MITOCHONDRIA: CRISTA AND TUBULUS TYPES, MITOCHONDRIAL NETWORKS, AND FISSION

Although known since the early days of microscopy, mitochondria continue to attract extraordinary interest because of their unique functions in both cell life and death. Dimensions, shapes, and locations of mitochondria are strikingly different in diverse types of cells in relation to the specific cellular functions. Because of their obligatory double membranes and characteristic inner compartmentalization, it is easy to discriminate mitochondria from other membrane-bound organelles, such as peroxisomes (cf. Fig. 79), under the electron microscope.

Panel A shows a mitochondrion of the crista type in a rat pancreatic acinar cell, surrounded by cytoplasm with densely packed cisternae of the rough endoplasmic reticulum. Mitochondria are located mainly at sites where energy is needed and, according to the requirements, change their locations and undergo temporary alterations in shape, forming long "filamentous" organelles and extended intracellular networks. A mitochondrial network with a ring-like architecture and branching arms is shown in panel C. Outer and inner mitochondrial membranes enclose the intermembrane space. The outer membrane contains voltage-dependent anion channels, the mitochondrial "porins" that allow ions and small molecules to enter the intermembrane space, creating a milieu resembling that of the cytoplasm. The inner membrane is impermeable to ions because of its enrichment in the phospholipid cardiolipin. It surrounds the mitochondrial matrix and contains the proteins for the oxidation reactions of the respiratory electron-transport chain, adenosine triphosphate (ATP) synthesis, and regulation of the metabolite transport into and out of the matrix. The inner membrane consists of two domains: the inner boundary membrane residing adjacent to the outer membrane and invaginations, which in most cells have the form of cristae (arrowheads in panel A), although other forms, such as tubular projections, occur as well. The latter are typical for steroid hormone-producing cells and are shown in panel B in an endocrine cell of the ovary (T-tubular projections). Inner boundary membranes and cristae membranes are connected by tubular openings, the crista junctions. For their maintenance and formation of contact sites to the outer membrane, a large heterooligomeric protein complex of the inner membrane, termed MICOS (mitochondrial contact site and cristae organizing system), has a pivotal role.

The matrix contains the enzymes of the citric acid cycle and enzymes engaged in fatty acid β-oxidation. In panel A, dense matrix granules are visible, being important for the storage of Ca^{2+} and other divalent cations. Furthermore, the mitochondrial DNA and the machineries for protein synthesis, ribosomes, and tRNAs are contained in the matrix. Only some of the mitochondrial proteins are encoded by the mitochondrial genome and synthesized in the matrix. Most of the mitochondrial proteins are synthesized on free ribosomes in the cytoplasm and are posttranslationally translocated across the mitochondrial membranes to reach their functional destinations inside the mitochondria. Three membrane protein complexes, the translocase of the outer membrane (TOM), the presequence translocase of the inner membrane (TIM 23), and the protein insertion complex of the inner membrane (TIM 22), build up the central machineries for recognition and translocation of mitochondrial precursor proteins.

Mitochondria are highly dynamic organelles. They increase in number by division throughout the interphase, taking place independent of the cell cycle. Ongoing fusion and fission events are required for the maintenance of regular mitochondrial structures and functions. A fission event is shown in panel D (arrows).

Mitochondria are sensitive to cellular stress and have a pivotal role in the initiation of programmed cell death. As a major event, cytochrome c is released from the intermembrane space into the cytoplasm, initiating the cascade of proteolytic reactions that result in the apoptotic changes of the cell (cf. Fig. 15).

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Magnification: ×49,000 (**A**); ×49,500 (**B**); ×26,000 (**C**); 20,000 (**D**)

