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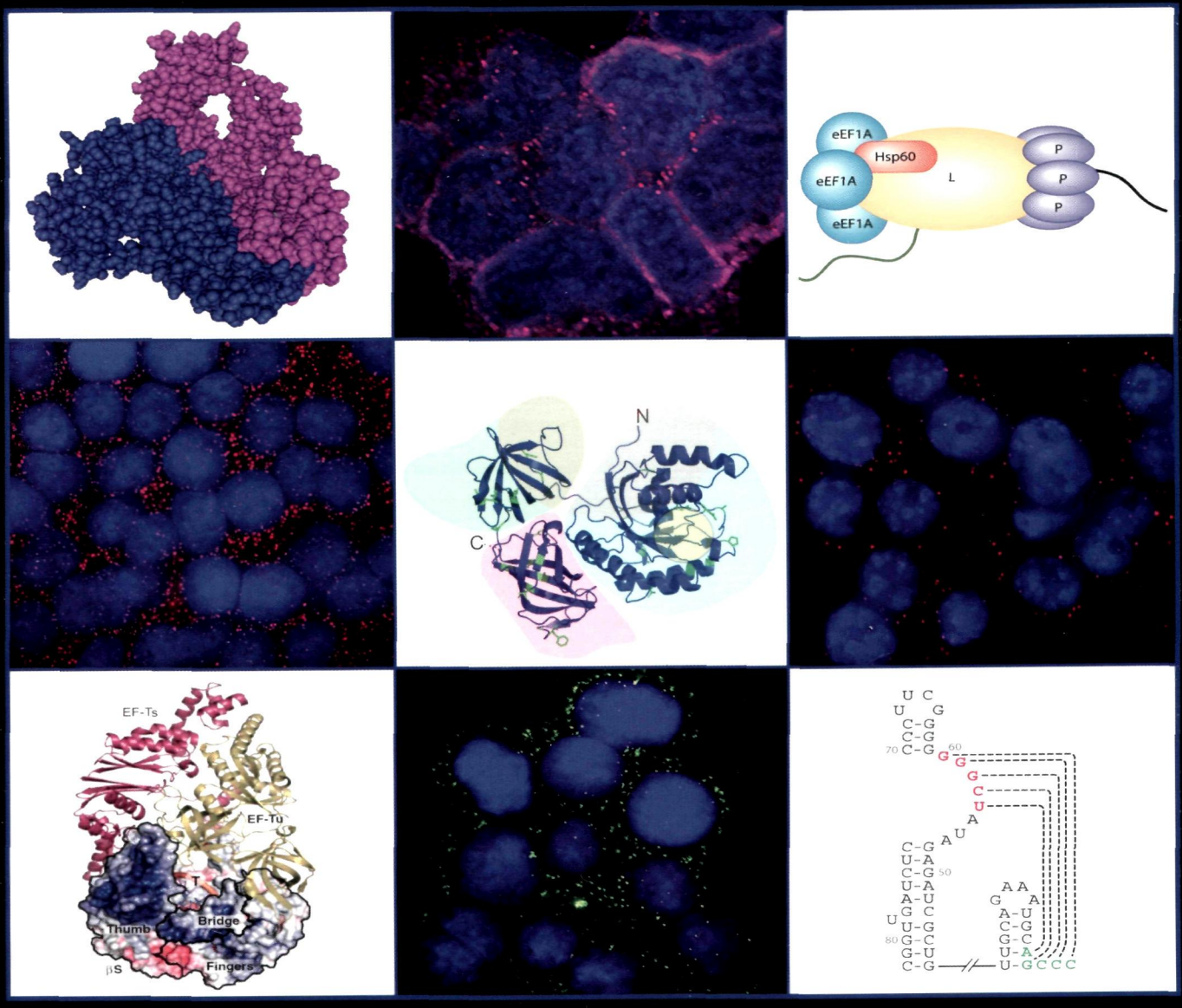
MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS



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REVIEWS

Summary: Brewing beer involves microbial activity at every stage, from raw material production and malting to stability in the package. Most of these activities are desirable, as beer is the result of a traditional food fermentation, but others represent threats to the quality of the final product and must be controlled actively through careful management, the daily task of maltsters and brewers globally. This review collates current knowledge relevant to the biology of brewing yeast, fermentation management, and the microbial ecology of beer and brewing.

Summary: Pore-forming toxins (PFTs) are the most common bacterial cytotoxic proteins and are required for virulence in a large number of important pathogens, including *Streptococcus pneumoniae*, group A and B streptococci, *Staphylococcus aureus*, *Escherichia coli*, and *Mycobacterium tuberculosis*. PFTs generally disrupt host cell membranes, but they can have additional effects independent of pore formation. Substantial effort has been devoted to understanding the molecular mechanisms underlying the functions of certain model PFTs. Likewise, specific host pathways mediating survival and immune responses in the face of toxin-mediated cellular damage have been delineated. However, less is known about the overall functions of PFTs during infection *in vivo*. This review focuses on common themes in the area of PFT biology, with an emphasis on studies addressing the roles of PFTs in *in vivo* and *ex vivo* models of colonization or infection. Common functions of PFTs include disruption of epithelial barrier function and evasion of host immune responses, which contribute to bacterial growth and spreading. The widespread nature of PFTs make this group of toxins an attractive target for the development of new virulence-targeted therapies that may have broad activity against human pathogens.

