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Article

Miniseries: Illustrating the Machinery of Life

Eukaryotic Cell Panorama

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Diverse biological data may be used to create illustrations of molecules in their cellular context. This report describes the scientific results that support an illustration of a eukaryotic cell, enlarged by one million times to show the distribution and arrangement of macromolecules. The panoramic cross section includes eight panels that extend from the nucleus to the cell surface, showing the process of protein synthesis and export. Results from biochemistry, electron microscopy, NMR spectroscopy and x-ray crystallography were used to create the image.

Keywords: Eukaryotic cell structure, B-cell, cellular biology, molecular biology, molecular visualization, textbook diagrams, protein synthesis, nucleus, endoplasmic reticulum, Golgi.

INTRODUCTION

As part of the book, "The Machinery of Life," [1], I wanted to include a panoramic image that captures the major features of eukaryotic cells, including their many internal compartments and their extensive infrastructure for managing these compartments. Eukaryotic cells are typically too large to show in their entirety and still show individual molecules: at 1,000,000 X magnification, the entire cell would be several meters wide. So instead, I extracted a long rectangular portion that extends from the nucleus to the cell surface, and presented it on eight successive pages.

I had several goals when designing the image. The first was to include the major compartments of the cell: the nucleus, the endoplasmic reticulum, the Golgi, and the cytoplasm. I presented the mitochondria in a separate image, as they are too large to include in this compressed panoramic view. The mitochondrion image was presented in a previous article [2]. The second goal was to capture the entire process of protein synthesis and export, from DNA to final protein. Finally, I wanted to highlight a few of the unstructured proteins in the cell, and their unusual functions.

I chose a B-cell for the panorama, for several reasons. I wanted a free-living cell, so that there would not be complications with cell junctions. I also wanted a cell that synthesized and exported a familiar and recognizable protein, so that the reader could easily follow it along the process of synthesis.

This article describes the science supporting the illustration. The four letter codes presented here (1i6h, etc.) correspond to structures in the Protein Data Bank and UniProt codes (Q# or P#) are given for amino acid sequences. Full references are not given for these files, as they are available at the RCSB PDB and UniProtKB WWW sites, http://www.pdb.org and http://www.uniprot.org.

Ultrastructure

The overall layout of the panorama was based on electron micrographs of plasma cells, obtained from the electron microscopic atlas of cells, tissues and organs, on the WWW at: http://www.uni-mainz.de/FB/Medizin/Anatomie/workshop/EM/EMPlasmaZ.html.

The amount of cytoplasm separating the nucleus and cell surface is typically larger than what is depicted in the panorama, with many layers of endoplasmic reticulum, mitochondria, and Golgi. Many micrographs, however, include sections where the nucleus approaches fairly closely to the cell membrane, with only a few layers of endoplasmic reticulum, as shown in the panorama. So, the painting presents one extreme.

The panorama is broken into four sections, each with two halves to fit on two facing pages. The first section (Figs. 1 and 2) is the nucleus, with the nuclear interior on the left and the nuclear membrane on the right. The next section shows the endoplasmic reticulum, with one long compartment on the left (Fig. 3), and a budding vesicle on the right (Fig. 4). The third section shows the edge of the Golgi, with a vesicle docking on the left side (Fig. 5)

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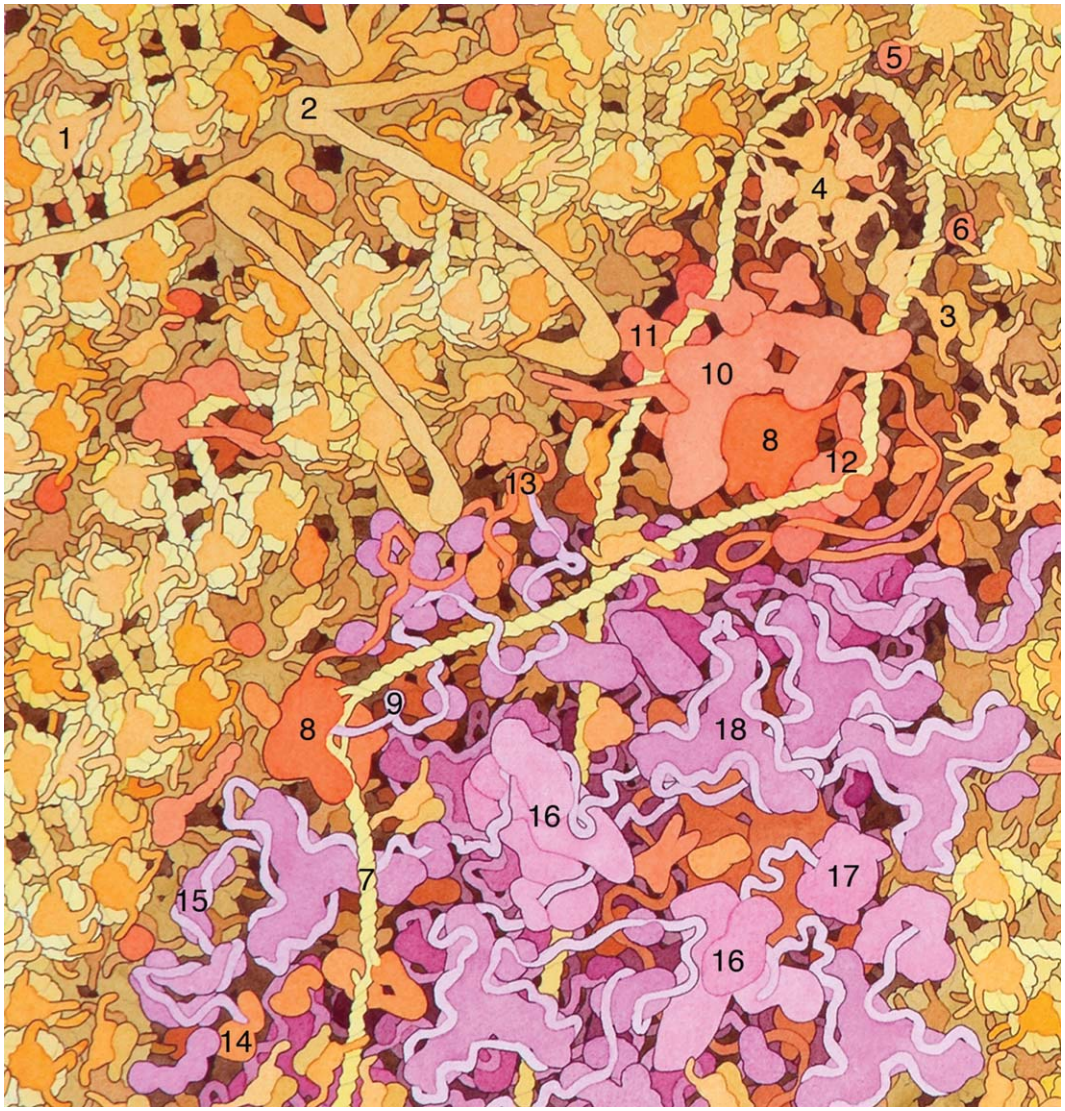

