GLOBAL EDITION

BROCK BIOLOGY OF MICROORGANISMS

SIXTEENTH EDITION

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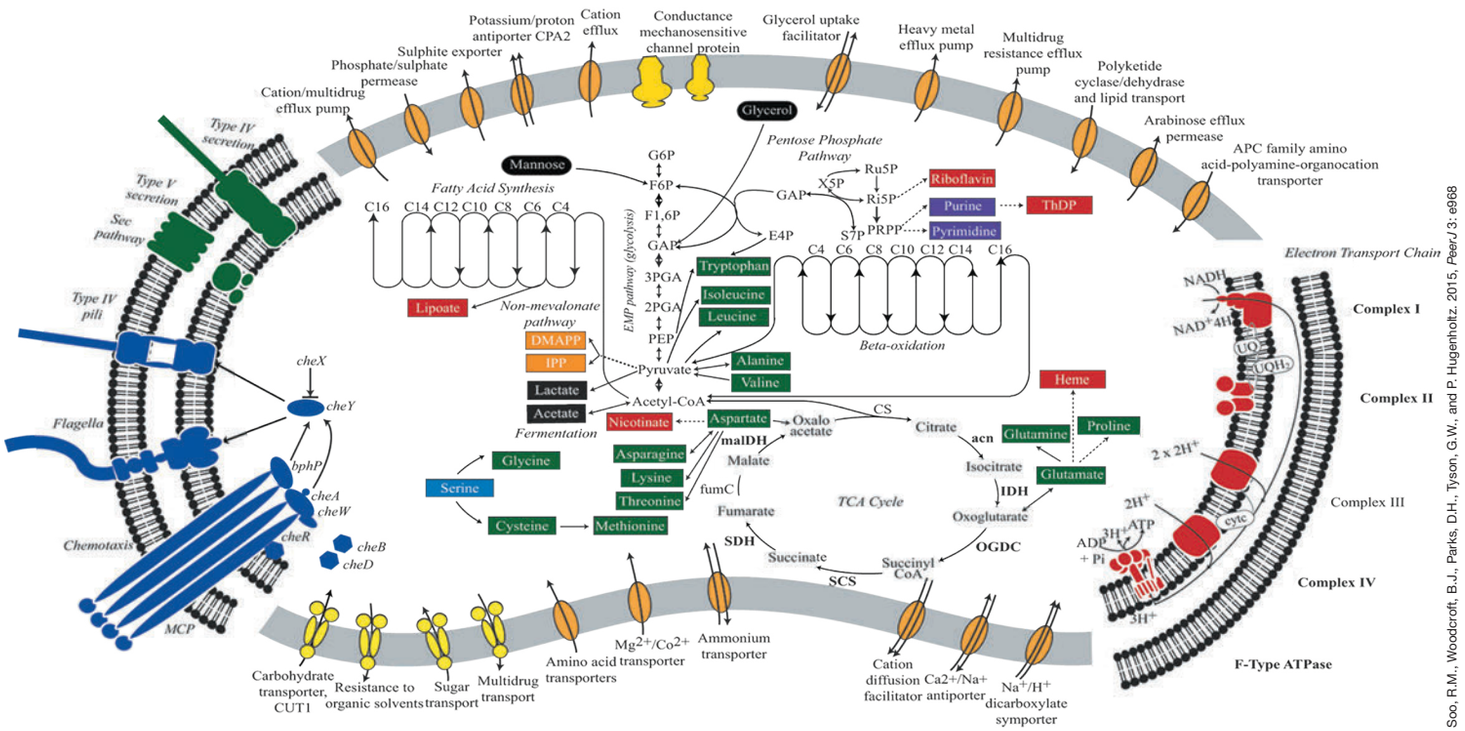
Gene Content of Bacterial Genomes

The complement of genes in a particular organism reveals its capabilities. Conversely, genomes are molded by adaptation to particular lifestyles. Comparative analyses are useful when searching for genes that encode enzymes that probably exist because of the lifestyle of an organism, and in some cases these searches yield big surprises. For example, *Vampirovibrio chlorellavorus* is a predatory bacterium that attacks its host, the green alga *Chlorella*, by surface attachment and ultimate ingestion of its cellular contents (thus the terms "vámpír" from Hungarian, meaning "blood sucker," and "vorus" from Latin, meaning "to devour," in the organism's name). Isolates of *V. chlorellavorus* existed only as 36-year-old freeze-dried samples that had not been successfully revived. However, by using advanced sequencing techniques, the genome of *V. chlorellavorus* was recovered, and surprisingly, genomic analyses indicated that *V. chlorellavorus* falls within the phylum *Cyanobacteria* (▶ Section 15.3) even though it lacks genes for photosynthesis.

