase I. A circular area (Ø = 3 µm; white circle) of a nucleolus was repeatedly bleached. Areas to be bleached are indicated by a circle in the pre-bleach panels. Corresponding quantitative data of fluorescence recovery kinetics are plotted below. Fluorescence intensities in the bleached nucleoplasm (□) or nucleolar (○) region were measured and expressed as the relative recovery over time after the bleach pulse (at 0 s). Mean values from at least six individual cells and three independent experiments are shown. Standard deviations were in each case less than 5% of the mean values (not displayed). Hatched lines represent the results of nonlinear regression analyses of the data. The inset shows FRAP kinetics obtained with cells expressing unfused GFP (□) or GFP-histone H3 (○).

C, FLIP analysis of cells expressing GFP-topoisomerase I. A circular area (Ø = 3 µm; white circle) of a nucleolus was repeatedly bleached. Cells were imaged before each new bleach pulse (selected images are shown at the top). Fluorescence intensities of neighboring nucleoli and nucleoplasm (black and white circles, respectively) were determined and plotted below (△, nucleoplasm; ○, nucleolus).

Early on. The enzyme stayed chromosome-bound until telophase (12–48 min). Finally, during the G1 phase (77 min to 3 h) it accumulated again in the reforming nucleoli and was otherwise distributed in the nucleoplasm in a uniform manner.

Next we applied photobleaching to probe the dynamic properties of GFP-topoisomerase I in interphase nuclei of living cells. To determine FRAP kinetics (12), cells expressing GFP-topoisomerase I were cultured under a confocal laser scanning microscope and GFP fluorescence was irreversibly bleached by high-powered laser pulses in circular areas of the nucleoplasm or the nucleoli, respectively. Subsequently, fluorescence recovery in the bleached spots as a consequence of other GFP-topoisomerase I molecules moving in from unbleached areas was recorded over time by sequential imaging scans (Fig. 2B).

As a control for a freely diffusible protein, we used cells expressing GFP alone, which exhibited FRAP kinetics too fast for recording with our experimental settings (Fig. 2B, inset). As a control for immobile proteins we used cells expressing GFP-histone H3 (Fig. 2B, inset) known to be firmly chromatin-bound (13). FRAP of GFP-topoisomerase I was complete after 30 s in nucleoplasm and nucleoli, indicating that the enzyme is entirely mobile in both compartments (as opposed to histone H3). However, GFP-topoisomerase I was clearly much slower than GFP alone, suggesting that the enzyme is not freely diffusible. Moreover, fluorescence recovery of GFP-topoisomerase I in the nucleoli was slower than in the nucleoplasm, demonstrating that the enzyme’s mobility at the two locations was restrained to a different extent. Nonlinear regression of these data (hatched lines in Fig. 2B) indicated with significance (p < 0.0001) that in both cases two different mobility states of the fluorescent enzyme contributed to the apparent FRAP kinetics. A major portion appeared to be moving fast (t1/2 = 1.1 ± 0.1 s and 1.9 ± 0.2 s for nucleoplasm and nucleoli, respectively), whereas a minor portion was moving much slower (t1/2 = 14.3 ± 2.3 s and 12.5 ± 1.4 s for nucleoplasm and nucleoli, respectively). The slow portion amounted to 28 ± 3% in nucleoli as opposed to only 16 ± 2% in nucleoplasm. This difference explains why overall mobility of GFP-topoisomerase I in the nucleoli was about 2-fold less than in the nucleoplasm.

Rapid fluorescence recovery in nucleoli and nucleoplasm, as observed here with GFP-topoisomerase I, suggests free and unrestricted exchange of the protein between nuclear compartments. We corroborated this notion by the FLIP approach (12). These experiments are summarized in Fig. 2C. When one nucleolus was repeatedly bleached, all topoisomerase I-linked GFP fluorescence was eventually lost from other nucleoli of the same nucleus and also from the surrounding nucleoplasm. Similar results were obtained when repeated bleaching was applied to the nucleoplasm (not shown). These data imply that fluorescent topoisomerase I molecules originally localized in both compartments were eventually hit by bleach pulses aimed to only one of them, thus demonstrating a rapid, continuous, and unrestricted traffic of all enzyme molecules between individual nucleoli and between nucleoplasm and nucleoli.

The Impact of Camptothecin on Topoisomerase I Mobility—In the light of these findings, we were curious how mobility and distribution of topoisomerase I would be influenced by camptothecin, which stabilizes covalent enzyme-DNA complexes. For this purpose, we cultured cells expressing GFP-topoisomerase I under a confocal laser scanning microscope...
and added camptothecin to the culture medium, while taking serial confocal scans every 3.1 s (Fig. 3A and supplemental QuickTime movie). The first image (0 s) recorded immediately before adding camptothecin shows the normal nucleolar accumulation of topoisomerase I. Subsequent images demonstrate a very rapid redistribution of topoisomerase I to the nucleoplasm. After 20–30 s nucleoli were largely reduced in fluorescence, and most of the enzyme was localized in radial substructures within the nucleoplasm.

Fig. 3B shows FRAP kinetics determined in the nucleoplasm of cells treated for 20 min with various concentrations of camptothecin. Nonlinear regression (Fig. 3B, hatched lines) again indicated with significance (p < 0.0001) the contribution of two different mobility states of the fluorescent enzyme to each of these curves. Upon plotting of the half-times (Fig. 3C) and the relative proportions (Fig. 3D) of slow (○) and fast (□) enzyme fractions against the log molar concentration of camptothecin, it becomes apparent that the drug acted preferentially on the slow fraction of topoisomerase I. This fraction was further retarded by camptothecin in a dose-dependent manner, whereas half-times of the fast fraction were not significantly altered (Fig. 3C). Coincidentally, an increasing proportion of the enzyme was recruited to the slow state, whereas only an insignificant portion became actually immobile (Fig. 3D, compare △ and ○).