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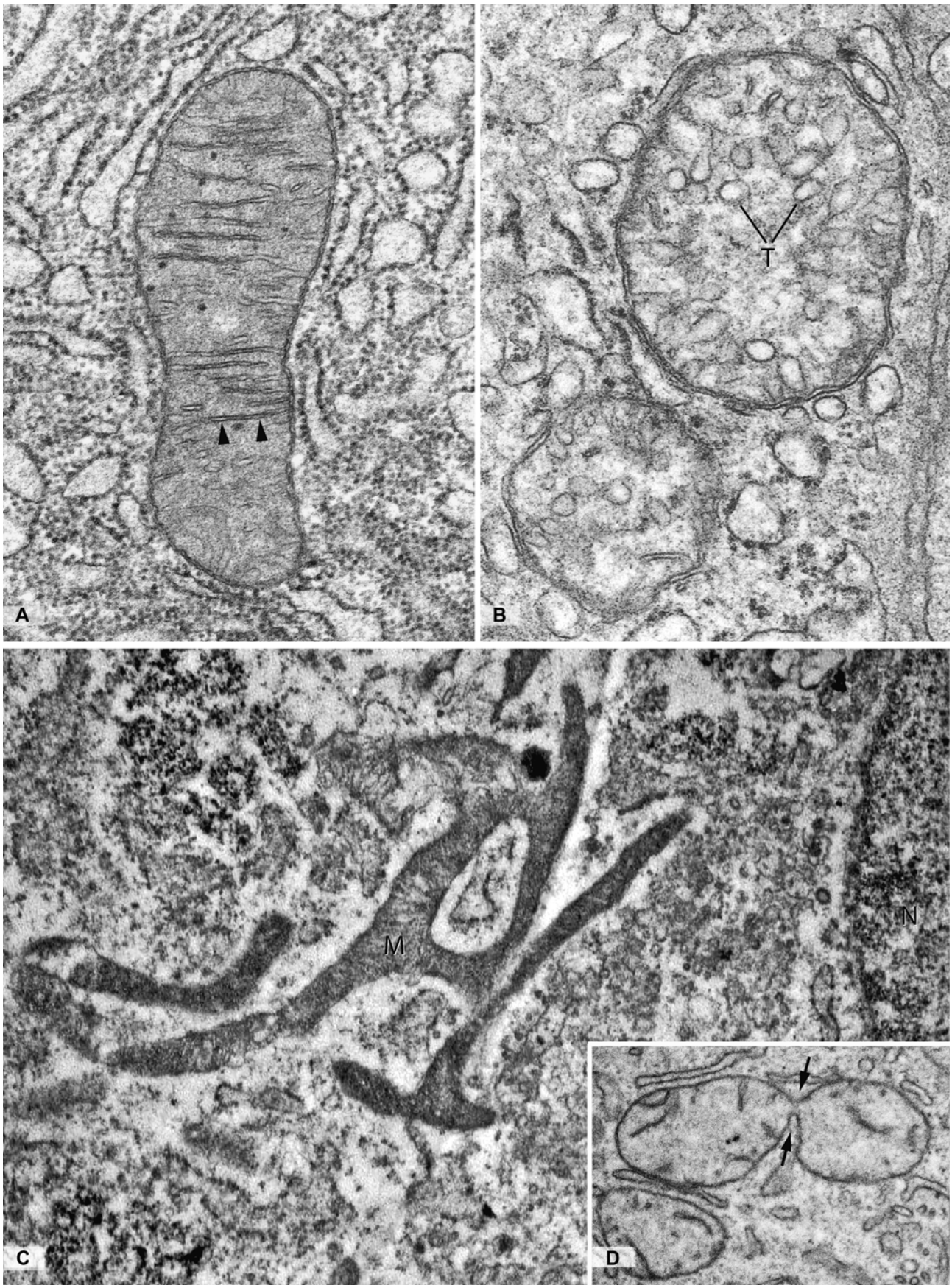
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ABNORMALITIES OF MITOCHONDRIA

Structural abnormalities of mitochondria are found most often in inherited disorders affecting the skeletal muscle (myopathies) and central nervous system and in addition can be caused by drug toxicity (alcohol, hydrazine, some antiretroviral drugs). Although these are quite different diseases and involve different pathogenetic mechanisms, the observed structural changes of the mitochondria are alike. These abnormalities consist not only of an increase of the number of mitochondria but also of an enlarged and abnormal shape, variations in the number of cristae and particular patterns of cristae, and abnormal inclusions. The functional consequences of these mitochondrial abnormalities can be far reaching and systemic due to the common underlying impairment of oxidative phosphorylation.

In panel A, a detail from a skeletal muscle fiber (cross-sectioned myofibrils marked by an asterisk) is shown with numerous mitochondria that contain several paracrystalline inclusions. Such paracrystalline inclusions can be observed in mitochondrial encephalomyopathies, which are a heterogeneous group of disorders. Furthermore, such inclusions occur in specific mitochondrial disorders.

In panel B, a group of mitochondria of various sizes and shapes is shown. Some contain cristae arranged in parallel order, which is normal, as is their size (arrows). However, other mitochondria are greatly enlarged and are filled with concentric cristae, which is abnormal (arrowheads). The mitochondrial matrix appears to be inexistent.

