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Miniseries: Illustrating the Machinery of Life

Mitochondrion*

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Diverse biological data may be used to create illustrations of molecules in their cellular context. I describe the scientific results that support a recent textbook illustration of a mitochondrion. The image magnifies a portion of the mitochondrion by one million times, showing the location and form of membranes and individual macromolecules, revealing the molecular basis of its role in energy metabolism and apoptosis. Results from biochemistry, electron microscopy, and X-ray crystallography were used to create the image.

Keywords: mitochondria, cellular biology, molecular biology, molecular visualization, textbook diagrams, energy metabolism, apoptosis, programmed cell death, endosymbiont hypothesis.

Mitochondria are organelles with many intriguing aspects [1]. They play a familiar role in energy metabolism, housing the machinery of ATP synthesis and harnessing chemical, electrical, chemiosmotic, and mechanical energy transformations in the process. They also play a major role in apoptosis (programmed cell death), amplifying the signal that ultimately leads to the death of the cell. In addition, mitochondria live their lives as more-or-less autonomous symbiotic units that live and reproduce inside our cells, which has been taken as evidence that mitochondria evolved from endosymbiotic cells that took up residence in eukaryotic cells early in the evolution of life [2, 3]. For the new edition of "The Machinery of Life" [4], I wanted to create an illustration that captured these many aspects of mitochondrial structure and function. Figures 1 and 2 show the illustrations used in the book, and Fig. 3 is a key to Fig. 2. I present here the scientific support for the molecular and ultrastructural details of the illustration, as well as some of the aesthetic and pedagogic choices that I made when designing the illustration.

MORPHOLOGY

The traditional model of mitochondria, inferred primarily from electron micrographs of thin sections, has a smooth outer membrane and a folded inner membrane, folded either into plate-like invaginations or tubules. The numerous folds of the inner membrane create a large surface area that is filled with the membrane-bound molecules of electron transport and ATP synthesis. However, more recent models based on electron tomography of mitochondria have shown that the traditional model may be too simplistic [5]. These studies suggest that the inner membrane folds to form two compartments that do not share soluble proteins. A portion of this membrane lies immediately inside the outer membrane, defining the intermembrane space between them. Another portion of the inner membrane surrounds the cristae, forming the intercristal space. The two compartments are connected by small (or no) openings that connect them, and the two compartments have a different complement of proteins.

I have drawn a speculative model that has the two spaces connected by narrow connections that are constricted by the protein OPA1 [6]. This protein is similar to dynamin, which forms helical assemblies that are important for pinching off membranes during the process of budding. I based the structure on a combined crystallographic/EM structure of dynamin [7]. There is also evidence for regions where the outer and inner membranes are closely opposed [8, 9], allowing transfer of small molecules and proteins between the cytoplasm and the matrix space. There are also connections between the infrastructure of the mitochondrion and the cytoskeleton. I have shown one such connection that links actin filaments in the cytoplasm with proteins in the mitochondrial membrane and inside to link to mitochondrial DNA, based on schematic diagrams from a review article [10]. To generate a model of this complex, the sizes and locations of intermembrane regions in the complex of MDM proteins (mdm10, mdm12, mmm1, mdm31, and mdm32) were taken from protein sequences at the ExPASy proteomic server (http://ca.expasy.org), and the Arp2/3 protein at the actin junction is taken from electron micrograph reconstruction [11].

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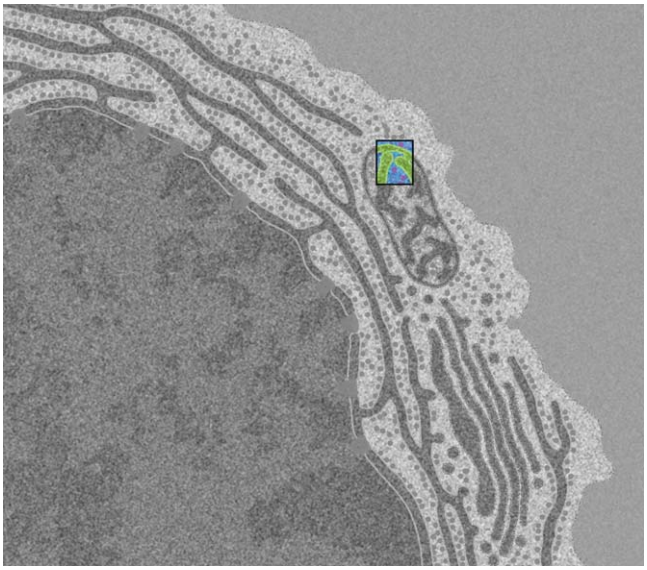

