Arginine methylation is a posttranslational protein modification catalyzed by a family of protein arginine methyltransferases (PRMT), the predominant member of which is PRMT1. Despite its major role in arginine methylation of nuclear proteins, surprisingly little is known about the subcellular localization and dynamics of PRMT1. We show here that only a fraction of PRMT1 is located in the nucleus, but the protein is predominantly cytoplasmic. Fluorescence recovery after photobleaching experiments reveal that PRMT1 is highly mobile both in the cytoplasm and the nucleus. However, inhibition of methylation leads to a significant nuclear accumulation of PRMT1, concomitant with the appearance of an immobile fraction of the protein in the nucleus, but not the cytoplasm. Both the accumulation and immobility of PRMT1 is reversed when re-methylation is allowed, suggesting a mechanism where PRMT1 is trapped by unmethylated substrates such as core histones and heterogeneous nuclear ribonucleoprotein proteins until it has executed the methylation reaction.

Methylation of arginine residues is a widespread posttranslational modification that increases the structural diversity of proteins and may modulate their function in the living cell. The modification is catalyzed by a family of specific enzymes, the protein arginine methyltransferases (PRMT), of which eight members have been described up to now (1). Enzymes of the PRMT family differ in activity, substrate specificity, and subcellular localization, but the precise roles of individual members of the family for the living cell remain to be elucidated. All PRMTs methylate guanidino nitrogens of arginine residues in their substrates to form monomethylarginine, a transient modification that can be converted to citrulline by deimination and presumably reverted to unmodified arginine (2, 3). In a second step, PRMTs catalyze the dimethylation of affected arginines, which is currently believed to be irreversible and to label the modified proteins for their entire lifetime. Except for PRMT5 and PRMT7, which appear to catalyze the symmetric dimethylation of arginines (4, 5), all other characterized PRMTs lead to asymmetric dimethylation of their specific targets.

Presently, the functional consequences of arginine (di-)methylation are much less understood than those of other posttranslational modifications such as phosphorylation or acetylation (for review, see Refs. 6 and 7). As methylation of characterized substrates occurs on residues in an RG (R, arginine; G, glycine) or RGG sequence context, a common feature of RNA-binding proteins, methylation might modulate protein-RNA or protein-protein interactions (8). It is likely, and examples have been reported, that this affects processes of signal transduction, subcellular protein trafficking, or gene expression. In particular, PRMT1 and -4 were implicated in transcriptional co-activation of nuclear hormone receptors, most probably because they methylate histones H3 and H4 and thereby facilitate histone acetylation and chromatin remodeling (9–13). In addition, arginine methylation of Sam68 and RNA helicase A affects the subcellular localization of these proteins, which in turn may modulate their activity (14, 15). However, interpretation of these results in terms of dynamic processes is complicated by the fact PRMTs are constitutively active, and there is only little evidence for regulation that could restrict methylation to specific cellular conditions such as the cell cycle or response to extracellular stimuli (16–18). As a result, most known target proteins are entirely methylated at any given time, and it is unlikely that methylation conveys a “signal” in the classical sense. A more detailed and comparative characterization of individual PRMTs will therefore be crucial to appreciate their specific roles in the living cell and the role of protein arginine methylation in general.

The predominant arginine methyltransferase in human cells, PRMT1, is responsible for at least 85% of all arginine methylation reactions (19, 20). PRMT1 is an essential enzyme, because embryos from Prmt1−/− knock-out mice die shortly after implantation; however, it is dispensable for basic cellular reactions such as gene expression and DNA replication, because embryonic stem cells from such embryos are viable under cell culture conditions (19). The major targets of PRMT1 were identified as nuclear proteins that interact with nucleic acids, such as the core histones H3 and H4, components of the heterogeneous nuclear ribonucleoprotein (hnRNP) particle involved in pre-mRNA processing and transport, or nucleolar components such as fibrillarin and nucleolin that are involved in pre-rRNA processing and ribosome biogenesis (8, 21–23). We have recently shown that PRMT1 is physically associated with hnRNP particles, which contain the predominant substrates of the enzyme, and is able to methylate its target proteins in situ (24). The interaction of PRMT1 with hnRNP complexes occurs via SAF-A, a well known constituent of hnRNP complexes and the nuclear scaffold, and is strongly enhanced when methylation is blocked by periodate-oxidized adenosine (Adox). Physical interaction of PRMT1 with its major substrates, the components of hnRNP particles, might therefore provide a means to ensure a high level of methylation of the preferred target proteins and might also contribute to substrate specificity. PRMT1 had previously been reported to interact with other proteins as well (25–28), but we were surprised to find that its binding to hnRNP complexes was dependent on the methylation status of the cell. This result, which was obtained by immunoprecipitation and gradient centrifugation experiments in vitro, motivated us to investigate PRMT1
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by non-invasive methods in vivo. Here, we report our results from in vivo mobility assays, which, for the first time, shed light on the dynamics of PRMT1 in live cells. We show that when methylation is inhibited PRMT1 reversibly relocates to the nucleus where it, but not the closely related enzyme PRMT6, becomes trapped by unmethylated substrates until the methylation reaction is successfully executed. Findings presented in this report show that PRMT1 is a highly dynamic enzyme with variable subcellular localization and mobility and provide insight into the mechanism of enzyme activity in vivo.

