Tubulin Is an Inherent Component of Mitochondrial Membranes That Interacts with the Voltage-dependent Anion Channel*

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We have previously reported that anti-tubulin agents induce the release of cytochrome c from isolated mitochondria. In this study, we show that tubulin is present in mitochondria isolated from different human cancerous and non-cancerous cell lines. The absence of polymerized microtubules and cytosolic proteins was checked to ensure that this tubulin is an inherent component of the mitochondria. In addition, a salt wash did not release the tubulin from the mitochondria. By using electron microscopy, we then showed that tubulin is localized in the mitochondrial membranous proteins rich in the class III β-tubulin isotype but contains very little of the class IV β-tubulin isotype. The mitochondrial tubulin is likely to be organized in α/β dimers and represents 2.2 ± 0.5% of total cellular tubulin.

Lastly, we showed by immunoprecipitation experiments that the mitochondrial tubulin is specifically associated with the voltage-dependent anion channel, the main component of the permeability transition pore. Thus, tubulin is an inherent component of mitochondrial membranes, and it could play a role in apoptosis via interaction with the permeability transition pore.

Mitochondria are key players in cell death. Proteins present in the mitochondrial intermembrane space have been shown to induce apoptosis (1). They are released into the cytosol in response to a variety of apoptotic stimuli (2). Cytochrome c initiates caspase activation when released from mitochondria during apoptosis. Cytosolic cytochrome c binds to apaf-1, ATP, and multiple procaspase-9 molecules to induce formation of the apoptosome. The caspase-9, in turn, activates downstream executioner caspases such as caspase-3, leading to characteristic morphological changes in apoptosis. Other mitochondrial proteins are released from mitochondria such as the apoptosis-inducing factor, which triggers caspase-independent cell death, or Smac/Diablo, which promotes apoptosis by inactivation of the inhibitors of apoptotic proteins (1).

Mitochondrial membrane permeabilization is critical for the release of proapoptotic factors from mitochondria (2). The exact mode of permeabilization of mitochondria has not been elucidated, and several hypotheses have been proposed. According to the main hypothesis, the permeability transition pore (PTP), a multiprotein complex that is formed at the contact sites between the inner and outer membrane, is responsible for mitochondrial permeabilization. The PTP contains transmembraneous proteins such as the adenine nucleotide translocator (ANT), the voltage-dependent anion channel (VDAC), and the peripheral benzodiazepine receptor as well as the mitochondrial membrane-associated proteins (hexokinase, creatine kinase and cyclophilin D). ANT and VDAC are the most abundant PTP components of the inner and outer mitochondrial membranes, respectively. An alternative hypothesis for mitochondrial permeabilization involves proapoptotic members of the Bcl-2 family, which can form pores in the outer membrane by oligomerization (2). However, the involvement of the Bcl-2 family members in the early events of the release of cytochrome c (3) and their interaction with PTP or isolated PTP components such as VDAC (4) remain controversial.

Microtubules are dynamic components of the cytoskeleton. They are critical for a wide variety of functions in eukaryotic cells. They are involved in the maintenance of cell shape, cell signaling, mitosis by the mediation of chromosome migration, mRNA localization, and vesicle and organelle trafficking mechanisms (5). Microtubules are the principal target in cells for a family of anticancer drugs, the so-called anti-tubulin agents. These agents strongly suppress microtubule dynamics that are essential for progression throughout mitosis (6), leading to sustained mitotic arrest and apoptosis (7). However, the molecular pathways involved in the apoptotic process induced by these agents are still not elucidated. We have recently shown (8) that paclitaxel acts directly on mitochondria isolated from human cancer cells to release cytochrome c. The release of cytochrome c is prevented by cyclosporin A, which prevents PTP opening by binding to cyclophilin D (9). This demonstrates the involvement of this pore. The release was also observed with other anti-tubulin agents, either microtubule-stabilizing agents like docetaxel or microtubule-depolymerizing agents like nocodazole, C1 980, and vinorelbine (10). Anti-mitochondrial agents such as carbonyl cyanide m-chlorophenylhydrazone (CCCP) and arsenic trioxide induce the release of cytochrome c from isolated mitochondria (11, 12) and, interestingly, also act like anti-tubulin agents by depolymerizing microtubules in intact cells and in vitro experiments (12–14). In con-