FIG. 1. **Simulated cross section through a eukaryotic cell, showing the location of the enlarged portion in Figure 2.**

The innermost compartment of the mitochondrion is termed the matrix. The matrix is one of the most densely packed portions of the cell; some estimates place it at greater than 50% protein [12]. It includes the enzymes of the tricarboxylic acid cycle and enzymes for fatty acid utilization, as well as an entire set of protein synthesis machinery, including DNA, polymerases, ribosomes, and transfer RNA, all described in more detail later.

ATP SYNTHESIS

The major task of the mitochondrion is the production of ATP. The enzymes of the tricarboxylic acid cycle are found in the matrix, along with a collection of enzymes for utilization of fat and other energy-rich molecules. These include two large multiprotein complexes, pyruvate dehydrogenase complex and alpha-ketoglutarate dehydrogenase complex, both drawn based on results from crystallography and electron microscopy [13, 14]. I have included little tails to represent the lipoic acid cofactors that are involved in substrate transfer between the subunits. Other tricarboxylic acid cycle enzymes are drawn based on crystallographic structures: citrate synthase (1cts), aconitase (1aco), isocitrate dehydrogenase (1lwd), succinyl-CoA synthetase (2fp4), succinate dehydrogenase (1zoy), fumarase (1yfm), and malate dehydrogenase (1mld). (4-letter codes included in this paper are accession codes for atomic structures at the Protein Data Bank, http://www.pdb.org.)

The electron transport chain is found in the membranes of the cristae. Decades ago, it was discovered that the large protein complexes of the electron transport chain are not arranged in a structured chain—rather, electrons are transferred by random diffusion of small carrier molecules between randomly-placed protein complexes in the membrane [15, 16]. More recently, however, there has been growing evidence that the proteins form a supercomplex in some organisms [17]. For this illustration, I have chosen to depict them as separate complexes in the membrane. NADH dehydrogenase complex is based on an electron micrograph reconstruction [18], and the other large complexes are based on atomic structures: cytochrome reductase (1bgy) and cytochrome oxidase (1oco). I have also included coenzyme q in the membrane and cytochrome c in the intercristal space (3cyt). Cytochrome c peroxidase (2pcc), also in the intercristal space, may play a role in detoxifying peroxide that leaks from the electron transport chain. ATP synthase (one of the wonders of the biomolecular world) is modeled after several crystal structures (1c17, 1e79, 1l2p, 2a7u).

I have also included a number of other enzymes involved in energy metabolism. I identified these using results from 2D gel electrophoresis [19] and by searching for "mitochondrial matrix human" in ExPASy. In the outer membrane, I included the membrane-linked enzyme monoamine oxidase (1gos). In the intermembrane and intercristal spaces, these include: creatine kinase (1qk1), adenylate kinase (1ak3), nucleotide diphosphate kinase (1ndl), and sulfate oxidase (based on molecular weight from ExPASy). In the matrix, I included manganese superoxide dismutase (1ja8) and copper-zinc superoxide dismutase (2sod), pyruvate carboxylase (2qf7), acyl-CoA dehydrogenase (3mdd), ornithine transcarbamoylase (1fb5), ornithine aminotransferase (2can), and glutamate dehydrogenase (1aup). I also included two forms of glycerol-3-phosphate dehydrogenase (1x0x), GPD1 in cytoplasm and GPD2 in the mitochondrion, which together form a shuttle.