FIG. 1. **Transcription and RNA processing in the nucleus.** (1) nucleosome; (2) SMC; (3) CIA and histone; (4). nucleoplasmin and histones; (5) histone acetyltransferase; (6) histone deacetylase;. (7) DNA; (8) RNA polymerase; (9) messenger RNA; (10) Mediator; (11) enhanceosome; (12) transcription factors; (13) capping enzyme; (14). poly-A polymerase; (15) poly-A-binding protein; (16) spliceosome; (17) exosome; (18) hnRNP-C.

and another vesicle leaving at the right (Fig. 6). The final section shows a vesicle being transported along a microtubule (Fig. 7), and second vesicle fusing with the cell surface at the far right (Fig. 8).

Concentrations

The concentration of macromolecules was by far the most difficult parameter to define for this illustration. A wide range of values are reported, for instance: 200–300 mg/mL for "cytoplasmic protein" [3], 17–26% protein by weight for "actively growing cells" [4], and 15–25% for the "average protein content of animal cells" [5]. I chose a value at the higher end of this scale, roughly 25% protein.

Nucleus

The interior of the nucleus includes DNA in chromatin as well as DNA that is being transcribed. The chromatin is shown at upper left in Fig. 1 and adjacent to the nuclear membrane in Fig. 2. The nucleosomes are based on the crystal structure (1aoi), with the unstructured tails of the histones extended to their actual length. An alternating solenoidal model is used for the chromatin fiber [6]. I have also included a structural maintenance of chromosomes (SMC) protein [7], drawn as a large star-shaped complex as observed in bacterial cells [8]. At the nuclear membrane, several proteins interact with the nucleosomes, as described below.

Nucleosomes and histones are dynamic structures, and there is a substantial infrastructure for coordinating their action. I have included several histone chaperones [9], including the protein CIA (CCG1-interacting factor A) interacting with free histone dimers and the protein nucleoplasmin associating with five histone octamers. In addition, a variety of histone acetyltransferases and deacetylases are shown modifying the tails of histones [10].