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Mitochondrial Tubulin

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Transmission Electron Microscopy—To detect whether microtubules were present on isolated mitochondria, samples from isolated mitochondria or polymerized tubulin were negatively stained with 2% uranyl acetate and loaded on Formvar-coated grids. Microtubules and mitochondria were visualized by using transmission electron microscopy (JEOL 1220). For immunodetection, secondary antibody, streptavidin horseradish peroxidase, and diaminobenzidine were performed according to the manufacturer’s recommendations (LSAB 2 system HRP kit K0673, Dako, Glostrup, Denmark). Cells, nuclei, or mitochondria were fixed in 1% osmic acid, dehydrated in acetone, embedded in araldite, and cut into 0.05–0.08-μm sections before electron microscopy observation.

Western Blotting—Isolated mitochondria and cells were resuspended in lysis buffer (200 mM EDTA, 100 mM NaCl, 1% Triton X-100, and 50 mM Tris-HCl, pH 7.5). SDS-PAGE was carried out, and visualization was accomplished using an enhanced chemiluminescence detection kit (Amersham Biosciences); immunoblot quantification was then performed using TrueImage, a homemade densitometric software, as described previously (22). At least three independent experiments were performed. Statistical analysis was performed using Student’s t test. Values are expressed as mean ± S.D. The determination of tubulin quantity in isolated mitochondria and whole cells was performed using a standard curve of pure tubulin previously extracted from pig brain as described (23). Because pure tubulin is composed of αβ dimers, the quantity of the individual α- and β-tubulins represents half of the total quantity of tubulin. The characterization of mitochondrial tubulin by comparison with cellular tubulin was performed by immunoblots on samples of isolated mitochondria and whole cell lysates containing equivalent quantities of tubulin. Several α-tubulin post-translational modifications and β-tubulin isoforms were also analyzed.

Immunoprecipitation of Mitochondrial Proteins—Isolated mitochondria were solubilized in lysis buffer (200 mM NaCl, 1% Triton X-100, 10 mM NaF, 10 mM NaF, orthovanadate, and protease inhibitors), and ultracentrifuged for 30 min at 150,000 × g at 4 °C. The collected supernatants were precleared by mixing with 50 μg of protein G-agarose beads (Roche Diagnostics) for 1 h with gentle rocking, and beads were removed by centrifugation for 2 min at 500 × g. The resulting supernatants were incubated with 4 μg of primary antibodies for 2 h at 4 °C. The samples were then washed three times, resuspended in lysis buffer (200 mM NaCl) and twice in the same buffer containing 500 mM NaCl to increase stringency and reduce nonspecific binding of proteins to immunoprecipitates. The protein G-agarose beads with immunoprecipitates were then suspended in loading buffer, boiled, and analyzed by Western blotting as described above.

RESULTS

Tubulin Is Present in Isolated Mitochondria from Seven Different Human Cell Lines—We have shown previously that α-tubulin is present in isolated mitochondria from human neuroblastoma SK-N-SH cells (8, 12). In addition to the presence of tubulin in SK-N-SH cells, we also find tubulin in the mitochondria isolated from another human neuroblastoma cell line (IMR-32) and from lung carcinoma (A549), breast adenocarcinoma (MCF-7), nasal septum adenocarcinoma (RPMI 2650), cervix carcinoma (HeLa), and non cancerous breast (HBL-100) cells (Fig. 1). Thus, tubulin is present in mitochondria from a wide range of cancerous and non-cancerous cells. The amount of mitochondrial tubulin appears to differ according to the cell lines from which mitochondria were isolated.