APOPTOSIS

The mitochondria also play an important role in apoptosis (programmed cell death). Cytochrome c is a "moonlighting" protein that plays a secondary role entirely unrelated to its primary function as an electron transport protein. If it leaks into the cytoplasm, it initiates the cascade of apoptosis. A complex set of cellular machinery receives apoptotic signals and then ruptures the outer mitochondrial membrane, thus releasing cytochrome c and other apoptotic proteins.

In this illustration, I included many of the mitochondrial proteins of apoptosis, including several in the outer membrane and in the intermembrane space. In the outer membrane, BID (2bid) and Bcl-2 (1g5m) are ready to initiate an apoptotic cascade [20]. Fzo1 protein (based on a schematic diagram of its domain structure [21]) may play a role in fusion of mitochondria. In the intermembrane space, I included Smac (1few), which plays a role in activating caspases, and the apoptotic ribonuclease EndoG (3ism) and serine protease HtrA2/Omi (1lcy). I also included several cytoplasmic apoptotic proteins, including caspase-7 in an inactive complex with XIAP (1nw9) and Apaf-1 (1z6t), the protein that associates with cytochrome c when it is released from the mitochondrion, triggering the apoptotic cascade.

I created a separate illustration to show a rupturing mitochondrion in the process of losing its cytochrome c, and the consequences for the cell. A detail is included in