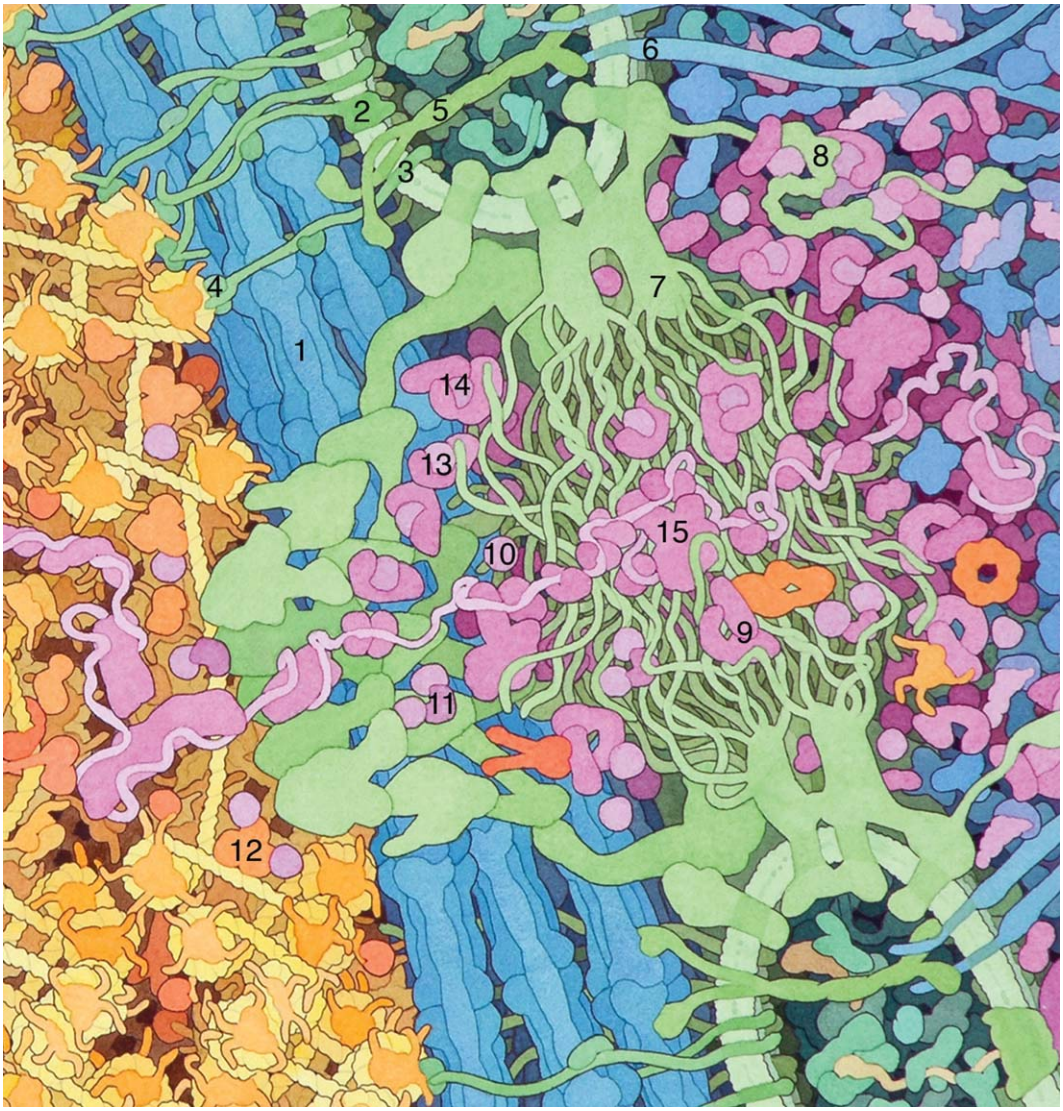

FIG. 2. **Transport through the nuclear pore.** (1) lamin; (2) LBR; (3) emerin; (4) BAF; (5) SUN; (6) nesprin; (7) nuclear pore complex; (8) Nup358 and associated proteins; (9) alpha/beta importin; (10) Ran; (11) NTF2; (12) RCC1; (13) Ran and beta importin; (14) alpha importin and CSE; (15) TAP/p15.

Two RNA polymerases are shown, one at initiation and one actively elongating an RNA transcript. The initiation complex includes a large Mediator complex based on an electron micrograph reconstruction [11], a complex of transcription factors based on crystallographic and electron microscope structures [12], and an enhanceosome taken from a structure-based model [13]. RNA polymerase is based on the crystal structure of the yeast enzyme (1i6h), with a long unstructured C-terminal tail based on the amino acid sequence (P24928). The second RNA polymerase is shown during elongation, with the transcribed RNA looping back and being processed by several capping enzymes [14]. The capping enzyme, along with other enzymes involved in modification, is shown bound to the unstructured tail of RNA polymerase [15].

RNA processing is shown at the bottom of the nuclear region in the image. At the 3′ end of the RNA chain, poly-A polymerase (1f5a) is adding the poly-A tail, which then associates with poly-A-binding protein (1cvj). Two spliceosome complexes are shown, one before splicing and one after splicing, based on structures from electron microscopy [16]. The introns are then degraded by exosomes (2nn6). The RNA is shown associating with hnRNP-C (heterogeneous nuclear ribonucleoprotein C), with the three-armed structure taken from electron micrograph structures [17]. These are shown dissociating as an RNA strand is transported through the nuclear pore.

Nuclear Membrane

The nuclear membrane, shown in Fig. 2, is composed of two lipid bilayers [18]. On the nuclear side, the membrane associates with the nuclear lamina, on the cytoplasmic side, it is continuous with the endoplasmic reticulum. The entire membrane is pierced by nuclear pores, which mediate transport into and out of the nucleus.

The nuclear lamina is composed of layers of lamin, a protein similar to cytoplasmic intermediate filaments. I have based these on electron micrograph structures of isolated intermediate filaments (described in more detail