Figure 10.9, reprinted from a scientific journal, is included here to give you an idea of why a microbe's genome should be sequenced and the amazing amount of information that can be gleaned from annotation, though the details are beyond the scope of this chapter. The figure summarizes some of the metabolic pathways and transport systems of *V. chlorellavorus* deduced from analysis of its genome. These include an electron transport chain for microaerobic growth (◀ Section 4.16), the ability to ferment (◀ Sections 3.6 and 3.7), chemotaxis abilities (◀ Section 2.11), and the synthesis of 15 of the 20 essential amino acids (◀ Figure 6.27). Comparative genomics also indicated that *V. chlorellavorus* used a conjugative type IV secretion system (◀ Section 6.13) to attack its prey, the first discovery of this strategy in a predatory bacterium.

A functional analysis of genes and their activities in several bacteria is given in **Table 10.4**. Thus far, a distinct pattern of gene distribution in *Bacteria* has emerged. Metabolic genes are typically the most abundant class in bacterial genomes, although genes for protein synthesis overtake metabolic genes on a percentage basis as genome size decreases (Table 10.4 and **Figure 10.10**). Although many genes can be dispensed with, genes that encode the protein-synthesizing apparatus cannot. Thus, the *smaller* the genome, the greater the percentage of genes that encode translational processes. Conversely, the *larger* the genome, the more genes there are for transcriptional regulation and signal transduction (Chapter 7).

Analyses of gene categories have also been done for several *Archaea*. On average, *Archaea* devote a higher percentage of their genomes to energy and coenzyme production than do *Bacteria* (this result is undoubtedly skewed a bit due to the large number of novel coenzymes produced by methanogenic *Archaea*, ▶ Section 14.15 and Figure 14.36). On the other hand, *Archaea* appear to contain fewer genes for carbohydrate metabolism and membrane functions



Soo, R.M., Woodcroft, B.J., Parks, D.H., Tyson, G.W., and P. Hugenholtz. 2015, *PeerJ* 3: e968

Figure 10.9 Functional and metabolic predictions for *Vampirovibrio chlorellavorus* based on genomic annotation. Although the details are beyond our discussion, the figure illustrates the power of genomic sequencing and annotation on piecing together the physiology of an organism. Within the cytoplasmic membrane, the following systems are highlighted: secretion (green), chemotaxis and movement (blue), electron transport (red), ATP-binding cassette transporters (yellow), and permeases/pumps/transporters (orange). Black ovals indicate substrates that enter the glycolysis pathway, while fermentation end products are indicated as black rectangles. Colors of internal compounds correspond to the following: green (amino acids), red (cofactors and vitamins), purple (nucleotides), and orange (non-mevalonate pathway products). Note that genes for synthesis of serine (highlighted in blue) are not present, so presumably it is transported into the cell. Adapted from Soo, R.M., et al. 2015. *Peer J. 3*: e968.

TABLE 10.4 Gene function in some genomes of *Bacteria*

Functional categories	Percentage of genes		
	Escherichia coli (4.64 Mbp)[a]	*Haemophilus influenzae* (1.83 Mbp)[a]	*Mycoplasma genitalium* (0.58 Mbp)[a]
Metabolism	21.0	19.0	14.6
Structure	5.5	4.7	3.6
Transport	10.0	7.0	7.3
Regulation	8.5	6.6	6.0
Translation	4.5	8.0	21.6
Transcription	1.3	1.5	2.6
Replication	2.7	4.9	6.8
Other, known	8.5	5.2	5.8
Unknown	38.1	43.0	32.0

[a]Chromosome size, in megabase pairs. Each organism listed contains only a single circular chromosome.

(such as transport and membrane biosynthesis) than do *Bacteria*. However, this conclusion may also be skewed a bit because the corresponding pathways have been less studied in *Archaea* than in *Bacteria* and many of the relevant archaeal genes remain unidentified.

We now transition to look at the genomes of eukaryotes and their major organelles, structures whose evolutionary roots lie in the *Bacteria*.

Check Your Understanding

- What lifestyle is typical of *Bacteria* and *Archaea* that contain fewer than 500 protein-encoding genes?
- Which is likely to have more genes, a species of *Bacteria* with 8 Mbp of DNA or a eukaryote with 10 Mbp? Explain.
- In prokaryotic cells with the largest genomes, which gene category contains the largest percentage of genes?