**MATERIALS AND METHODS**

**Cell Culture, Transfection, and Treatment with Periodate-oxidized Adenosine**—Human embryonic kidney 293 cells were cultivated on plastic dishes in Dulbecco's modified Eagle's medium with 10% fetal calf serum in a humidified atmosphere containing 5% CO2, and were split 1:5 every second day. Cells were transfected by polyethylenimine (29) with expression vectors encoding enhanced green fluorescent protein (EGFP) fusions of PRMT1 or PRMT6 (30), and stably expressing cell lines were created by selection with G418 for 4 weeks. For inhibition of methylation and for preparation of hypomethylated cell extracts, the medium of human embryonic kidney 293 cells was supplemented with 15 μM periodate-oxidized adenosine (adenosine-2'-3'-dialdehyde, A7154; Sigma), and cells were cultured for an additional 48 h before they were analyzed or harvested.

**Live Cell Microscopy**—For live cell microscopy, cells were split onto 35-mm culture dishes with a glass bottom (Mattek) and analyzed 2 days after splitting, either untreated or treated with Adox as described above. For the analysis, cells were placed on the heated stage of a Zeiss Meta 510 confocal laser-scanning microscope. Fluorescence recovery after photobleaching (FRAP) experiments were performed by bleaching a narrow strip across the cells by 50 iterations at 488 nm and 75% laser output. The prebleaching status, bleaching, and fluorescence recovery were recorded by the "time series" module of the Zeiss software (version 3.2), using 1% laser output to minimize further bleaching. 128 × 128 pixel resolution at Zoom factor 3–5, and a 4 Airy pinhole. For quantitative analysis, a minimum of 25 individual cells was measured, and mean pixel intensities in specified regions of interest were determined with the freeware image analysis software ImageJ by Wayne Rasband (rsb.info.nih.gov/ij/). Non-bleached reference regions were analyzed in each cell for data normalization.

**Preparation of Total Cell Extract**—Semiconfluent to confluent cells were harvested by scraping off the culture dishes with a rubber policeman after two washes with phosphate-buffered saline and collected by centrifugation (200 × g, 5 min). For the preparation of hypomethylated extract, cells were resuspended in water and disrupted by sonication. Extract for immunoprecipitation was prepared by resuspending cells in lysis buffer (1.5× phosphate-buffered saline, 1% Triton X-100, and protease inhibitor mixture "Complete, EDTA-free" (Roche Applied Science)), incubating on ice for 5 min, and clearing by centrifugation for 15 min in an Eppendorf microcentrifuge at full speed.

**Immunoprecipitation and Western Blotting**—For immunoprecipitation, extract from 1–5 × 10⁶ cells was supplemented with 5 μg of antibodies against GFP (Roche Applied Science) or PRMT1 (07–404; Upstate Biotechnology) and incubated for 2 h at 4 °C. Immune complexes were collected by incubation with protein G-Sepharose for an additional hour. Immune complexes were washed thoroughly six times before bound proteins were eluted with SDS-PAGE sample buffer.

Western blotting was performed as described previously using a methylation-sensitive antibody against SAF-A (24) or commercially available antibodies against GFP (Roche Applied Science), the protein arginine methyltransferases PRMT1 and -6 (07–404, Upstate, and IMG-506, Inugenex, respectively), Sam68 (sc-1238, Santa Cruz Biotechnology), histone H3 (ab1791; Abcam), or asymmetrically dimethylated arginine (ASYM24; Upstate). For detection, horseradish peroxidase-conjugated secondary antibodies (Sigma) and ECL chemiluminescent reagent (Amersham Biosciences) were used. For the experiment in Fig. 7, immunoprecipitated proteins were visualized by silver staining as described previously (31).