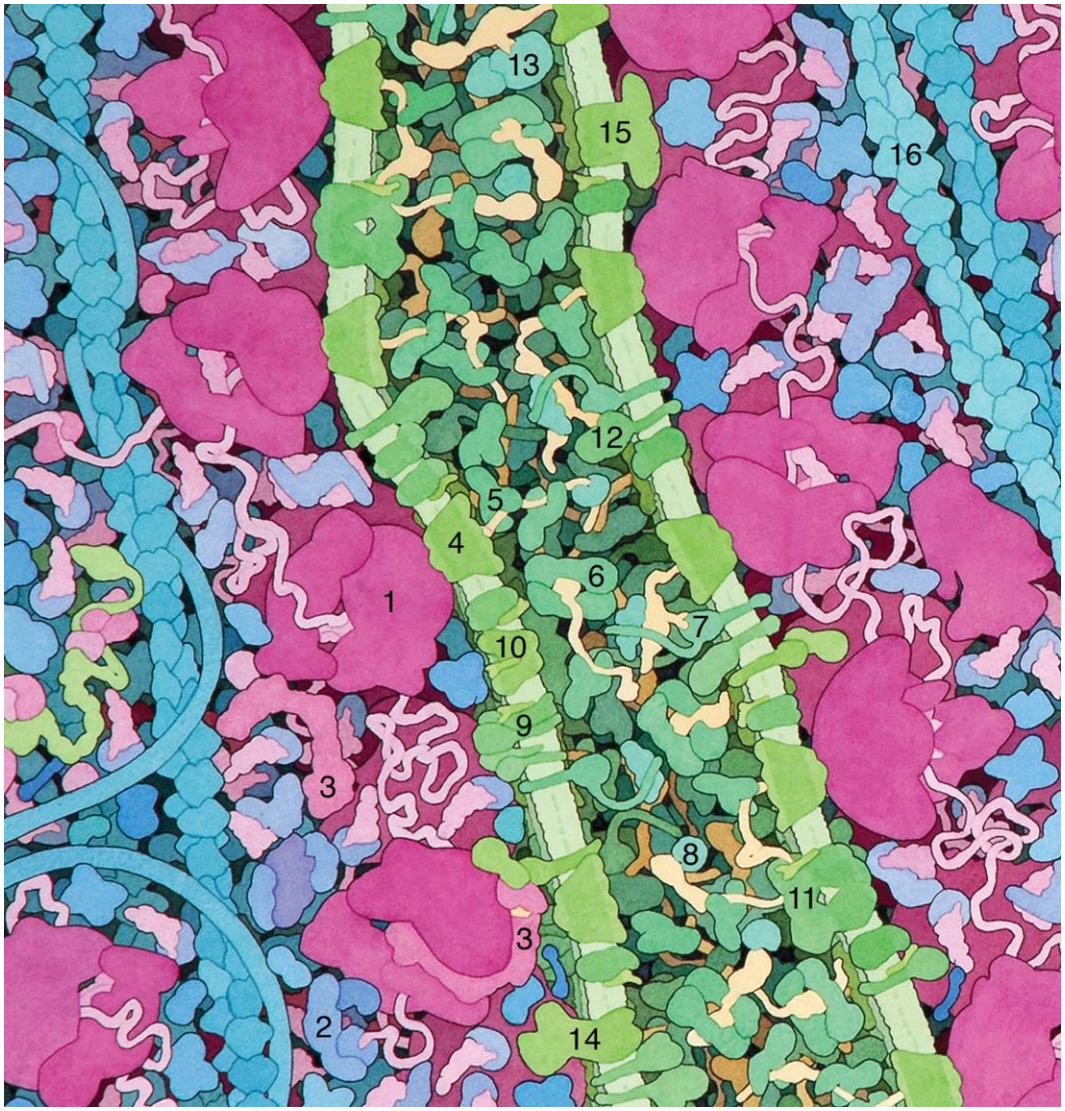

FIG. 3. **Endoplasmic reticulum.** (1) ribosome; (2) initiation factors; (3) signal recognition particle; (4) Sec61/SecY channel; (5) BiP; (6) GRP94; (7) calnexin and Erp57; (8) cyclophilin; (9) glycotransferases; (10) flippase RFT1; (11) oligosaccharide transferase; (12) GlsI; (13) GlsII; (14) calcium pump; (15) IP3R; (16) actin.

below) and electron micrographs of the lamina [19]. The lamina is connected to the membrane through a variety of membrane-bound proteins, including lamin-B receptor (LBR) and emerin. I based these structures on the amino acid sequences (Q14739 and P50402) and schematic diagrams [20]. They are drawn as unstructured proteins, with small proteins such as BAF (barrier-to-autointegration factor, 2odg) associating with the lamin and with nucleosomes.

A SUN protein (Sad1 and UNC84 domain containing protein) is shown bridging the two membranes and interacting with nesprin outside [21]. Nesprin is a long structural protein that interacts with cytoskeletal proteins [22]. I have included the chaperones and other proteins of the endoplasmic reticulum between the two membranes—these are described in more detail below.

The nuclear pore was the most exciting subject that I researched and rendered for this image. Current models of the pore include a large collection of unstructured nucleoporin proteins extending into the lumen of the pore, mediating the flow of proteins in and out [23–25]. The overall shape of the pore is based on electron micrograph reconstructions [26]. The Nup358 nucleoporin extending on the cytoplasmic side, and its interaction with transport proteins ras-related nuclear protein (Ran), Ran GTPase-activating protein (RanGAP), small ubiquitin-related modifier (SUMO), and ubiquitin-conjugating enzyme (UBE2I), is based on the annotation in UniProtKB entry P49792.

The entire transport cycle for nuclear proteins is shown [27]. This includes alpha and beta importin [28] transporting a cargo of a topoisomerase, a DNA clamp, and a repressor. Also, two copies of the Ran protein are being transported inwards by NTF2 (nuclear transport factor). Once inside, the GDP in Ran is exchanged for GTP by RCC1 (regulator of chromosome condensation, 1a12), which is shown bound to DNA [29]. Ran then associates with beta importin, and with a complex of alpha importin and CSE (importin alpha re-exporter, or chromosome segregation protein), carrying them back out through the nuclear pore. The export of RNA is also shown, with the