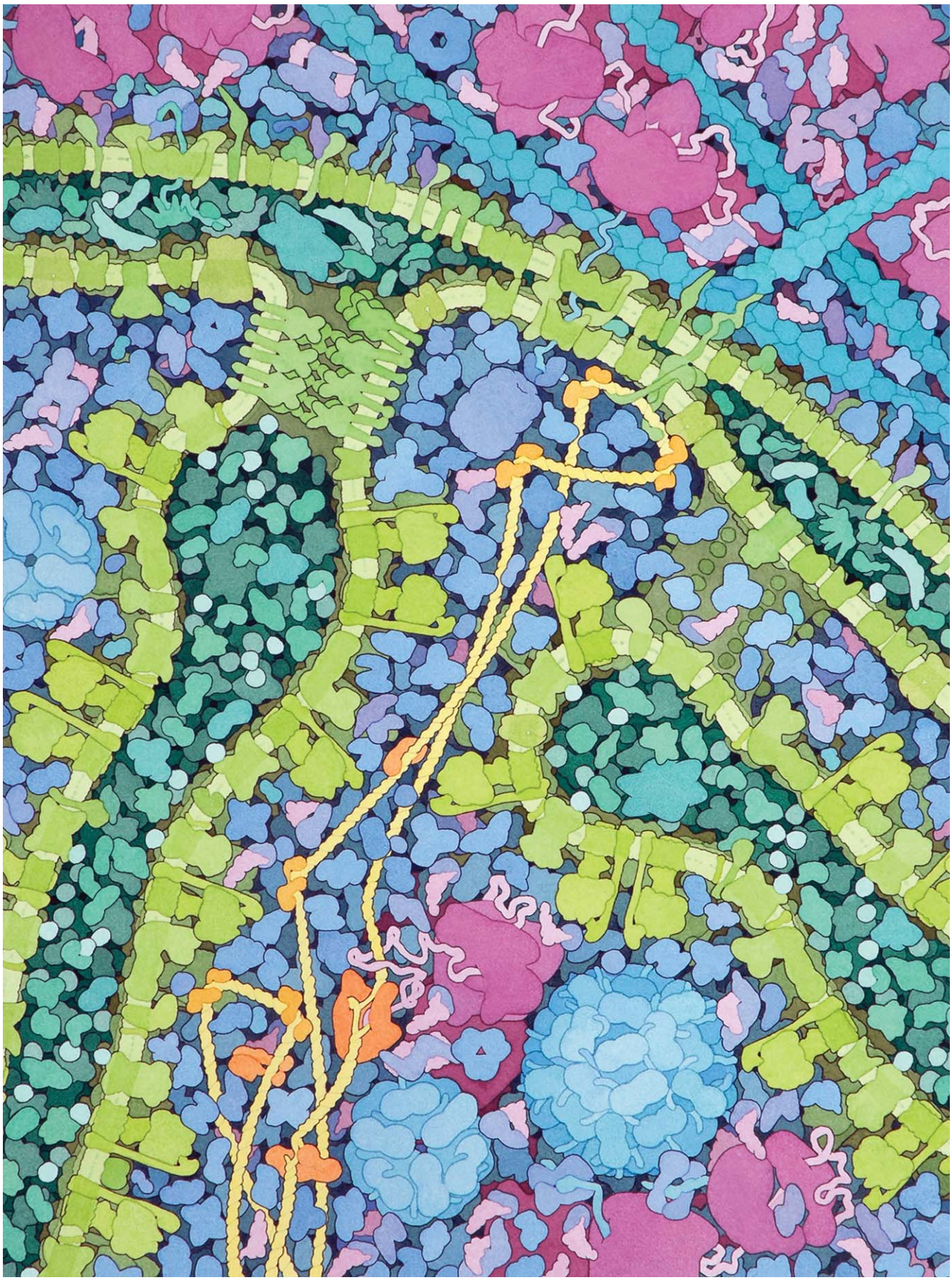

FIG. 2. **Cross section through a mitochondrion at 1,000,000× magnification.** All macromolecules and membranes are shown, but small molecules, ions and water are omitted for clarity. The cellular cytoplasm is at the top, and the mitochondrion fills most of the lower portion of the image. Soluble proteins are shown in shades of blue, and membranes and membrane-bound proteins are shown in green. RNA is shown in pink and ribosomes in magenta. DNA and DNA-associated proteins are shown in yellow and orange.