**In Vitro Methylation Assay**—GFP fusion proteins of PRMT1 or PRMT6 were immunoprecipitated from ~1 × 10⁶ cells with anti-GFP antibodies as described above. After washing thoroughly six times, bound PRMTs were checked for activity by radioactive methylation assays exactly as described earlier (24). Briefly, immunoprecipitated PRMT (on 20 μl of Protein G-Sepharose beads) was combined with heat-inactivated extract from hypomethylated cells and 5 μCi of S-adenosyl-l-[methyl-³H]methionine (TRK865, specific activity 2.96 TBq/mmol; Amershams Biosciences), and reactions were incubated for 2 h at 37 °C. The reaction mixture was then resolved by SDS-PAGE, and radioactively labeled proteins were visualized by fluorography with enhanced reagent (PerkinElmer Life Sciences).

**RESULTS**

We recently reported that PRMT1 associates with its preferred substrate proteins in hnRNP particles, depending on the methylation status of the substrates. In particular, immunoprecipitation and glycerol gradient centrifugation experiments revealed that PRMT1 was enriched in hnRNP particles from cells in which methylation was inhibited. Although very clear in their results, these experiments were performed in vitro and did not allow us to formally rule out fortuitous binding during extraction from cells. We were therefore motivated to utilize non-invasive methods to investigate the localization, mobility, and interactions of PRMT1 in living cells. To this end, we created stable cell lines expressing fusion proteins of PRMT1 and, as a control, PRMT6 with EGFP. Cell lines were selected that express approximately physiological amounts of the PRMTs, and the proteins from these cells were characterized by a variety of different means to ensure that they behave like their endogenous counterparts (Fig. 1A). These experiments demonstrate that both PRMTs can be co-immunoprecipitated in complex with their respective endogenous equivalent. This strongly suggests that both GFP fusion proteins are properly folded and faithfully incorporated into oligomeric complexes, which is a prerequisite for enzymatic activity (32, 33). In fact, the immunoprecipitated complexes exhibit enzymatic activity with distinct substrate specificities. Thus, GFP fusion proteins are suitable to analyze the mobility of the catalytically active PRMT oligomers in vivo. While PRMT6 was exclusively located in the cell nucleus as described previously (30), PRMT1 was found in both the nucleus and the cytoplasm (also compare supplemental Fig. S1). This has also been reported before, but individual reports on the localization of PRMT1 were quite variable, ranging from a predominant cytoplasmic to a predominant nuclear localization (14, 17, 30). In our hands, quantifications of PRMT1 in microscopic investigations and in biochemical fractionation experiments reveal that endogenous PRMT1 and PRMT1: EGFP are ~6-fold more abundant in the cytoplasm than in the nucleus (Fig. 1A, lanes 8 and 9, Fig. 1B, upper panel, and Fig. 2). Thus, although most known substrate proteins for PRMT1 are nuclear (see the Introduction), the enzyme is not preferentially located in the nucleus, compatible with the lack of a functional nuclear localization signal on the PRMT1 amino acid sequence. Importantly, however, conditions that lead to the presence of unmethylated substrates (supplemental Fig. S2) concomitantly lead to an accumulation of PRMT1 in the nucleus by a
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2.5-fold factor in comparison to untreated cells (Fig. 2). In vivo mobility measurements by FRAP experiments reveal that nuclear PRMT1 not only increases in its amount but also changes its mobility (Figs. 3 and 4). Under normal cell culture conditions, which allow a complete methylation of substrate proteins, PRMT1 behaves as a completely soluble protein with diffusion characteristics of an oligomeric complex both in the cytoplasm and the nucleus. This changes upon inhibition of methylation by Adox, which leads to the appearance of an immobile (or very slow diffusing) fraction of PRMT1 exclusively in the nucleus, but not the cytoplasm. The alteration of mobility affects ~25% of the nuclear PRMT1 and is specific for PRMT1 because neither the closely related enzyme PRMT6 (Fig. 4C) nor unrelated proteins such as an artificial soluble construct of β-galactosidase with a nuclear localization signal (Fig. 5) is affected by Adox treatment. Identical mobility before and after inhibition of methylation is also observed for hnRNP-C, a component of the hnRNP particles to which PRMT1 binds upon inhibition of methylation but which is not a substrate of the enzyme itself. Our FRAP analysis shows that hnRNP-C diffuses slowly, consistent with the megadalton size of hnRNP particles to which it is bound (24) and has a recovery curve similar to that of nuclear PRMT1 after Adox treatment. Importantly, the nuclear accumulation and mobility change of PRMT1 is maintained only under persistent inhibition but is fully reversible when re-methylation of substrates is allowed (Fig. 6). Complete re-establishment of rapid diffusion characteristics of nuclear PRMT1 is observed ~6 h after removal of Adox, in parallel with the disappearance of unmethylated substrate protein SAF-A, which is responsible for attachment of PRMT1 to hnRNP particles (24). To determine whether the immobility of PRMT1 is a result solely of interaction with the megadalton hnRNP complex, we used immunoprecipitation and silver staining to identify proteins that change their interaction with PRMT1 dependent on the methylation status of the cell. Fig. 7 shows that, indeed, the pattern of co-immunoprecipitated protein changes in the absence of methylation. Most prominent is the strong increase of co-precipitated core histones. However, there are several other proteins where a methylation-dependent change of interaction is evident; for example, three proteins with apparent molecular masses of 50, 97, and 120 kDa are enriched in the +Adox precipitates, whereas a 70-kDa protein is reduced (denoted by dots in Fig. 7). These results provide the first in vivo evidence for a mechanism by which PRMT1 associates with its
unmethylated substrates, corroborating our earlier results obtained in vitro, and is released only after it has executed its methylation reaction.