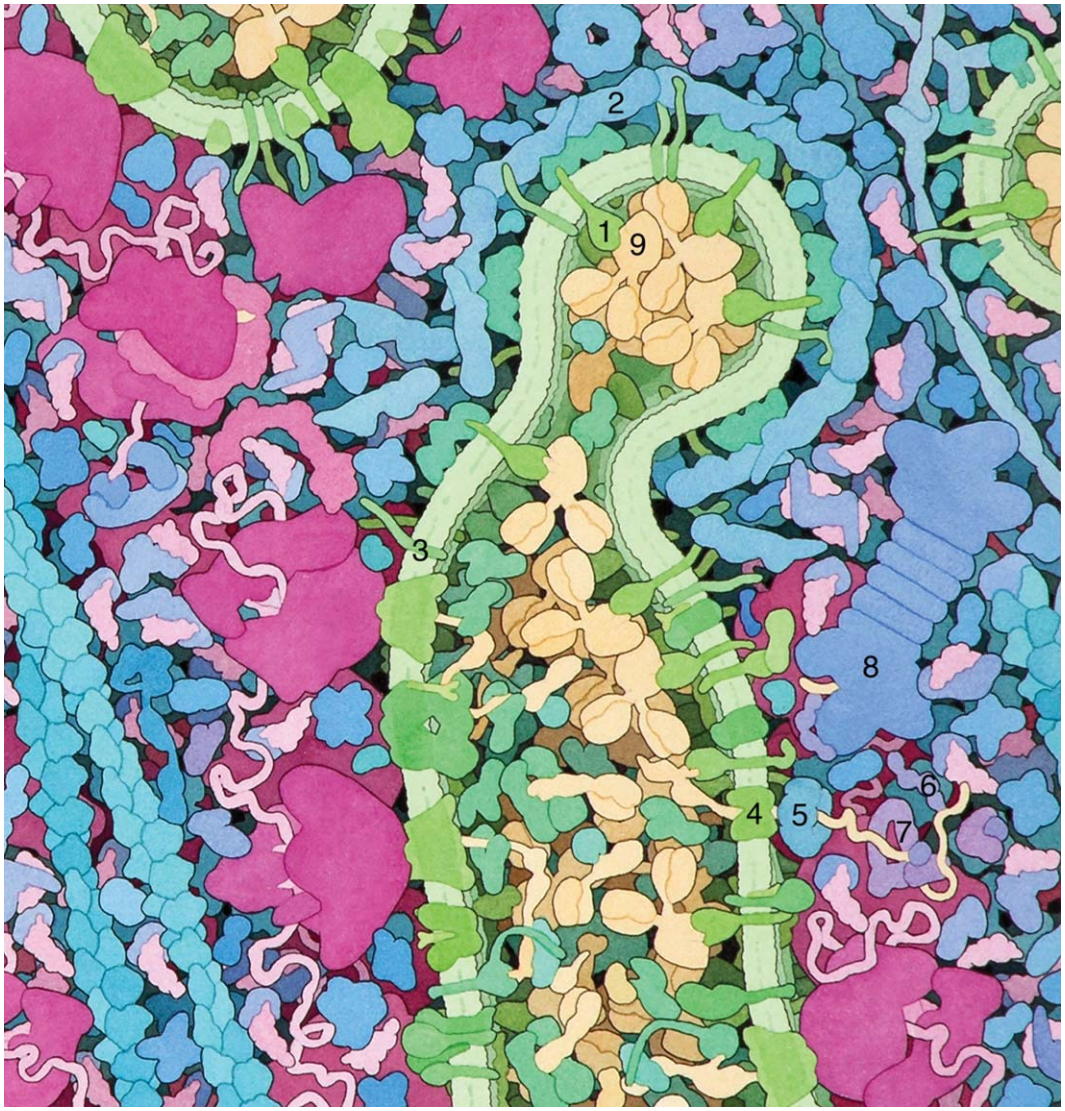

FIG. 4. **Transport from the endoplasmic reticulum.** (1) cargo receptor protein; (2) COPII; (3) SNAP; (4) EDEM; (5) AAA+ protein; (6) ubiquitin; (7) ubiquitin-conjugating proteins; (8) proteasome; (9) antibody.

complex of TAP (nuclear RNA export factor, or Tip-associated protein) and p15 proteins guiding the RNA outwards [27].

Endoplasmic Reticulum (ER)

Once the RNA leaves the nucleus, it is picked up by ribosomes and used to direct the synthesis of proteins, as shown in Fig. 3. At lower left, a ribosome has started synthesis, initiated by the complex of initiation factors [30]. A signal recognition particle (1ry1) has bound to the complex, recognizing the short signal sequence that is translated first. Interaction of the signal recognition particle with the ribosome was taken from a review [31], and eukaryotic ribosome structures were taken from electron micrograph reconstructions [32]. Binding of the signal recognition particle to its receptor delivers the ribosome to Sec61/SecY, the channel through the ER membrane, and the protein BiP (ER luminal binding protein) acts as a ratchet binding to the nascent protein inside the ER and ensuring that it stays inside [33, 34].

A variety of chaperonin proteins inside the ER assist with folding, including GRP 94 (glucose-regulated protein 94, modeled after HSP 90, 2cg9), calnexin (1jhn) [35] and protein disulfide isomerase ERp57 (2h8l), and cyclophilin (2cpl). Studies have shown that immunoglobulins are largely folded in the ER, not proceeding to the Golgi until they are in their proper oligomeric state [36, 37].

The ER also glycosylates proteins [38]. Ig-G molecules contain one N-linked site for glycosylation in the constant domain, and this glycosylation is important for structural stability, for interaction of antibodies with other serum proteins, and for transport and secretion of antibodies from the plasma cell [39]. The oligosaccharides are built on a lipid anchor by a collection of glycotransferases [40], shown here based on amino acid sequences of the yeast enzymes, taken from UniProtKB. Strangely, this process starts with the growing oligosaccharide chain facing outwards, and then the flippase RFT1 (based on the primary sequence from the yeast protein, UniProtKB P38206, which shows 13 transmembrane helices) flips the lipid toward the inside. Once the oligosaccharide is