Tubulin Is an Inherent Component of Mitochondria—We then focused our study on the SK-N-SH cell line to determine whether tubulin is an intrinsic component of the mitochondria. First, we checked that the tubulin detected by Western blotting was not present in the form of microtubules associated with the mitochondria. Using transmission electron microscopy, we compared, at the same magnification, suspensions of whole...
isolated mitochondria and in vitro polymerized microtubules (Fig. 2A). No microtubules were seen within the isolated mitochondria suspension. Moreover, we showed by Western blotting that proteins that are normally associated with microtubules such as the light chains of the motor proteins dynein and kinesin were also absent from the isolated mitochondria (Fig. 2B). These results imply that the mitochondrial tubulin detected by Western blotting does not come from microtubules pelleted during the mitochondrial isolation procedure or attached to the mitochondria and that mitochondrial tubulin is not linked to mitochondria through binding with motor proteins. Moreover, the cytosolic enzyme NSE, a cell-specific isoenzyme of the glycolytic enzyme enolase (24) that is present throughout the cytoplasm but not in mitochondria (25), was not detected in our mitochondrial preparation (Fig. 2B). This indicates that no contaminating cytosolic protein was present in the isolated mitochondria. To test the association of tubulin with mitochondria, we performed a salt wash of the isolated mitochondria (21) with 2 M KCl for 2 h at 37 °C. Tubulin was barely detectable in the supernatant of the KCl-incubated mitochondria. The small quantity of both tubulin and VDAC detected in the supernatant from salt-washed mitochondria (Fig. 2C) is probably derived from damaged mitochondria. It is clear that the presence of tubulin in mitochondria is not sensitive to ionic strength, suggesting that the tubulin is an inherent protein component of the mitochondria.

Tubulin Is Localized in the Mitochondrial Membranes—To determine the localization of the mitochondrial tubulin, we used immunoperoxidase labeling coupled with anti-α- and anti-β-tubulin monoclonal antibodies and transmission electron microscopy. We visualized α- and β-tubulin in the membranes of isolated mitochondria but not in their matrix (Fig. 3A). We then confirmed the presence of tubulin in mitochondrial membranes in intact cells, which strengthens the interpretation that the association of tubulin with the mitochondria is not due to the extraction procedure. Because the nuclear membranes were not stained in intact cells, we then isolated nuclei and performed the same immunostaining protocol as for isolated mitochondria. Tubulin was not detected in nuclear membranes (Fig. 3B), further demonstrating the specificity of the tubulin staining on mitochondrial membranes. Altogether, these results show that αβ-tubulin is specifically associated with mitochondrial membranes.

Quantification of Mitochondrial Tubulin—The quantity of tubulin in whole cells and in mitochondria was determined by using a standard curve with pure tubulin (Fig. 4). Mitochondrial αβ-tubulin represents 0.53 ± 0.02% of total mitochondrial protein, and cellular αβ-tubulin represents 1.70 ± 0.05% of whole cell protein. Thus, there is a substantial amount of tubulin in the mitochondria. Mitochondrial protein represents 7 ± 1% of the total cellular protein as determined by cellular and mitochondrial protein measurements, taking into account the yield of the mitochondrial isolation procedure (28 ± 2%). Altogether, these data allow us to conclude that mitochondrial tubulin represents ~2.2% of the total pool of tubulin in SK-N-SH cells and isolated mitochondria. Interestingly, α- and β-tubulin were present at comparable levels in mitochondria (0.26 ± 0.02% and 0.27 ± 0.01% of the mitochondrial proteins, respectively; p > 0.05), strongly suggesting that mitochondrial tubulin is present as αβ dimers.

Characterization of Mitochondrial Tubulin by Comparison with Cellular Tubulin—To compare the pattern of distribution of α-tubulin post-translational modifications and β-tubulin isoforms between mitochondrial and cellular tubulin, we performed immunoblotting using samples of isolated mitochondria and whole cell lysates containing equivalent quantities of tubulin. Significant differences were found between cellular and mitochondrial tubulins (Fig. 5). Mitochondrial α-tubulin was more tyrosinated and more acetylated than cellular α-tubulin (a 6.0 ± 0.3-fold and a 1.9 ± 0.5-fold increase, respectively; p < 0.01). Moreover, differences in the distribution of β-tubulin isoforms were also evident. The main differences were a 2.9 ± 0.6-fold increase in the class III β-isotype and a 2.5 ± 0.1-fold
cells were immunoprecipitated with an antibody to tubulin and both VDAC and ANT, the two major proteins of the mitochondrial PTP (8), we investigated whether mitochondrial tubulin could be associated with the proteins of this complex. Therefore, we searched for an interaction between mitochondrial tubulin and ANT by immunoblotting. Then, mitochondrial lysates were immunoprecipitated with an antibody to VDAC, and the resulting precipitates were analyzed for the presence of VDAC and ANT by immunoblotting. The white arrow indicates the absence of staining of nuclear membranes (bars, 500 nm). Data shown are representative of three independent experiments.