In panel C, a mitochondrial abnormality caused by drug toxicity is exemplified. These mitochondria of hepatocytes are from a liver biopsy of a patient receiving an antiretroviral drug. Cristae can be observed only rarely (arrow), and the matrical substance is increased. However, the outer and inner mitochondrial membrane is unmistakably seen, excluding the possibility that these could be peroxisomes (cf. Fig. 79). Paracrystalline mitochondrial inclusions as shown in panel A can also occur during the course of treatment with antiretroviral drugs. Antiretroviral treatment with nucleoside analog reverse transcriptase inhibitors results in impaired oxidative phosphorylation through inhibition of DNA polymerase γ. This causes myopathy, neuropathy, hepatic steatosis (lipid accumulation in hepatocytes), and lactic acidosis. Treatment with AZT (zidovudine) results in oxidative damage of mitochondrial DNA through production of peroxide. As a consequence, this seems to affect mitochondrial DNA replication and to reduce mitochondrial renewal. However, free radical scavengers can be applied to protect against the AZT-induced oxidative damage of mitochondrial DNA.

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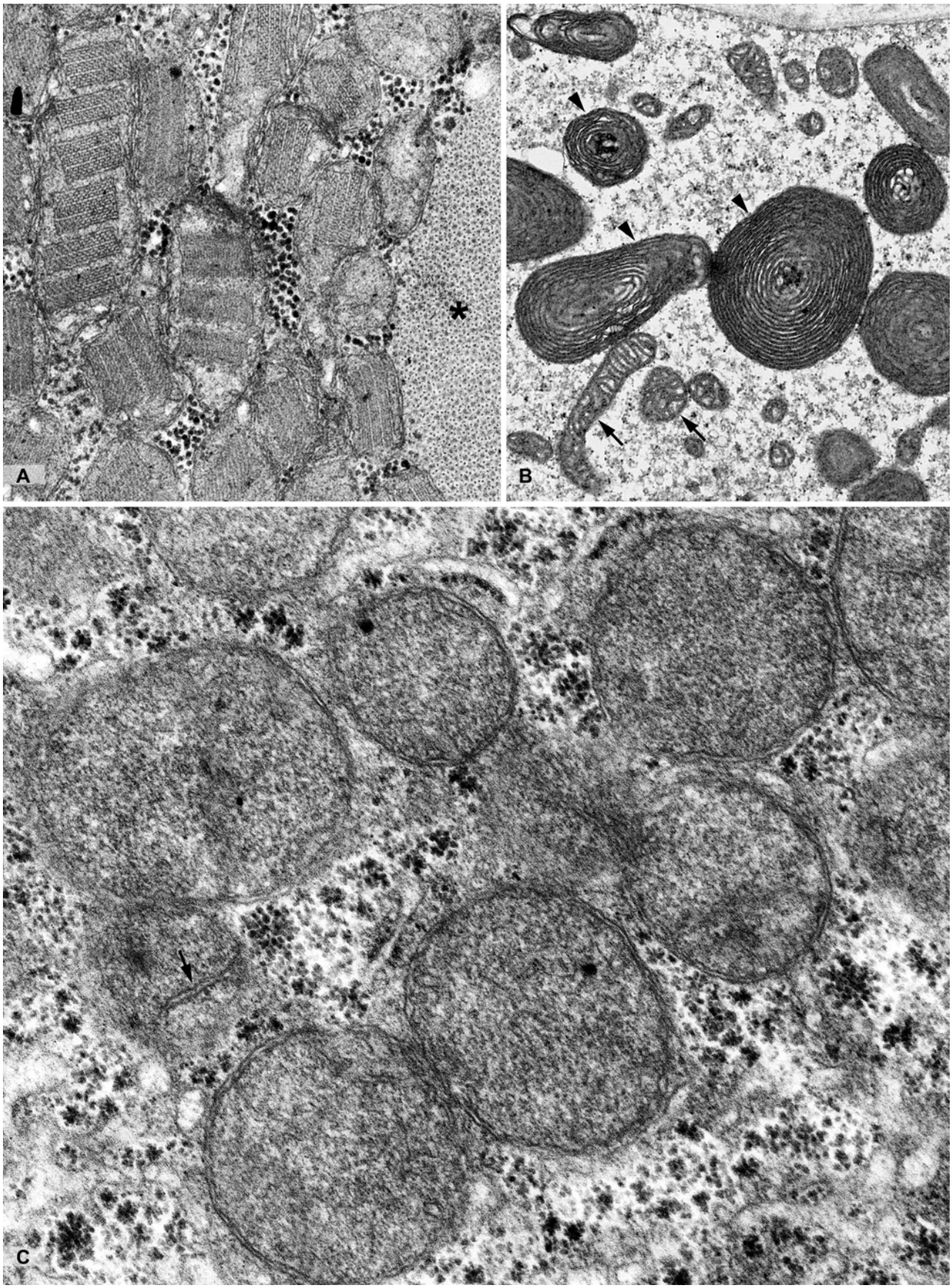
Magnification: ×56,000 (**A**); ×9,500 (**B**); ×62,500 (**C**)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