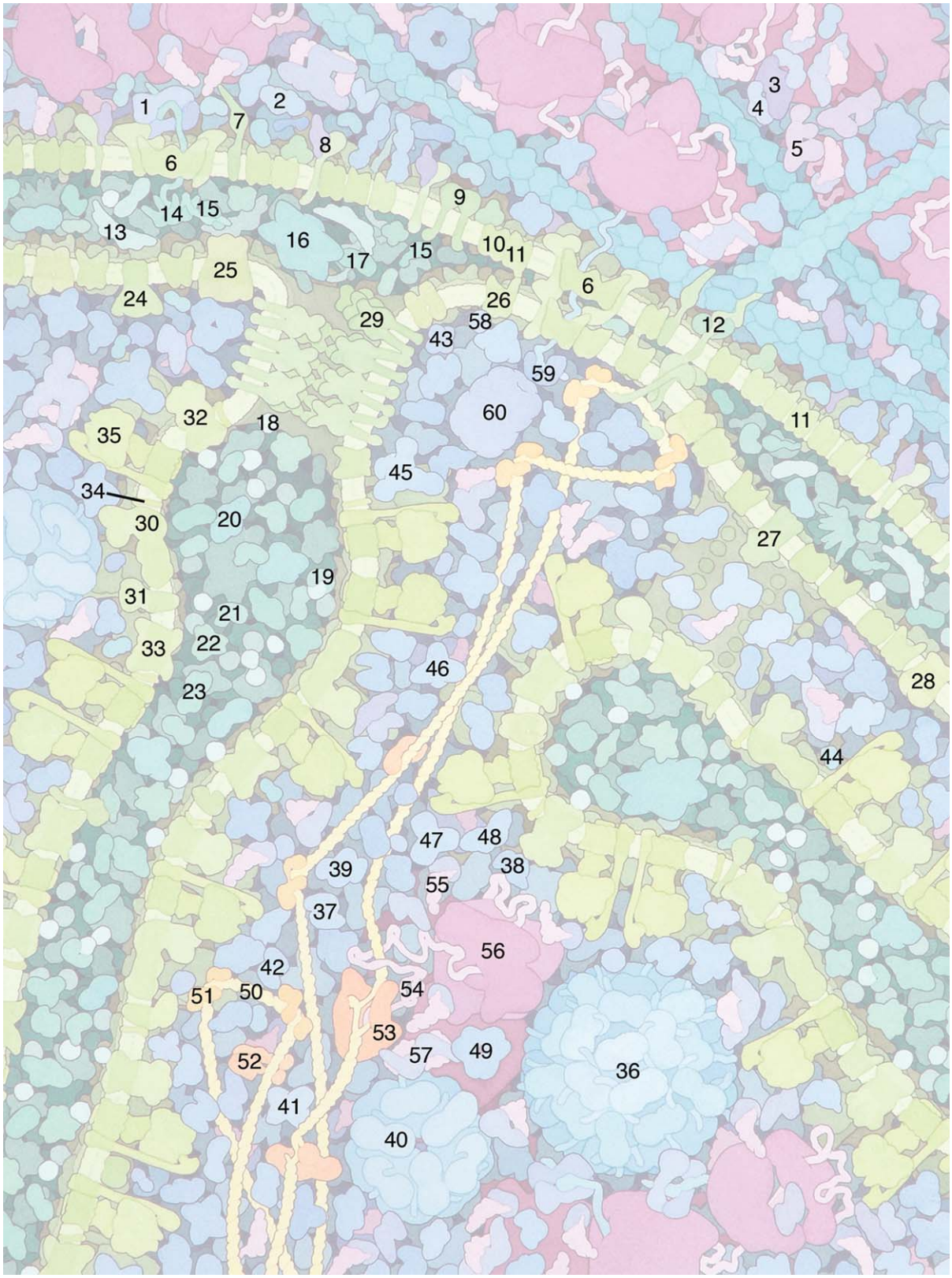

FIG. 3. **Key to Figure 2.** *Cytoplasm:* 1. Hsp90; 2. glycerol-3-phosphate dehydrogenase 1; 3. caspase-7; 4. XIAP; 5. Apaf-1. *Outer Membrane:* 6. protein transporter; 7. Fzo1; 8. BID/Bcl-2 complex; 9. monoamine oxidase; 10. PBR; 11. VDAC; 12. MDM complex bound to Arp2/3 and actin. *Intermembrane Space:* 13. Smac; 14. TIM9/10; 15. HtrA2/Omi; 16. creatine kinase; 17. EndoG. *Intercristal Space:* 18. cytochrome c; 19. cytochrome c peroxidase; 20. glycerol-3-phosphate dehydrogenase 2, 21. adenylate kinase; 22. nucleotide diphosphate kinase; 23. sulfate oxidase. *Inner Membrane:* 24. magnesium transporter; 25. RyR1; 26. ADP/ATP carrier; 27. potassium channel; 28. ABC-type transporter; 29. Opa1; 30. NADH dehydrogenase; 31. succinate dehydrogenase; 32. cytochrome bc1 reductase; 33. cytochrome oxidase; 34. coenzyme q; 35. ATP synthase. *Matrix: TCA enzymes:* 36. pyruvate dehydrogenase complex; 37. citrate synthase; 38; aconitase; 39. isocitrate dehydrogenase; 40. alpha-ketoglutarate dehydrogenase complex; (31. succinate dehydrogenase); 41. fumarase; 42. malate dehydrogenase; *Other enzymes:* 43. manganese superoxide dismutase; 44. copper-zinc superoxide dismutase; 45. pyruvate carboxytransferase; 46. acyl CoA dehydrogenase; 47. ornithine transcarbamoylase; 48. ornithine aminotransferase; 49. glutamate dehydrogenase; *Protein synthesis:* 50. DNA; 51. TFAM; 52. steroid receptor; 53. RNA polymerase; 54. messenger RNA; 55. transfer RNA; 56. ribosome; 57. aminoacyl-tRNA synthetase; 58. cyclophilin D; 59. MPP, 60. Hsp60.