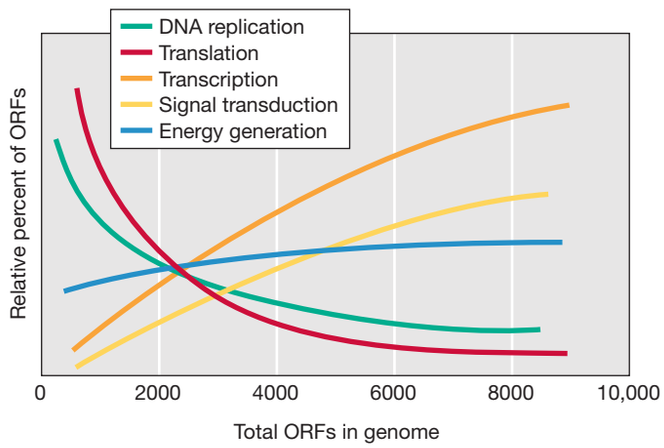


Figure 10.10 Functional category of genes as a percentage of the genome. The percentage of genes encoding products for translation or DNA replication is greater in organisms with small genomes, whereas the percentage of transcriptional regulatory genes is greater in organisms with large genomes.

10.4 Organelle and Eukaryotic Microbial Genomes

Mitochondria and chloroplasts are eukaryotic cell organelles derived from endosymbiotic bacteria (◀ Section 2.14 and ▶ Section 18.1) and thus share many fundamental traits with *Bacteria* to which they are phylogenetically related. The genomes of both organelles encode the machinery necessary for protein synthesis including ribosomes, transfer RNAs, and the other components necessary to drive translation. The genomes of several microbial eukaryotes have also been sequenced (**Table 10.5**), and their size varies widely (Figure 10.2). Certain single-celled protozoans, including the free-living ciliate *Paramecium* (40,000 genes) and the pathogen *Trichomonas* (60,000 genes), have significantly more genes than do humans (Table 10.5). In this section we focus on organellar genomes and the genomes of a few select microbial eukaryotes.

The Chloroplast Genome

Green plant and algae cells contain chloroplasts, the organelles that perform photosynthesis (▶ Section 14.3 and Figure 14.9). Each chloroplast contains several identical copies of the genome. Until recently, it was accepted that all chloroplast genomes were circular DNA molecules. However, with the power of next-generation sequencing, linear and single-stranded plasmid-like chloroplast genomes have also been detected. In fact, most of the chloroplast genomes in corn (maize) are linear in structure. Based on the over 800 chloroplast genomes in the databases, the typical chloroplast genome is about 100–200 kbp and contains two inverted repeats of 6–76 kbp that each encode copies of the three rRNA genes (**Figure 10.11**). As might be expected, many

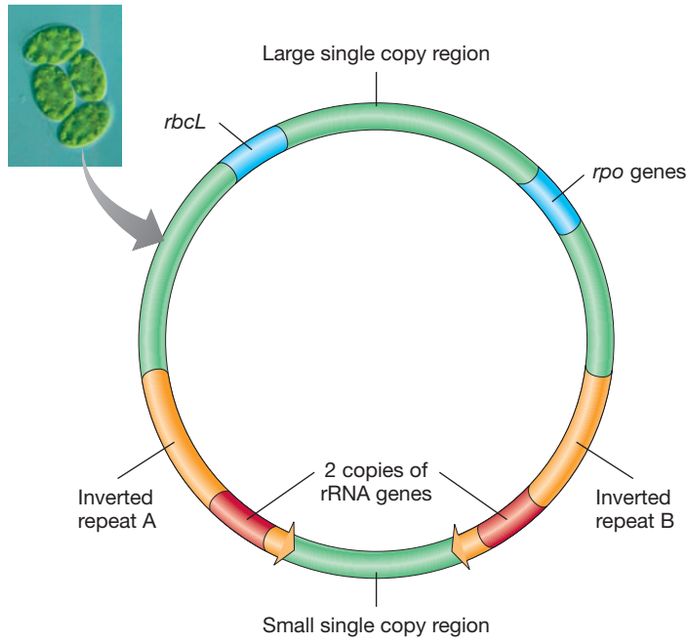


Figure 10.11 Map of a typical chloroplast genome. The inverted repeats each contain a copy of the three genes for rRNA (5S, 16S, and 23S). The large subunit of RuBisCO is encoded by *rbcL* and the chloroplast RNA polymerase by *rpo* genes. Inset: Photo of four cells of the green alga *Makinoella* with chloroplasts clearly visible.