Association of Mitochondrial Tubulin with VDAC—Because several anti-tubulin agents, whose target is tubulin, trigger cytochrome c release from mitochondria through the opening of the PTP (8), we investigated whether mitochondrial tubulin could be associated with the proteins of this complex. Therefore, we searched for an interaction between mitochondrial tubulin and both VDAC and ANT, the two major proteins of the PTP. First, lysates of isolated mitochondria from SK-N-SH cells were immunoprecipitated with an antibody to α-tubulin, and the resulting precipitates were analyzed for the presence of VDAC or ANT by immunoblotting. Then, mitochondrial lysates were immunoprecipitated with an antibody to VDAC, and the resulting precipitates were analyzed for the presence of tubulin. These experiments demonstrated that the antibody to α-tubulin co-immunoprecipitated tubulin and VDAC and that the immunoprecipitation of VDAC brought down tubulin (Fig. 6A). Thus, mitochondrial tubulin interacts with the PTP through its binding to the outer membrane protein VDAC. Similar results were found under the same stringent conditions (500 mM NaCl washes) on mitochondria isolated from A549 cells (data not shown), confirming the interaction between tubulin and VDAC in another cancer cell type. Co-immunoprecipitation experiments performed with mitochondrial tubulin and ANT did not reveal an interaction between these two proteins (Fig. 6B), proving the specificity of association between VDAC and mitochondrial tubulin.

![Cell and Mito](image1.png)

**Fig. 3.** Tubulin is located on mitochondrial membranes. A, representative images of intact cells or isolated mitochondria that were treated as described under “Materials and Methods” to stain α- or β-tubulin and visualized by transmission electron microscopy. Black arrows show the mitochondrial tubulin staining. White arrow shows that no staining is observed on nuclear membranes. B, isolated nuclei with α-tubulin immunoperoxidase staining visualized by transmission electron microscopy. The white arrow indicates the absence of staining of nuclear membranes (bars, 500 nm). Data shown are representative of three independent experiments.

![Nuclei](image2.png)

**Fig. 4.** Quantification of mitochondrial tubulin. The quantity of tubulin in whole cell and isolated mitochondria (Mito.) was determined by using a standard curve of pure tubulin. Equal quantities of cellular and mitochondrial proteins (50 μg) were analyzed by Western blotting for α- and β-tubulin. The percentage that represents mitochondrial α- and β-tubulin among total mitochondrial proteins and the percentage of tubulin cellular tubulin among whole cell proteins are shown. Data represent the mean ± S.D. of at least three independent experiments.

**DISCUSSION**

In this study, we showed that tubulin is an inherent component of mitochondrial membranes in several human cancer cell lines as well as in a non-cancerous cell line. Differences in the pattern of distribution of α-tubulin post-translational modifications and β-tubulin isotypes between the mitochondrial and cellular tubulins were shown. We also demonstrated that mitochondrial tubulin is specifically associated with VDAC, the main PTP component located in the mitochondrial outer membrane.

The presence of tubulin in mitochondria was initially surprising because tubulin was thought to be primarily a cytosolic protein involved in microtubule formation by an equilibrium between free and assembled αβ-tubulin dimers. Nevertheless, several studies reported the presence of tubulin in organelle or plasma membranes about 20 years ago (15, 17). Recently, Walss et al. (26) demonstrated the existence of αβ-II-tubulin dimers in the matrix of nuclei, and Chabin-Brion et al. (21) showed that γ-tubulin is associated with the Golgi apparatus, indicating that the Golgi could play the role of a microtubule-organizing organelle. Thus, the tubulins are a large protein superfamily (5) with various members whose localization in cells is widespread.