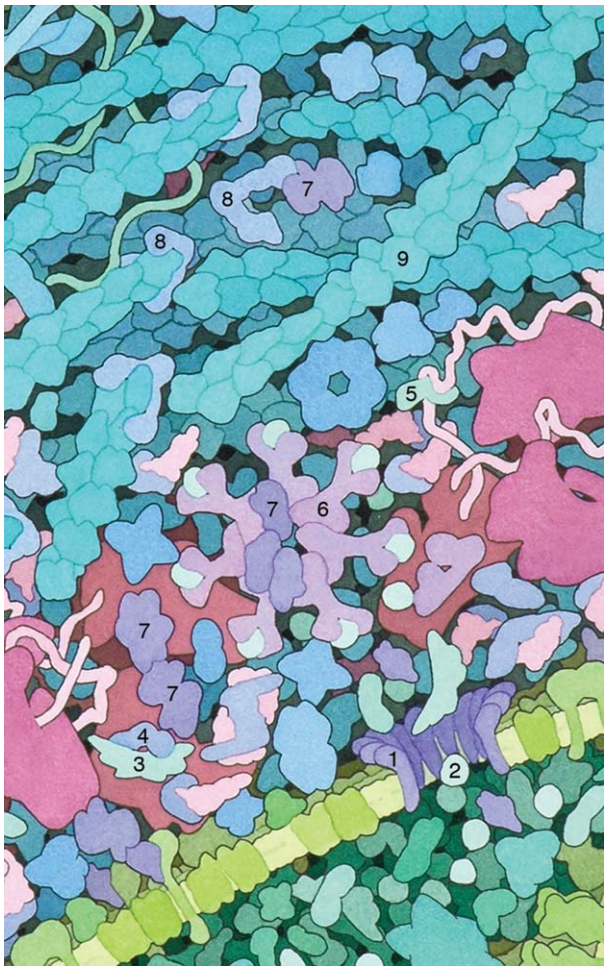

FIG. 4. **Apoptosis (detail)**. The outer membrane of the mitochrondrion has been ruptured, releasing mitochondrial proteins that trigger and assist with apoptosis. 1. BAX; 2 cytochrome c; 3. Smac; 4. XIAP; 5. EndoG; 6. Apaf-1; 7. caspase; 8. gelsolin; 9. actin.

Fig. 4. The BAX protein has formed a speculative pore through the membrane [22], and presumably the intercristal space is also breached, allowing cytochrome c, EndoG [23], HtrA2/Omi [24], and Smac to exit. Cytochrome c associates with Apaf-1 to form a beautiful seven-membered apoptosome [25], which then activates caspases and starts the destruction of proteins throughout the cell. Smac removes XIAP from caspases, further assisting the activation. EndoG attacks messenger RNA molecules, halting translation of new proteins, and caspases activate enzymes such as gelsolin [26], which disassembles actin filaments.

MITOCHONDRIAL DNA

The mitochondrial matrix includes an entire mechanism for protein synthesis, different and separate from the protein synthesis machinery in the cytoplasm. Moreover, the mitochondrial ribosomes, polymerases and other protein synthesis molecules are very similar to those found in bacteria. The presence of this bacteria-like protein synthesis machinery is one of the main clues that mitochondria evolved from endosymbiotic bacteria. This machinery is an evolutionary artifact, however, and is currently used to make only 13 proteins involved in the electron transfer chain and ATP synthase, as well as 22 mitochondrial transfer RNA and two ribosomal RNA [27]. The 700 or so other mitochondrial proteins [28], including the bacteria-like polymerases and translation factors, are made in the normal way by cytoplasmic ribosomes, and then imported into the proper compartment in the mitochondrion [29].

The mitochondrial ribosomes, transfer RNA, polymerases and other protein synthesis machinery are more similar to their bacterial counterparts than to the ribosomes and other machinery found in the cytoplasm of the cell. I have included many of these molecules in the illustration, including ribosomes modeled after the ones in *Thermus thermophilus* (1yl3, 1yl4), bacterial elongation factors EFTu (1ttt) and EFG (1dar), transfer RNA (1ttt), aminoacyl-tRNA synthetases (1asz, 1ffy, 1gax, 1euq, 1eiy, 1qf6), RNA polymerase (2e2i), and DNA. The chaperone Hsp60 was modeled after bacterial GroEL (1aon). The mitochondrial transcription factor TFAM is based on HMG-domain structures (1qrv, 2gzk), and the steroid receptor is based on the nuclear vitamin D receptor (1db1,1kb6).