DISCUSSION

The predominant protein arginine methyltransferase of human cells, PRMT1, has been implicated in a variety of different biological functions, including transcriptional regulation, cell proliferation, differentiation, and protein trafficking. It is possible that many of the functions ascribed to PRMT1 will eventually be explainable as the consequence of a single underlying mechanism, but currently more information about the enzyme and its activity must be gathered to decide on its physiological role. In this report, we have demonstrated that PRMT1 accumulates in the nucleus when methylation is inhibited and is tethered to unmethylated substrate proteins such as the core histones and components of the hnRNP particle unless the methylation reaction is accomplished.

Results reported here answer several open questions regarding the localization, dynamics, and activity of PRMT1 in living cells. First, we found that PRMT1 is localized preferentially in the cytoplasm of human embryonic kidney cells, spatially separated from its major substrate proteins that reside in the cell nucleus (7, 20–23). This result could have been predicted from the lack of a nuclear localization signal in the PRMT1 sequence. However, previous work by others gave conflicting results, ranging from predominantly nuclear to predominantly cytoplasmic localization (14, 17, 30). These differences in the localization of PRMT1 may reflect a variability of different cell lines with regard to the expression of substrate proteins that need to be methylated and, as shown here, lead to an accumulation of PRMT1 in the nucleus. On the other hand, some of the discrepancies can possibly be explained by a problem inherent in immunofluorescence studies of soluble proteins, inefficient fixation. In fact, our own experiments to localize PRMT1 by

![FIGURE 4. Quantitative mobility measurements on PRMT1 and PRMT6. Photobleaching experiments similar to the one shown in Fig. 3 were performed on cells stably expressing PRMT1 or PRMT6, both with (gray curves) and without (black curves) prior Adox treatment. Mobility of PRMT1 was quantified separately for the nuclear (A) and the cytoplasmic (B) fraction of the protein; PRMT6 was only examined in the nucleus (C), as it is exclusively nuclear irrespective of Adox treatment. A minimum of 25 individual cells was examined for each analysis; error bars indicate the S.D. Note the presence of an immobile fraction of PRMT1 in the nucleus of Adox-treated cells, whereas neither cytoplasmic PRMT1 nor nuclear PRMT6 is affected by inhibition of methylation.

![FIGURE 5. Inhibition of methylation does not affect the mobility of hnRNP complexes, the major in vivo substrate of PRMT1, or of unrelated proteins. Quantitative FRAP experiments were performed and analyzed as described in Fig. 4 with cells stably expressing GFP fusions of hnRNP-C or an artificial control protein, β-galactosidase-NLS (gray, with Adox; black, untreated). Note that β-galactosidase-NLS behaves as a soluble nuclear protein that fully recovers within ~20 s, whereas hnRNP-C is characterized by a low mobility compatible with the megadalton size of hnRNP particles.