Since the first suggestion of its existence, mitochondrial tubulin has been controversial (16). Mitochondrial tubulin was considered as a possible artifactual consequence of the cell fractionation process. To exclude such a possibility in this study, we determined that our mitochondrial preparation did not contain any assembled microtubules, microtubule-linked proteins, or a cytosolic protein.

By using electron microscopy, we then showed that tubulin is an inherent component of mitochondrial membranes. Mitochondrial tubulin represents 0.5% of mitochondrial protein, which is consistent with results published previously (17, 27). Interestingly, α- and β-tubulin is present in equivalent quantities in mitochondria, strongly suggesting that mitochondrial tubulin is organized in αβ dimers. At present, we do not know...
whether these tubulin dimers in mitochondrial membranes are individual or in oligomeric form.

A study of α-tubulin post-translational modifications and β-tubulin isotypes revealed that mitochondrial tubulin has a specific pattern of distribution that is different from that of total cellular tubulin. Mitochondrial tubulin contains very little of the class IV β-tubulin isotype but is rich in the class III β-tubulin isotype. Because the class III β-tubulin lacks the highly oxidizable Cys-239, it is much more resistant to free radicals, and it is not surprising that mitochondria are enriched for this isotype because mitochondria are a major site of free radical production (28). Thus, even if mitochondrial tubulin is synthesized in the cytosol, a selection related to the inherent characteristics of tubulin and the mitochondrial environment seems to be made, leading to a mitochondrial-specific distribution of tubulin isotypes. These data suggest that mitochondrial tubulin may have specific functions.

When studies on mitochondrial tubulin were first published, mitochondria were only regarded as cell power plants, so the functions of mitochondrial tubulin were hard to imagine. Nevertheless, colocalization of mitochondria with microtubules in cells had already been described (29), and mitochondrial tubulin was suggested as providing an interaction site for the transport of mitochondria along microtubules via motor proteins (16).
Recently, Ngan et al. (30) hypothesized that Vinca alkaloids may be sequestered within the cell to explain the differences between the intracellular concentrations of drugs and the observed effects on the microtubule network in the cells. Because mitochondrial tubulin represents 2.2% of the total cellular tubulin, mitochondria may participate at least in part in drug sequestration through binding of the anti-tubulin agents to mitochondrial tubulin.

However, it seems that the main functions of mitochondrial tubulin may be due to the major involvement of mitochondria in apoptosis through the PTP opening. In the present study, we demonstrate that mitochondrial tubulin is specifically associated with VDAC, the main outer membrane PTP component. Such an association between PTP and mitochondrial tubulin might explain why anti-tubulin drugs such as vinorelbine and paclitaxel directly induce the PTP opening and the release of cytochrome c from isolated mitochondria (8). Anti-tubulin drugs could bind to mitochondrial tubulin and thus change the conformation of the tubulin that consequently modifies the conformation of PTP, leading to its opening. As mitochondria are regarded as new targets for anti-cancer agents (31) and more widely as death sensors (32, 33), the existence of mitochondrial tubulin should not be restricted to its function during apoptosis induced by anti-cancer drugs. Mitochondrial tubulin may participate in a pathway for death signals from the cytoskeleton to the mitochondria via the VDAC (34) or could be involved on its own in the apoptotic mechanism.

Whether the association of mitochondrial tubulin with VDAC is or is not a direct interaction remains to be elucidated. Linden et al. (27) previously showed that the immunoprecipitation of VDAC brought down microtubule-associated protein 2 (MAP2). VDAC, tubulin, and MAP2 could form a complex in which MAP2 or tubulin may be an intermediary partner. Even if we have shown that mitochondrial tubulin is not associated with ANT, we cannot exclude an interaction with another component of the PTP such as hexokinase, which can bind tubulin in vitro (35), or with another mitochondrial protein.

In summary, in the present paper we demonstrate the presence of tubulin in mitochondrial membranes and its association with the main PTP outer membrane component, VDAC. It seems very likely that mitochondrial tubulin could act as a regulator of the PTP state. However, the roles of mitochondrial tubulin have to be further investigated. Further characterization of mitochondrial tubulin is currently in progress and could lead to the identification of specific isotypes as targets for new anti-tumor drugs.

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