TABLE 10.5 Some eukaryotic nuclear genomes[a]

Organism	Comments	Lifestyle[b]	Genome size (Mbp)	Haploid chromosomes	ORFs
Nucleomorph of *Bigelowiella natans*	Degenerate endosymbiotic nucleus	E	0.37	3	331
Encephalitozoon intestinalis	Smallest known eukaryotic genome, human pathogen	P	2.3	11	1,800
Cryptosporidium parvum	Parasitic protozoan	P	9.1	8	3,800
Plasmodium falciparum	Malignant malaria	P	23	14	5,300
Saccharomyces cerevisiae	Yeast, a model eukaryote	FL	12.1	16	5,400
Ostreococcus tauri	Marine green alga, smallest free-living eukaryote	FL	12.6	20	8,200
Aspergillus nidulans	Filamentous fungus	FL	30	8	9,500
Giardia intestinalis (also called *Giardia lamblia)*	Flagellated protozoan, causes acute gastroenteritis	P	12	5	9,700
Drosophila melanogaster	Fruit fly, model organism for genetic studies	FL	180	4	13,600
Caenorhabditis elegans	Roundworm, model for animal development	FL	97	6	19,100
Mus musculus	Mouse, a model mammal	FL	2,500	23	25,000
Homo sapiens	Human	FL	2,850	23	25,000
Arabidopsis thaliana	Model plant for genetics	FL	125	5	26,000
Paramecium tetraurelia	Ciliated protozoan	FL	72	> 50	40,000
Pinus taeda	Loblolly pine tree	FL	20,000	19	50,000
Trichomonas vaginalis	Flagellated protozoan, human pathogen	P	160	6	60,000

[a]All data are for the haploid nuclear genomes of these organisms in megabase pairs. For most large genomes, both size and ORFs listed are best estimates due to large numbers of repetitive sequences and/or introns in the genomes.
[b]E, endosymbiont; P, parasite; FL, free-living.

chloroplast genes encode proteins for photosynthetic reactions and autotrophy. For example, the enzyme RuBisCO, which is composed of a small and large subunit, catalyzes the first step in CO_2 fixation in the Calvin cycle (◀ Section 3.12 and ▶ Section 14.2). The *rbcL* gene encoding the large subunit of RuBisCO is present on the chloroplast genome (Figure 10.11), whereas the gene for the small subunit, *rbcS*, resides in the plant cell nucleus and its protein product must be imported from the cytoplasm into the chloroplast after synthesis.

The chloroplast genome also encodes tRNAs used in translation, several proteins used in transcription and translation, and some other proteins. Not all chloroplast proteins are encoded by the chloroplast genome; some are nuclear encoded. These are likely genes that migrated to the nucleus as the chloroplast evolved from an endosymbiotic cell into a photosynthetic organelle. Introns, the hallmark of genes in eukaryotes, are common in chloroplast genes and are primarily of the self-splicing type (◀ Section 6.6).

Mitochondrial Genomes and Proteomes

Mitochondria are the eukaryotic cell's respiratory organelles and are present in all but a few eukaryotes (◀ Section 2.14 and ▶ Section 18.1). Mitochondrial genomes primarily encode proteins for oxidative phosphorylation and, like chloroplast genomes, also encode proteins, rRNAs, and tRNAs for protein synthesis. However, most mitochondrial genomes encode far fewer proteins than those of chloroplasts. The largest mitochondrial genome known has only 62 protein-encoding genes, but others contain as few as three. The mitochondria of almost all mammals, including humans, encode only 13 proteins in addition to 22 tRNAs and 2 rRNAs. **Figure 10.12*a*** shows a map of the 16,569-bp human mitochondrial genome. While human mitochondrial genomes are circular, diverse arrangements exist in other organisms. For example, some mitochondrial genomes are linear, including those of certain algae, protozoans, and fungi. Finally, the mitochondria of many fungi and flowering plants contain, in addition to the mitochondrial genome, small circular or linear plasmids (◀ Section 6.2).

Mitochondria require many more proteins than their genome encodes (in particular, proteins needed for translation), and thus many mitochondrial proteins are encoded by genes in the nucleus. The yeast mitochondrion contains as many as 800 different proteins in its proteome (all the proteins encoded by a genome; Section 10.9). However, only eight (~1%) of them are encoded by the yeast mitochondrial genome, the remaining proteins being encoded by nuclear genes (Figure 10.12*b*). The nuclear-encoded proteins required for translation and energy generation in mitochondria are more closely related to their counterparts in *Bacteria* than to those in the eukaryotic cytoplasm, consistent with both the evolutionary history of the mitochondrion (▶ Section 13.4) and with a scenario—like that seen in the chloroplast—of genes having migrated from the original endosymbiont to the host cell nucleus.