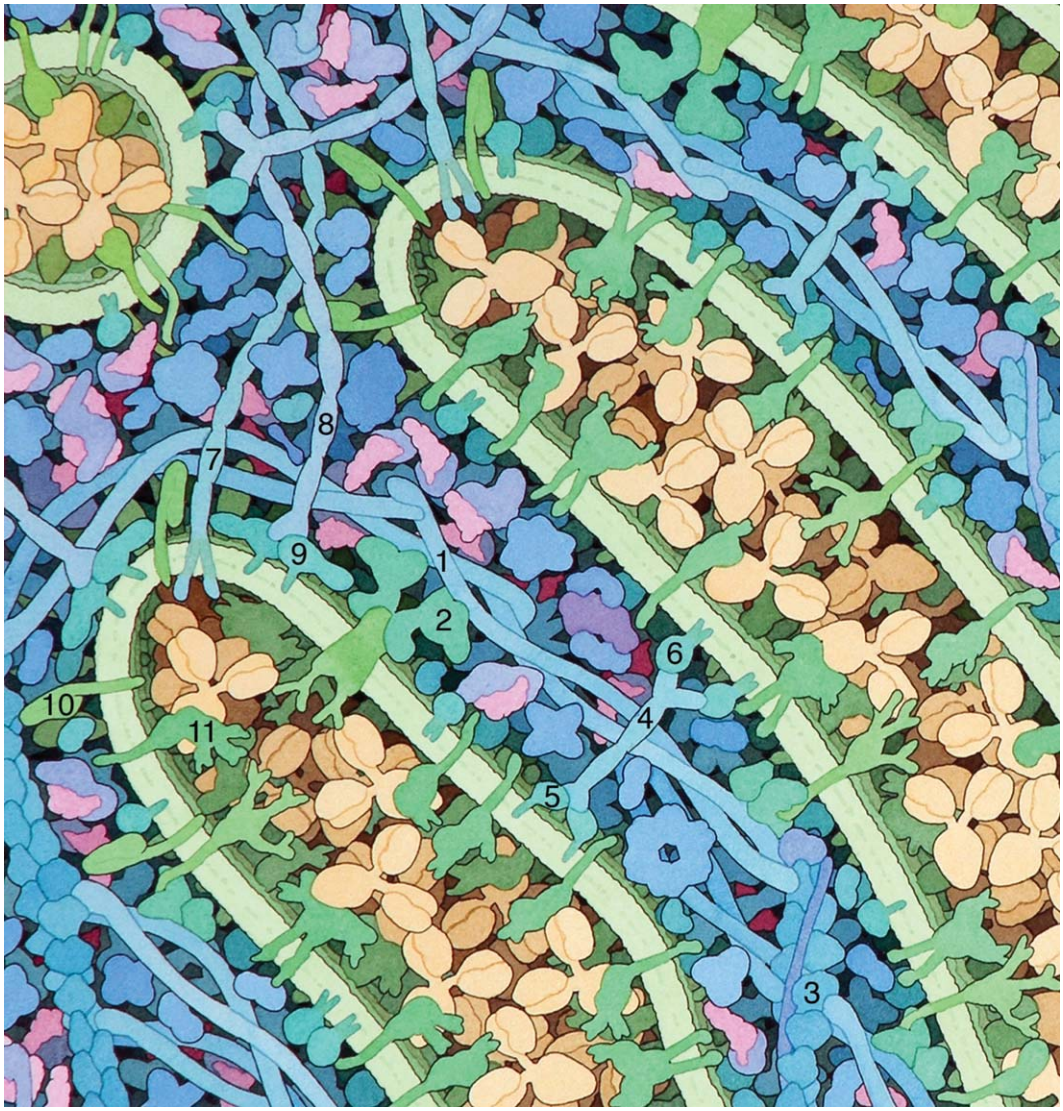

FIG. 5. **Protein sorting in the golgi.** (1) spectrin; (2) ankyrin; (3) actin; (4) golgin45; (5) GRASP55; (6) RAB2; (7) gigantin; (8) GM130; (9) GRASP65; (10) SNARE; (11) glycosyltransferase.

built, it is transferred from the lipid to the protein by oligosaccharide transferase, a large protein complex based on electron micrograph reconstructions [41]. Finally, several glucosidases, such as GlsI and GlsII [42] trim the oligosaccharides.

The ER is the major storage space for calcium ions in most cells, which is used for signaling [43]. I have included two proteins in ER membrane that are important in this process, a calcium pump (1su4), which transports calcium into the ER, and IP_3R (inositol 1,4,5-triphosphate receptor/calcium channel) [44], which releases calcium for signaling.

I found very little information on the infrastructure that is used to maintain the overall ultrastructure of the ER. There is evidence that microtubules are involved in the generation of the structure of the ER in human cells [45, 46], although actin plays this role in plant and yeast cells. However, there is also evidence that microtubules are not needed for maintaining the structure of the ER [46]. I chose to gloss over this point by simply including a few generic actin filaments in the image, without showing any specific interaction between the cytoskeleton and the ER membranes.

Figure 4 shows a vesicle being removed from the ER. Cargo receptor proteins, modeled here after ERGIC-53 (ER-Golgi intermediate compartment protein, 1r1z) [47], have captured antibodies and are interacting with COPII proteins (vesicle coat proteins) that are forming the vesicle, based on atomic structures (1m2v, 2pm7) and electron micrograph reconstructions [48]. Several SNAP proteins (synaptosomal-associated protein) are also included, which will be important for the fusion of the vesicle at its next stop, the Golgi. Finally, at lower right, I have included EDEM (ER degradation-enhancing alpha-mannosidase-like protein), a protein that recognizes faulty proteins from the ER [38]. I have shown a hypothetical transport protein powered by an AAA+ protein ejecting this protein from the ER, where it is ubiquinated and ultimately destroyed by a proteasome. Ubiquitin and ubiquitin-conjugating enzymes were based on crystal structures (1r4n, 1fxt, 1ldk, 1fqv), and the proteasome is based on an electron micrograph reconstruction [49].