A comparison of FRAP kinetics determined in nucleoli and nucleoplasm of camptothecin-treated cells (Fig. 3E) showed that in the nucleoli topoisomerase I was retarded to a much lesser extent than in the nucleoplasm, suggesting that camptothecin acted preferentially on topoisomerase I in the nucleoplasm. As a consequence, the enzyme was moving much faster in the nucleolus than in the nucleoplasm in a camptothecin-treated cell, whereas in an untreated cell it was the other way around (Fig. 3C, compare open and closed symbols). Thus, nucleolar accumulation and camptothecin-induced nucleolar delocalization of topoisomerase I seem to be driven by differences in mobility. Support of this notion was gained from the behavior of the catalytically inactive mutant topoisomerase I<sup>Phe-723</sup>. FRAP kinetics of GFP-topoisomerase I<sup>Phe-723</sup> were virtually the same in nucleoli and nucleoplasm (Fig. 3F, compare circles and triangles) and with and without camptothecin (Fig. 3F, compare open and closed triangles), attesting to the fact that mobility of the inactive enzyme was the same in both compartments and not affected by camptothecin. Consequently, topoisomerase I<sup>Phe-723</sup> did not accumulate in nucleoli and did not delocalize from nucleoli upon exposure to camptothecin (Fig. 3F, inset). Interestingly, FRAP kinetics of topoisomerase I<sup>Phe-723</sup> were in general slower (t<sub>1/2</sub> = 2.5 ± 0.2 s and 22.4 ± 2.2 s for fast and slow subpopulations in both compartments, respectively) than those of the active enzyme, suggesting that DNA catalysis somehow facilitates detachment of the enzyme from its binding sites.

**DISCUSSION**

We present here for the first time data on the mobility and the dynamics of human topoisomerase I in living cells. We show that the enzyme is fully mobile and in continuous flux between nucleoli and the nucleoplasm. These findings conform to the general concept that nuclear compartments are generated by a binding equilibrium of entirely mobile proteins (14). In keeping, we show here that topoisomerase I is not restricted to the nucleoli but imposes as a nucleolar protein, because it is moving more slowly in the nucleoli than in the nucleoplasm,
whereas the inactive mutant topoisomerase I\(^{Pho-723}\) has the same mobility in both compartments and is therefore more evenly distributed between them.

A comparison of FRAP kinetics of GFP-topoisomerase I and untagged GFP shows that, overall, topoisomerase I moves slower than to be expected from free diffusion, which is a usual feature of proteins with a nuclear function (14). We show in addition that in each nuclear compartment topoisomerase I is divided into a slow and a fast fraction. We do not know whether these fractions are interconvertible, but the most plausible interpretation is that the enzyme switches between an \(on\) state, where it is more or less freely diffusible \((t_{1/2} = 1–2\ s)\), and an \(off\) state, where it’s mobility is about 10-fold reduced \((t_{1/2} = 12–14\ s)\). Since topoisomerase I is continuously scanning the entire nuclear space, interactions of the enzyme with processes and places where its activity is required must implicitly be transient. It stands to reason that such interactions will involve less mobile nuclear components, such as chromatin, nuclear matrix, multiprotein complexes, etc. and, therefore, slow down the enzyme (14, 15). Thus, the slow fraction (the \(on\) state) most likely represents topoisomerase I engaged in processes, whereas the fast fraction (the \(off\) state) represents topoisomerase I moving between processes. This interpretation of our data is in good agreement with a “stop-and-go” model recently suggested for the interaction of histone H1 with chromatin (16, 17).

How does camptothecin fit into such a revised perception of topoisomerase I? The drug is known to bind and stabilize the covalent topoisomerase I-DNA intermediate (18). We show here that camptothecin further attenuates the slow fraction of nucleoplasmic topoisomerase I, which supports the above notion of this fraction being the one engaged in DNA turnover. At least in living cells, the drug does not immobilize topoisomerase I completely, which fits some previous biochemical data (19) showing that topoisomerase I-DNA intermediates stabilized by camptothecin have a comparatively short half-life (\(<1\ min)\). Why does topoisomerase I disappear so rapidly from its favored nucleolar residence when camptothecin is present? It has been proposed that nucleolar delocalization is triggered by conjugation of the enzyme with small ubiquitin-like modifiers (7). However, this process is operating on a minute scale (20), whereas we show here that nucleolar delocalization occurs within seconds. Moreover, it is unlikely that an entirely mobile protein like topoisomerase I should require specific signals to move from one place in the nucleus to another. As elaborated in the first paragraph, topoisomerase I is prone to accumulate in the nucleoli, because here it is moving more slowly than in the nucleoplasm. In the presence of camptothecin, however, the situation is rapidly reversed. Now, the enzyme is moving more slowly in the nucleoplasm than in the nucleoli. Accordingly, it accumulates in the nucleoplasm and delocalizes from nucleoli, although it is still freely exchanging between the two compartments. Thus, nucleolar delocalization of topoisomerase I upon exposure to camptothecin seems to be a plausible epiphenomenon of the enzyme’s nuclear traffic and not a reflection of some specific cellular response to the drug. In keeping, topoisomerase I\(^{Pho-723}\), which cannot be stabilized in covalent DNA complexes by camptothecin, does not delocalize from nucleoli upon exposure to the drug, as should be the case, if nucleolar delocalization was due to some kind of a coordinated stress reaction and not a direct consequence of the altered mobility of the enzyme.

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