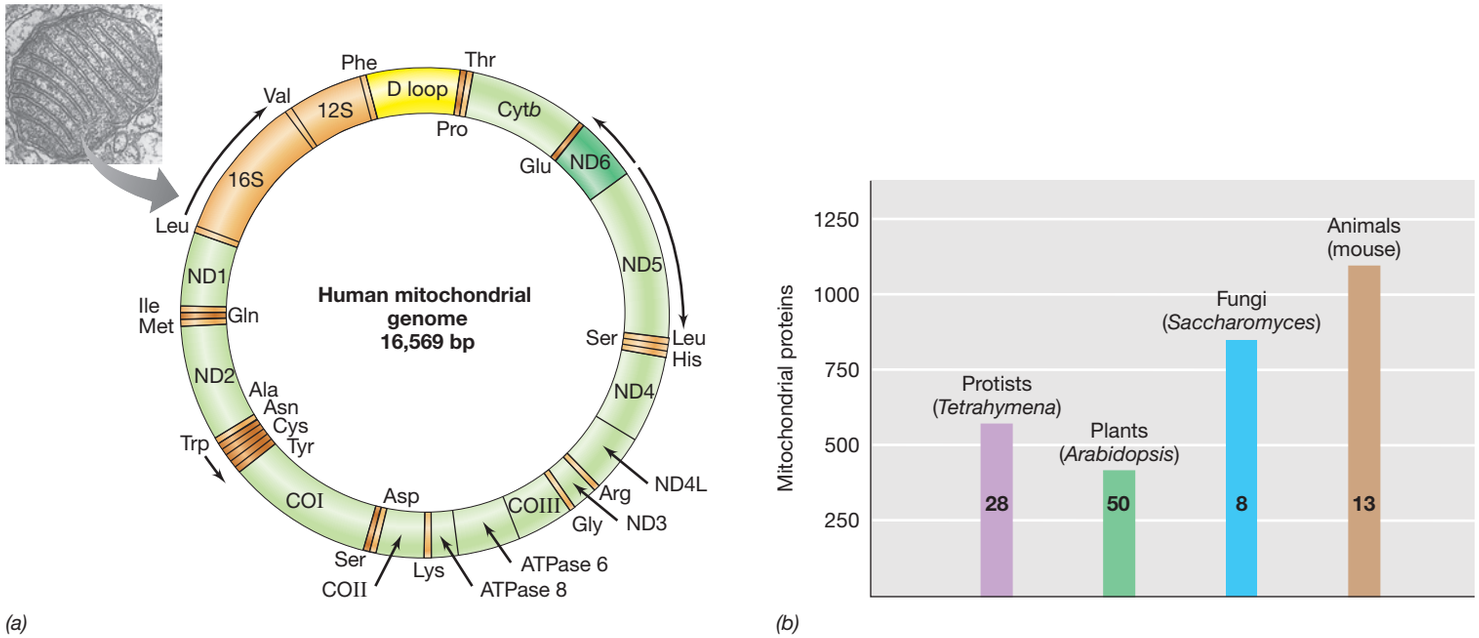


Figure 10.12 **Map of the human mitochondrial genome and the mitochondrial proteome.** *(a)* The genome encodes rRNAs, 22 tRNAs, and several proteins. Arrows show direction of transcription for genes of a given color, and the three-letter amino acid designations for tRNA genes are also shown. The 13 protein-encoding genes are in green. Cyt*b*, cytochrome *b*; ND1–6, components of the NADH dehydrogenase complex; COI–III, subunits of the cytochrome oxidase complex; ATPase 6 and 8, polypeptides of the mitochondrial ATPase complex. The two promoters are in the region called the D loop, which is also involved in DNA replication. Inset: Transmission electron micrograph of a mitochondrion (credit, D.W. Fawcett). *(b)* Mitochondrial proteomes. The numbers in each colored bar are the number of proteins encoded on the mitochondria of some model eukaryotes.

Genomes and Introns in Some Microbial Eukaryotes

Apart from the human pathogenic protozoan *Trichomonas*, which contains almost three times more genes than human cells, parasitic eukaryotic microorganisms typically have relatively small genomes of 10–40 Mbp containing between 4000 and 11,000 genes. For example, *Trypanosoma brucei*, the agent of African sleeping sickness (▶ Section 34.6), has 11 chromosomes, 35 Mbp of DNA, and almost 11,000 genes. The four species of *Plasmodium* that infect humans (causing malaria, ▶ Section 34.5) have genomes ranging from 23 to 27 Mbp arranged in 14 chromosomes containing a total of about 5500 genes.

As in *Bacteria*, the smallest eukaryotic genome belongs to an endosymbiont. Known as a *nucleomorph*, it is the degenerate remains of a eukaryotic endosymbiont of a certain green alga that has acquired the ability to photosynthesize by secondary endosymbiosis (▶ Section 18.1). Nucleomorph genomes range from about 0.37 to 0.85 Mbp. The smallest genome in a *parasitic* eukaryote belongs to *Encephalitozoon intestinalis*, an intracellular pathogen of humans and other animals. *E. intestinalis* even lacks mitochondria, and although its haploid genome contains 11 chromosomes, the genome size is only 2.3 Mbp with approximately 1800 genes (Table 10.5); this is smaller than many bacterial genomes (Table 10.1).