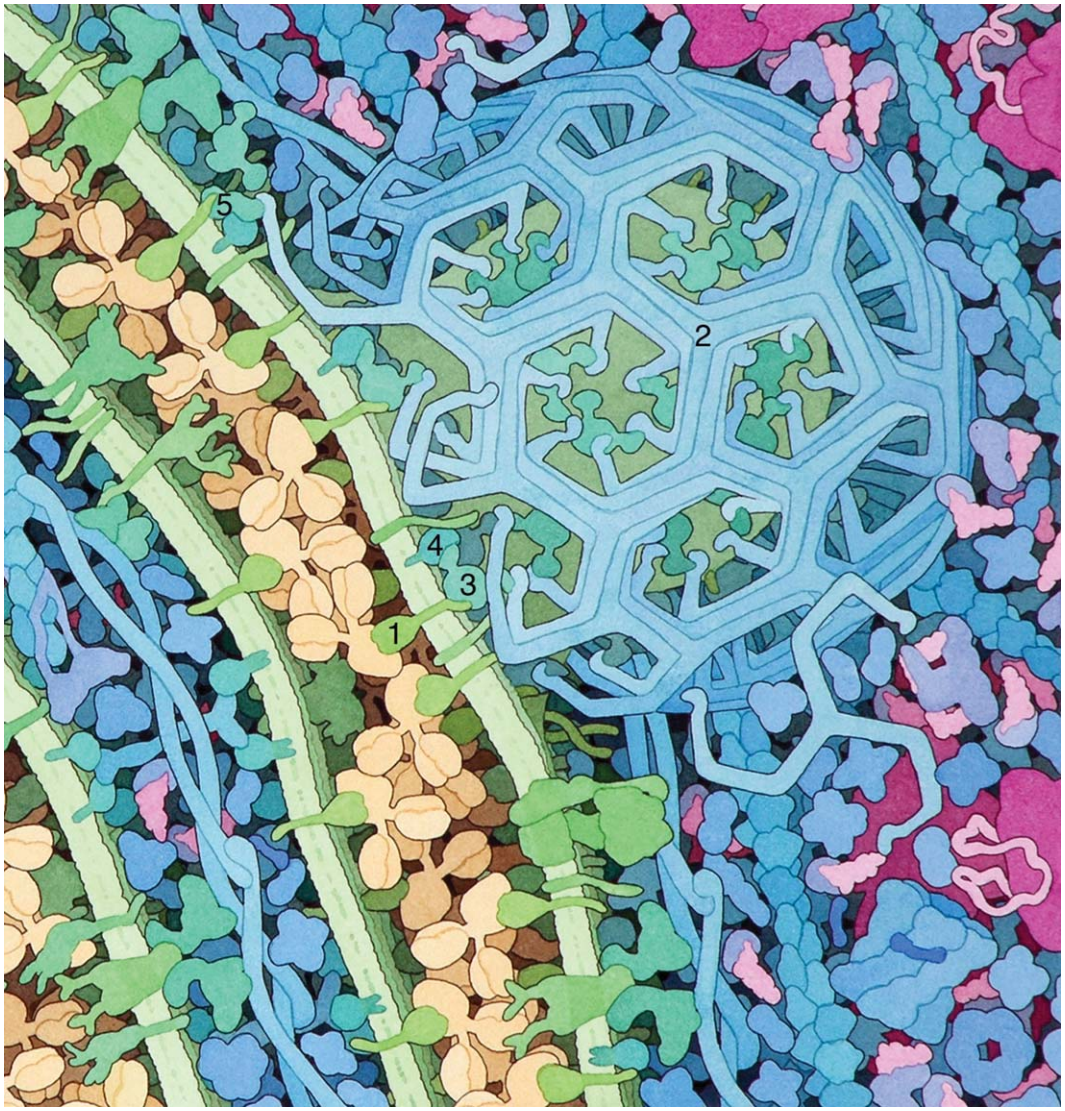

FIG. 6. **Transport from the golgi.** (1) cargo receptor protein; (2) clathrin; (3) AP2; (4) ARF; (5) GGA.

Golgi

The Golgi, shown in Figs 5 and 6, is the site of fine-tuning and sorting of proteins. I have included three layers of the Golgi, ranging from cis to trans as you move from left to right through the panorama. I have included many infrastructure proteins, based on biochemical studies and schematic diagrams. These include spectrin, bound to the Golgi membrane through ankyrin and linked through short filaments of actin [50]. The spectrin and ankyrin structures are based on a combination of primary sequence, electron microscopy and crystal structures of domains [51]. I have included a speculative complex of golgin45 protein linking between the Golgi stack, associating with GRASP55 (Golgi reassembly-stacking protein) and RAB2 (Ras-related protein) in the membrane surface [52]. Huge proteins like gigantin and GM130 (cis-Golgi matrix protein, bound to GRASP65) extend from the Golgi, acting as tethers to trap vesicles [53–56], bringing them close enough for membrane fusion by SNARE proteins [57]. Many of these proteins are characterized by long helical bundles, forming a flexible ropelike structure.

Inside the Golgi, a variety of glycosyltransferases modify the oligosaccharides on the antibodies [58]. I have drawn them as bound to the Golgi membrane by a transmembrane segment [59]. In the trans compartment, cargo receptor proteins capture antibodies and prepare them for transport to the surface. I have shown a clathrin-based mechanism for creation of vesicles, based on schematic diagrams from a review article [60], although other mechanisms may be important [61]. The clathrin coat is composed of three-armed triskelions based on the crystal structure (1xi4). The adaptor protein AP2 (1gq5, 1ky7, 2g30) links the clathrin coat to the cytoplasmic portion of the receptor, with the help of the regulatory protein ARF (ADP-ribosylation factor, 1rrf). GGA (Golgi-localized gamma-ear-containing ARF-binding protein) is also shown in the process of recruiting the receptor, AP2 (adapter protein) and ARF to the clathrin coat. The clathrin coat then disassembles after formation of