![FIGURE 6. Immobilization of nuclear PRMT1 is fully reversible when re-methylation of substrate proteins is allowed. A, quantitative FRAP experiments were performed on cells stably expressing PRMT1 without Adox treatment (green curve), after 2 days of Adox treatment (red curve), or 7 h after removal of Adox (blue curve). B, time course of substrate re-methylation after removal of Adox. Cells treated with Adox for 2 days were thoroughly washed and cultured in Adox-free medium for 2, 4, 6, and 8 h. Total cell extracts were prepared and analyzed by Western blotting with antibodies against SAF-A, a substrate of PRMT1. Upper panel, Western blot with an antibody recognizing SAF-A irrespective of its methylation status. Lower panel, blot with an antibody recognizing only unmethylated SAF-A. Note that the amount of unmethylated SAF-A becomes undetectably low after 6 h of recovery, but the amount of total SAF-A remains identical.
immunofluorescence were also biased toward a more nuclear localization, together with a granular appearance in the cytoplasm (data not shown). However, a similar effect was also evident in cells that express other soluble proteins such as EGFP, which allows for a direct comparison of protein localization in vivo and after processing cells for immunofluorescence. This let us to conclude that different efficiency of fixation in different organelles is a source of potential artifacts in the localization of soluble proteins. We therefore exclusively used non-disruptive in vivo experiments to clarify the localization of PRMT1.

Quantification of fluorescence intensity in different organelles of living cells demonstrates that PRMT1 is ~6-fold more abundant in the cytoplasm than in the nucleus under normal cell culture conditions. Intriguingly, this ratio is not fixed but changes significantly when cells are treated with Adox, which results in an increase in type I methyl acceptors by inhibiting the breakdown of S-adenosyl-l-homocysteine, the product inhibitor of AdoMet-dependent methylation reactions (24, 34, 35). Thus, accumulation of unmethylated substrates leads to an accumulation of the enzyme in the nucleus, which is maintained only as long as the inhibition of methylation persists. This speaks against an alternative interpretation for the predominantly cytoplasmic localization of PRMT1, namely that the enzyme methylates its nuclear substrate co-translationally, or at least shortly after translation while they are still cytoplasmic. We do not currently know how PRMT1 enters the nucleus and how it is re-exported from the nucleus when re-methylation of substrates is allowed. Most probably, PRMT1 is piggybacked on unmethylated substrates such as newly synthesized hnRNP proteins and cotransported through the nuclear pore. In contrast, the related PRMT6 enzyme that we investigated in parallel contains a functional nuclear localization signal close to the amino terminus of the protein and appears to be transported on its own. We were surprised to find that PRMT1 gains an immobile (or at least very slow moving) fraction exclusively in the nucleus, but not the cytoplasm, of the same cell when methylation is inhibited. This is compatible with the notion that the major site of PRMT1 activity is the cell nucleus and a mechanism where PRMT1 gets trapped on unmethylated substrates during its reaction cycle. In fact, PRMT1 preferentially associates with the low mobility nuclear scaffold protein SAF-A (24, 36) and with the almost immobile core histones in chromatin (Fig. 7, compare Ref. 37, for histone mobility) when methylation is inhibited. Thus, at least two low mobility entities in the nucleus are involved in immobilizing PRMT1 under these conditions.

Interestingly, the related enzyme PRMT6, the substrate spectrum of which significantly overlaps with that of PRMT1 (30), changes neither its subcellular localization nor its mobility in the presence of unmethylated substrates (Fig. 1A). This supports the idea that PRMT6 does not form complexes with other polypeptides (30) in contrast to PRMT1, which has been reported to associate with a large variety of proteins (24–28). It could be that the enzymatic mechanism of PRMT6 is different from that of PRMT1 and does not include a step where the enzyme forms a stable intermediate with the substrate. This hypothesis can now be tested in structure/function experiments by switching regions of PRMT1 and -6. It will be interesting for future experiments to also characterize the dynamics and distinct interactions of other members of the growing PRMT family. These investigations will shape our understanding of PRMT enzymatic function, will help to determine the physiological role of the individual family members, and hopefully will elucidate novel pathways involving arginine methylation.

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