The baker's yeast *Saccharomyces cerevisiae* is widely used as a model eukaryote and its genome contains 16 chromosomes (13.4 Mbp of DNA). Yeast has approximately 6000 ORFs, which is fewer than that of some genomes of *Bacteria* (Tables 10.1 and 10.5). How many of these yeast genes are actually essential? This question has been addressed by systematically inactivating each gene in turn with *knockout mutations* (mutations that completely inactivate genes, ▶ Section 12.4). Knockout mutations cannot normally be obtained in essential genes in a haploid organism. However, yeast can be grown in both diploid and haploid states (▶ Section 18.10). By generating knockout mutations in diploid cells and then investigating whether they can also exist in haploid cells, it is possible to determine whether a particular gene is essential for cell viability. Using knockout mutations, it has been shown that around 900 yeast ORFs (17% of its genome) are absolutely essential. Note that this number of essential genes is much greater than the approximately 300 genes estimated to be the minimal number required in a bacterial cell (Section 10.3).

Being a eukaryote, the yeast genome contains introns (◀ Section 6.6). However, the total number of introns in the protein-encoding genes of yeast is a mere 225. Most yeast genes that contain introns have only a single small intron near the 5′ end of the gene. This situation differs greatly from that seen in more complex eukaryotes (**Figure 10.13**). For example, in the worm *Caenorhabditis elegans*, the average gene has five introns, and in the fruit fly *Drosophila*, the average gene has four. Introns are also common in the genes of plants, averaging around four per gene. The model flowering plant *Arabidopsis* averages five introns per gene, and over 75% of *Arabidopsis* genes have introns. In humans almost all protein-encoding genes have introns, and it is common for a single gene to have 10 or more. Moreover, introns in human genes are typically much longer than exons, the DNA that actually encodes proteins. Indeed, exons make up only about 1% of the human genome, whereas introns account for 24%. The remaining

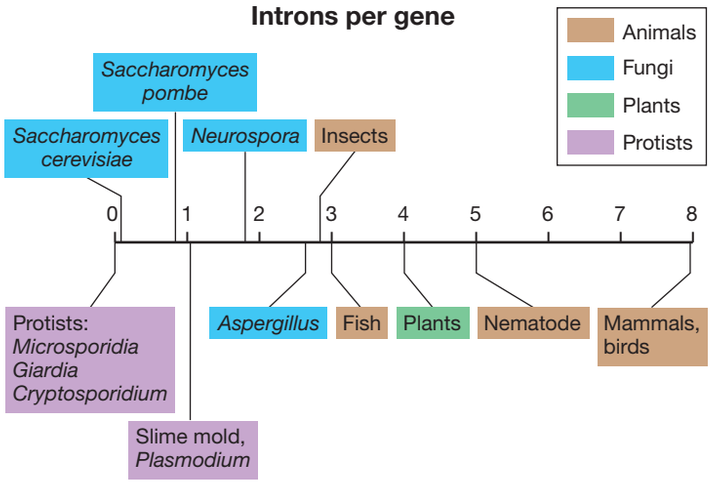


Figure 10.13 Intron frequency in the genes of different eukaryotes. The average number of introns per gene is shown for a range of eukaryotic organisms; microbial species tend to have fewer introns per gene, whereas plants and animals have the most.

DNA is made up of repetitive sequences, noncoding RNA, and regulatory regions.

We will discuss how comparative genomics can be used to determine evolutionary relationships and how genomes evolve in Chapter 13. For now, we turn our focus to how various omic approaches can be used to determine the function of each gene product. The dynamic nature of microbes and how they interact with their environment can be characterized through the use of functional omics.

Check Your Understanding

- What is unusual about the genes that encode mitochondrial proteins?
- What do chloroplast genomes typically encode?
- What is unusual about the genome of the eukaryote *Encephalitozoon*?

II • Functional Omics

Knowing an organism's genome sequence may not reveal what all the genes encode and when and why they are transcribed and translated. These topics require functional analyses of molecular events downstream of the genome itself.

Despite the major effort required to generate an annotated genome sequence, the net result is simply a "list of parts." To understand how a cell *functions*, we need to know more than which genes are present. We must also understand (1) gene expression, (2) the function of gene products, (3) the activity of the proteins made, and (4) the metabolites produced during growth.