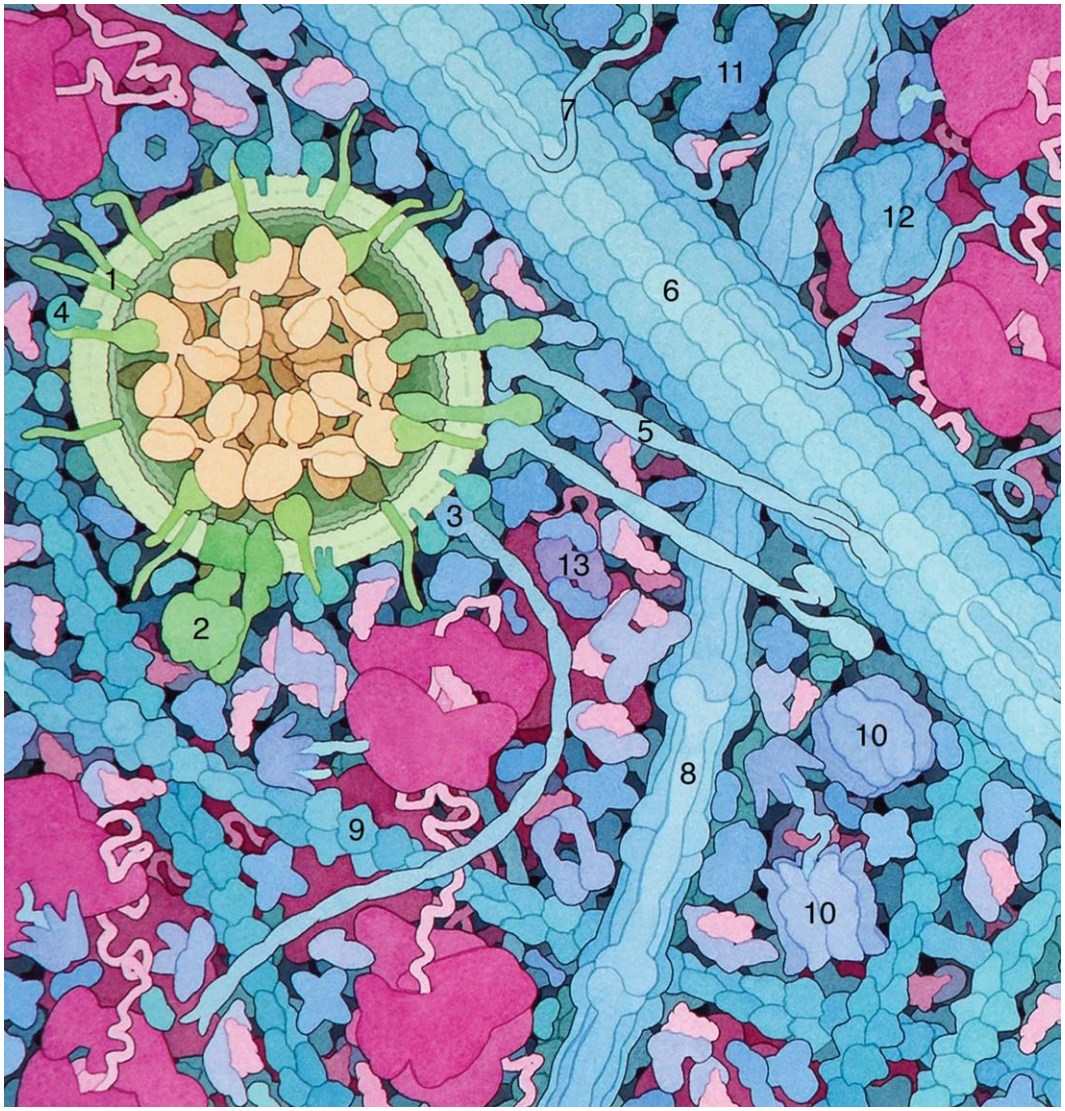

FIG. 7. **Transport of a vesicle through the cytoplasm.** (1) SNARE; (2) vacuolar ATPase; (3) golgin; (4) Rab; (5) kinesin; (6) microtubule; (7) MAP; (8) intermediate filament; (9) actin; (10) TRiC/CCT chaperonin; (11) fatty acid synthase; (12) calcium/calmodulin-dependent protein kinase II; (13) caspase 7 and XIAP.

the vesicle, but there was not room in the panorama to show this process.

Cytoplasm and Cell Surface

Figure 7 shows the journey of a vesicle to the cell surface. The vesicle includes SNARE proteins [62], a vacuolar ATPase (based on ATP synthase, 1c17 and 1e79), and several long golgin tether proteins connected to the vesicle through ARL (ADP-ribosylation factor-like protein) [54]. Small regulatory Rab proteins are bound to the vesicle surface with lipid anchors (3rab). Two kinesin proteins are transporting the vesicle along a microtubule (3kin) [63].

Three types of filaments from the cytoskeleton are shown. The microtubule is based on the crystal structure of a tubulin dimer fit to a cryo-EM map of the intact filament [64], shown here associated with unstructured MAP proteins, also based on electron microscopy [65]. The intermediate filament is based on electron micrographs and structural models of the coiled-coil regions [66], and the actin filaments are based on the crystal structure of the subunit and electron micrographs of the filament [67]. Several Arp2/3 (actin-related protein) junctions are shown in the actin network [68], which connect actin filaments with a characteristic 70 degree angle. The overall arrangement of filaments is based roughly on results from electron microscopy [69].

Many enzymes are shown in the cytoplasm. These include familiar enzymes of protein synthesis, glycolysis and other metabolic tasks, described in more detail in the previous article on the *Escherichia coli* illustration [70]. A few of the most showy examples include the TRiC/CCT chaperonin (TCP1-ring complex or chaperonin containing TCP1) in its open and closed forms (3iyg) [71], fatty acid synthetase (2cf2), and calcium/calmodulin-dependent protein kinase II [72] with calmodulin (3cln). Also included are caspase 7 bound to XIAP (X-linked inhibitor

FIG. 8. **Export of proteins across the cell membrane.** (1) Arp2/3; (2) c-Abl; (3) gelsolin; (4) spectrin; (5) ankyrin; (6) Fas receptor; (7) magnesium transporter; (8) immunoglobulin M; (9) interleukin receptor; (10) Src tyrosine kinase; (11) exocyst; (12) Rab; (13) Rho; (14) SNARE complex; (15) NSF.

of apoptosis, 1i4o), oncogene c-Abl tyrosine kinase (1opk), and gelsolin [73].

The cell membrane, shown in Fig. 8, is braced on the inside by a spectrin network, attached to the membrane through ankyrin. Cell surface proteins include Fas receptor (P25445), a magnesium transporter (based on bacterial MteE, 2yvy) and a membrane-bound form of immunoglobulin M (1igt). The large signaling complex is an interleukin receptor (3bpl) and Src tyrosine kinase (2src). Interleukins and similar signals are important for the survival of plasma cells [74].

A vesicle is shown midway through the process of fusion. The exocyst complex, bound to the membranes through Rab and Rho, acts as a tether to bring the vesicle to the membrane. The structure is based on electron microscopy [75]. The SNARE complexes shown on either side of the vesicle power the fusion of membranes [62]. The NSF (N-ethylmaleimide-sensitive factor) protein is shown separating a SNARE complex after membrane fusion (1d2n).

Aesthetics and Pedagogy

The design of this illustration was highly constrained, both by the need to be consistent with other illustrations in the book [1] and previous articles in BAMBED [2, 70, 76], and by the size of the book. The colors, magnification, and style are all similar to the other illustrations, so readers can compare the structure of the eukaryotic cell with the structure of a simpler bacterial cell. The consistent scheme, for instance, highlights the similar function of the bacterial nucleoid and the eukaryotic nucleus.

Each illustration is presented at 1,000,000× magnification in the book, and slightly reduced here. A simplified shape is shown for each macromolecule, since atoms are too small to be visible at this magnification. Molecules in the nucleus are colored yellow and orange and proteins in the cytoplasm are colored blue. Molecules with RNA, and many of the enzymes that process and transport RNA, are colored magenta. Membranes are colored green to highlight the different compartments in the cell, and mole-

cules inside the ER and Golgi are also colored green. The antibodies being produced are colored tan to set them apart from the cellular macromolecules.

The layout of the illustration is designed to tell the story of protein synthesis and export in a series of page-sized panels, while still connecting into a continuous panoramic cross-section. Each pair of panels presents a particular compartment on the left-hand page, and a mechanism of transport from the compartment on the right-hand page. In this way, readers are drawn through the panorama as they follow the transcription, translation, processing and export of antibodies.

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