TRANSPORT

Since mitochondria are surrounded by two membranes, there are potential challenges with transport. Like the outer membrane in *Escherichia coli*, the outer membrane of the mitochondrion is leaky. It is filled with voltage-dependent anion channel (VDAC), a protein similar to bacterial porins that forms a pore through the membrane. This pore is roughly 20–30 Å in size, large enough for small molecules like ATP and glucose to pass, but small enough to exclude larger molecules like proteins. VDAC is the most abundant protein in the outer membrane, and was found in large, densely packed clusters in a high-resolution atomic force microscopy study [30], where each pore was spaced by about 53 Å apart. I have modeled the structure after PDB entry 2k4t. I also included the PBR (peripheral-type benzodiazepine receptor), a protein involved in transport of cholesterol and other molecules [31]. I have shown it interacting with VDAC and the ADP/ATP carrier at the contact site shown at the center of membrane in Fig. 2 [9].

The inner membrane, however, must be sealed to allow generation of proton gradients to power ATP synthase. A large collection of transporters facilitate movement of molecules across this membrane. These include at least 49 different specific transport proteins of the mitochondrial carrier family [32]. The most abundant is the ADP/ATP carrier (1okc) that transports nucleotides in and out of the mitochondrion [33]. Other members of the mitochondrial carrier family, which have similar pore-like structures, transport pyruvate and other important metabolites, cofactors, and inorganic molecules. I have also included several other classes of transporters and channels [34], including the magnesium transporter (2bbj), RyR1 (ryanodine receptor, a possible calcium transporter), a potassium channel (1f6g) and several ABC-type transporters modeled after the vitamin B12 transporter system (2qi9).