In analogy to the term "genome," the entire complement of RNA, proteins, or metabolites produced under a given set of conditions is called the *transcriptome*, *proteome*, and *metabolome*, respectively. The suffix "omic" denotes their corresponding areas of study. Table 10.6 summarizes some of the "omics" terminology used in microbiology today.

10.5 Functional Genomics

As previously discussed (Section 10.2), genome sequencing, assembly, and annotation yields an abundance of information. However, the roles of many open reading frames (ORFs) remain unknown after annotation and are thus classified as encoding "hypothetical proteins." The percentage of hypotheticals in a given microbial genome averages 30% of the total annotated ORFs. This value even holds true for the minimal *Mycoplasma* genome created by synthetic biologists, which possesses a trim 473 genes (▶ Section 12.12). In fact, the function of less than 1% of the approximately 120 million protein sequences that exist in public databases is known! Thus, obtaining a genome sequence is only the *beginning* of teasing apart how a microbe functions and survives in its environment.

In this unit of the chapter we discuss how to gain insight into gene function through the analysis of RNA, protein, and metabolites, and we begin with how comparative genomics, genetic tools, and next-generation sequencing can be used to determine gene function.

UNIT 3

Functional Genomics and Heterologous Expression

How do microbes get selected for genome sequencing? This selection is usually a result of an interesting phenotypic trait displayed by the microbe. Such was the case with the multi-antibiotic-resistant,

TABLE 10.6 Some omics terminology

DNA	**Genome** the total complement of genetic information of a cell or a virus **Metagenome** the total genetic complement of all the cells present in a particular environment **Epigenome** the total possible epigenetic changes **Methylome** the total methylated sites on the DNA (whether epigenetic or not) **Mobilome** the total set of mobile genetic elements in a cell **Resistome** the total set of antibiotic resistance genes in a cell
RNA	**Transcriptome** the total RNA produced in an organism under a specific set of conditions **Exome** the part of the RNA pool encoded by exons that remains after introns are removed
Protein	**Proteome** the total set of proteins encoded by a genome; sometimes also used in place of *translatome* **Translatome** the total set of proteins present under specified conditions **Interactome** the total set of interactions between proteins (or other macromolecules) **Secretome** the total set of proteins secreted by a cell **Kinome** the total set of protein kinases encoded by a genome
Metabolites	**Metabolome** the total complement of small molecules and metabolic intermediates **Glycome** the total complement of sugars and other carbohydrates
Organisms	**Microbiome** the total complement of microorganisms in an environment (including those associated with a higher organism) **Virome** the total complement of viruses in an environment **Mycobiome** the total complement of fungi in a natural environment

gram-positive bacterium *Paenibacillus* species strain LC231 (**Figure 10.14**). While *Bacteria* displaying resistance to multiple drugs is not unique (▶ Section 28.7), strain LC231 was cultured from an underground cave ecosystem that has been isolated from the surface for over 4 million years (Figure 10.14*a*). With no exposure to current pathogens (where it could have picked up genes by horizontal transfer, Chapter 9) or to antibiotics used in clinical or veterinary medicine, this bacterium displayed resistance—surprisingly—to at least 14 different classes of antibiotics! How did such resistance come about?

In an effort to understand the gene products or *resistome* (Table 10.6) responsible for the multidrug resistance of strain LC231, bioinformatics revealed ten ORFs known to encode resistance to seven different types of antibiotics (Figure 10.14*b*). This comparative genome analysis was facilitated by an online program called *Resistance Gene Identifier*, which allows for genome sequences to be searched against a database of known antibiotic resistance genes from other bacteria. However, the mechanism by which LC231 was resistant to seven *other* antibiotic types was not evident from comparative genomics. To attack this question, microbiologists used a common functional genomics approach that employs the model bacterium *Escherichia coli*. This approach is based on *heterologous expression*, which is the process of expressing a gene from one organism in a different, host organism (Chapter 12). To heterologously express LC231 genes in *E. coli*, the LC231 genome was fragmented and inserted into plasmids. The resulting plasmids were transformed into *E. coli* to create a clone library of transformants, with each transformant containing a plasmid with a different piece of the LC231 genome (Figure 10.14*a* and Chapter 12). *E. coli* colonies that resulted from this clone library were then screened and selected for resistance to the antibiotics of interest. To determine the identity of the LC231 genome fragment responsible for conferring antibiotic resistance to