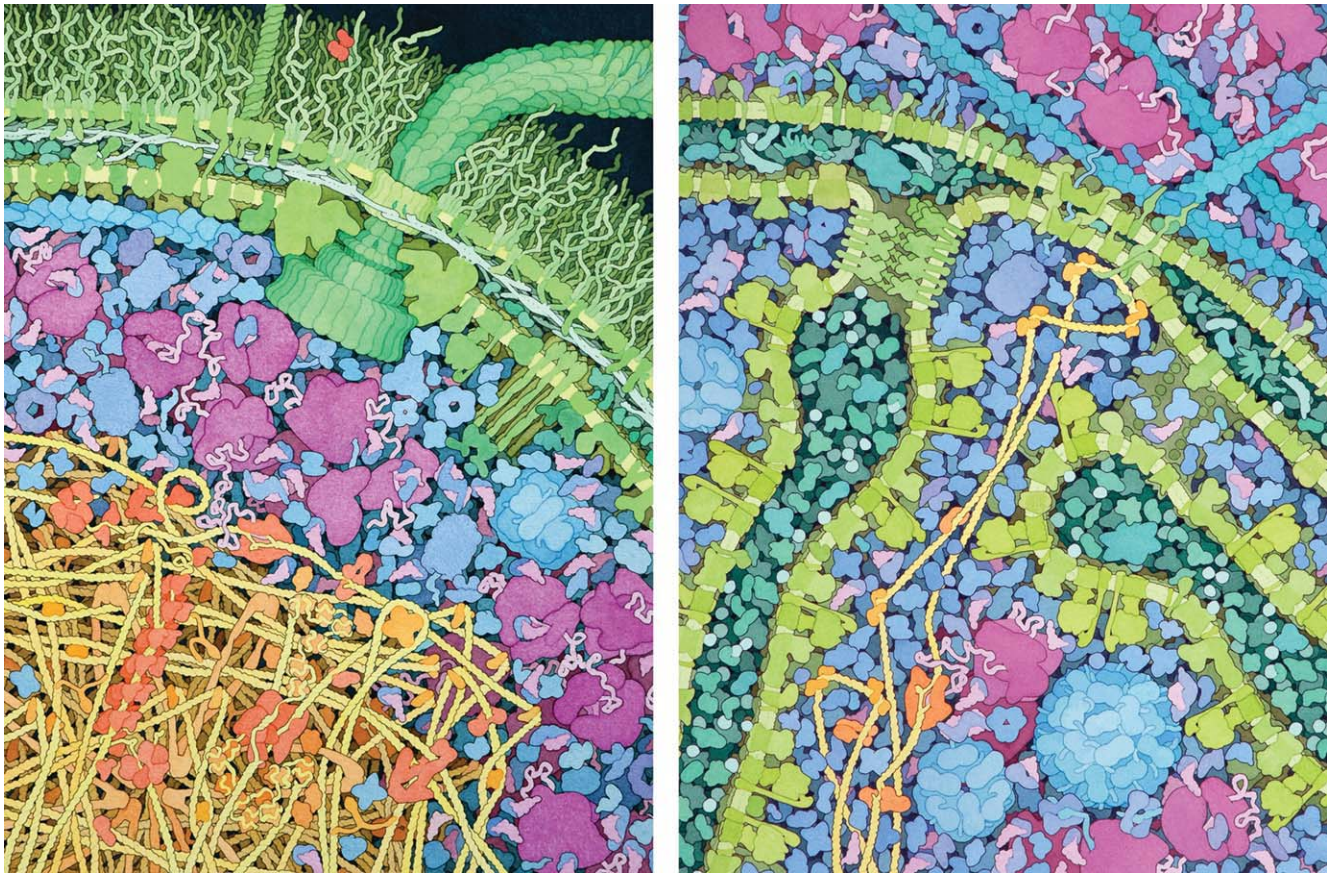

FIG. 5. **Illustrations of cross sections of *Escherichia coli* (left) and the mitochondrion (right) are designed to show structural and functional similarities.**

There are also several specific transporters for importing proteins into the intermembrane space or into the matrix [29]. I included two separate protein transporters. The one on the left in Fig. 2 is shown transporting an unfolded protein from Hsp90 (2cg9) in the cytoplasm and delivering it to the intermembrane space, where it is picked up by the chaperonin TIM9/10 (2bsk) and possibly HtrA2/Omi (1lcy). The one on the right is shown transporting the protein through both membranes into the matrix, where it is processed by the mitochondrial-processing peptidase MPP (1hr6).

AESTHETIC AND PEDAGOGIC CONSIDERATIONS

I designed the layout of this painting to match the layout of the *Escherichia coli* picture that was presented in an earlier chapter in the book (Fig. 5), to highlight the evolutionary relationship between mitochondria and bacteria [2, 35], and to show their many structural and functional similarities [3]. As with the other illustrations, a cross-section at 1,000,000× magnification is depicted, with the section chosen to place the membranes roughly perpendicular to the plane of the cut. The level of magnification is a compromise between two pedagogic goals: to show the entire subject in one comprehensive illustration, but still be able to see the shape and form of each macromolecule. This magnification allows display of a section of the mitochondrion that is large enough to see the major ultrastructural features as well as the molecular details of its major functions.

The colors are chosen to match the colors used for illustrations throughout the book. This scheme is designed to highlight the functional compartments of the cell/organelle, as described in my earlier article [36]. In this scheme, soluble proteins are shown in shades of blue, and membranes and membrane-bound proteins are shown in green. RNA is shown in pink and ribosomes in magenta. DNA and DNA-associated proteins are shown in yellow and orange. This consistent scheme integrates the illustrations throughout the book, allowing readers to compare the features presented in the different scenes, but it also poses a few problems. For instance, the mitochondrial matrix is rendered with similar colors as the cytoplasm. This has the advantage of showing the similarities between the two compartments (e.g., that both compartments are performing protein synthesis with similar molecular machinery), but it introduces the disadvantage of making it difficult to distinguish the mitochondrion from the cytoplasm. The consistent coloring scheme also required one unfortunate choice: after much vacillation, I chose to color cytochrome c in turquoise to match the other molecules in the intermembrane space, rather than coloring it its actual red color.

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