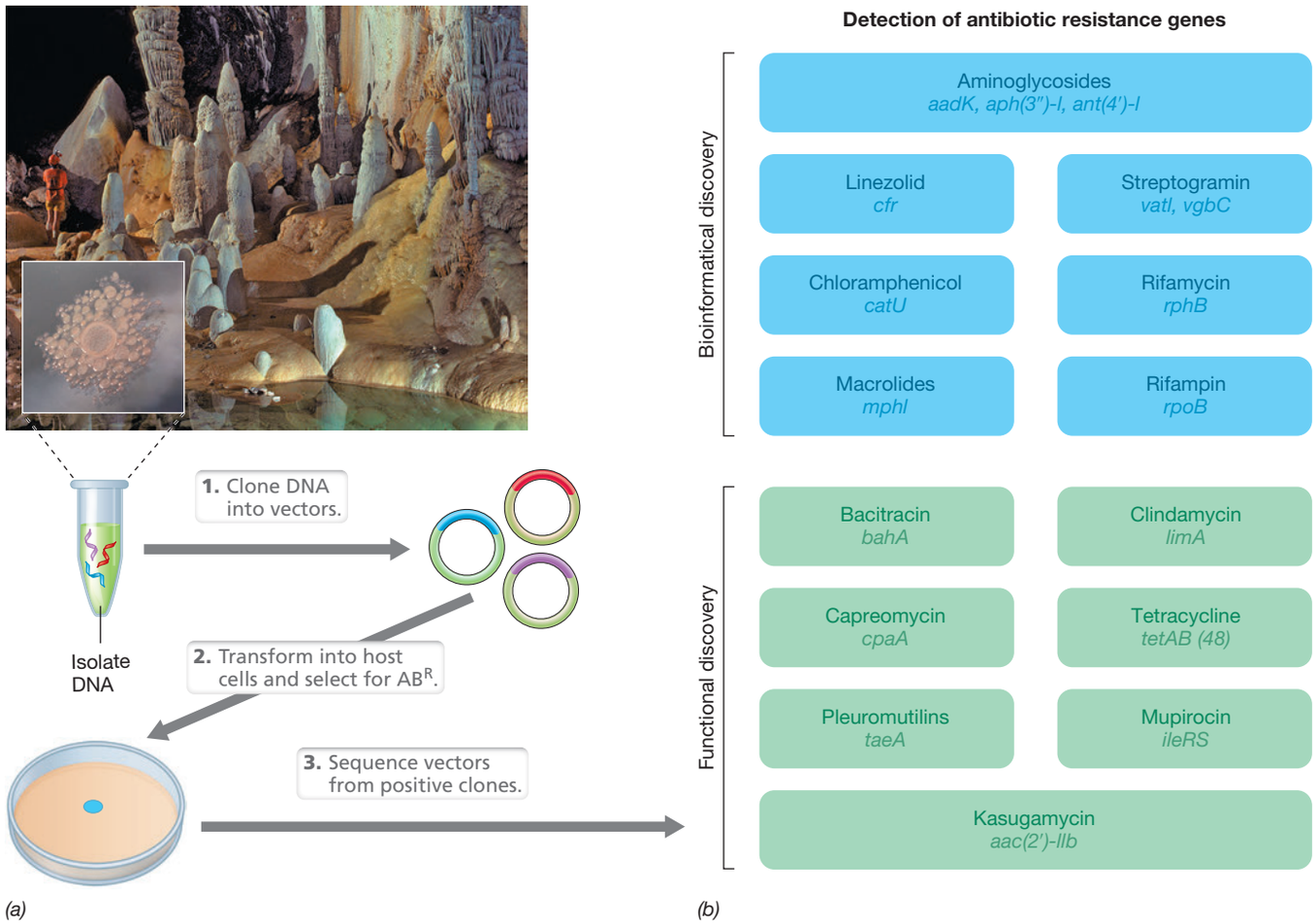


Figure 10.14 Functional genomics and discovery of new antibiotic resistance genes. *(a)* Heterologous expression of *Paenibacillius* strain LC231 DNA and selection of antibiotic-resistant transformants for sequence analysis. DNA from *Paenibacillus* strain LC231, isolated from Lechuguilla Cave, Carlsbad Caverns, New Mexico, USA (inset photo of *Paenibacillus* colonies courtesy of L. Ejim, C. Groves, and G. Wright), is extracted and inserted into plasmids for expression in *Escherichia coli*. Plasmid DNA from antibiotic-resistant *E. coli* colonies is sequenced and analyzed for the presence of new genes conferring antibiotic resistance (AB^R). *(b)* Discovery of genes conferring resistance to 14 different types of antibiotics in *Paenibacillus* strain LC231. Gene names are listed under the type of antibiotic they confer resistance to. Genes discovered by genome database searches are in blue, while genes identified by functional genomics and heterologous expression in *E. coli* from part *a* are in green. Data adapted from Pawlowski, A.C., Wenliang, W., Koteva, K., Barton, H.A., McArthur, A.G., and Wright, G.D. 2016. *Nat. Commun. 7*: 13803.