Summary: In both humans and animals, *Clostridium perfringens* is an important cause of histotoxic infections and diseases originating in the intestines, such as enteritis and enterotoxemia. The virulence of this Gram-positive, anaerobic bacterium is heavily dependent upon its prolific toxin-producing ability. Many of the ~16 toxins produced by *C. perfringens* are encoded by large plasmids that range in size from ~45 kb to ~140 kb. These plasmid-encoded toxins are often closely associated with mobile elements. A *C. perfringens* strain can carry up to three different toxin plasmids, with a single plasmid carrying up to three distinct toxin genes. Molecular Koch's postulate analyses have established the importance of several plasmid-encoded toxins when *C. perfringens* disease strains cause enteritis or enterotoxemias. Many toxin plasmids are closely related, suggesting a common evolutionary origin. In particular, most toxin plasmids and some antibiotic resistance plasmids of *C. perfringens* share an ~35-kb region containing a Tn*916*-related conjugation locus named *tcp* (transfer of clostridial plasmids). This *tcp* locus can mediate highly efficient conjugative transfer of these toxin or resistance plasmids. For example, conjugative transfer of a toxin plasmid from an infecting strain to *C. perfringens* normal intestinal flora strains may help to amplify and prolong an infection. Therefore, the presence of toxin genes on conjugative plasmids, particularly in association with insertion sequences that may mobilize these toxin genes, likely provides *C. perfringens* with considerable virulence plasticity and adaptability when it causes diseases originating in the gastrointestinal tract.

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Summary: *Neisseria meningitidis* is a Gram-negative microorganism that exists exclusively in humans and can cause devastating invasive disease. Although capsular polysaccharide-based vaccines against serogroups A, C, Y, and W135 are widely available, the pathway to a broadly protective vaccine against serogroup B has been more complex. The last 11 years has seen the discovery and development of the *N. meningitidis* serogroup B (MnB) outer membrane protein factor H binding protein (fHBP) as a vaccine component. Since the initial discovery of fHBP, a tremendous amount of work has accumulated on the diversity, structure, and regulation of this important protein. fHBP has proved to be a virulence factor for *N. meningitidis* and a target for functional bactericidal antibodies. fHBP is critical for survival of meningococci in the human host, as it is responsible for the primary interaction with human factor H (fH). Binding of hfH by the meningococcus serves to downregulate the host alternative complement pathway and helps the organism evade host innate immunity. Preclinical studies have shown that an fHBP-based vaccine can elicit serum bactericidal antibodies capable of killing MnB, and the vaccine has shown very encouraging results in human clinical trials. This report reviews our current knowledge of fHBP. In particular, we discuss the recent advances in our understanding of fHBP, its importance to *N. meningitidis*, and its potential role as a vaccine for preventing MnB disease.

Summary: The prokaryotic translation elongation factors were identified as essential cofactors for RNA-dependent RNA polymerase activity of the bacteriophage Qβ more than 40 years ago. A growing body of evidence now shows that eukaryotic translation elongation factors (eEFs), predominantly eEF1A, acting in partially characterized complexes sometimes involving additional eEFs, facilitate virus replication. The functions of eEF1A as a protein chaperone and an RNA- and actin-binding protein enable its "moonlighting" roles as a virus replication cofactor. A diverse group of viruses, from human immunodeficiency type 1 and West Nile virus to tomato bushy stunt virus, have adapted to use eEFs as cofactors for viral transcription, translation, assembly, and pathogenesis. Here we review the mechanisms used by viral pathogens to usurp these abundant cellular proteins for their replication.

Summary: In its early history, life appeared to depend on pyrophosphate rather than ATP as the source of energy. Ancient membrane pyrophosphatases that couple pyrophosphate hydrolysis to active H^+ transport across biological membranes (H^+-pyrophosphatases) have long been known in prokaryotes, plants, and protists. Recent studies have identified two evolutionarily related and widespread prokaryotic relics that can pump Na^+ (Na^+-pyrophosphatase) or both Na^+ and H^+ (Na^+,H^+-pyrophosphatase). Both these transporters require Na^+ for pyrophosphate hydrolysis and are further activated by K^+. The determination of the three-dimensional structures of H^+- and Na^+-pyrophosphatases has been another recent breakthrough in the studies of these cation pumps. Structural and functional studies have highlighted the major determinants of the cation specificities of membrane pyrophosphatases and their potential use in constructing transgenic stress-resistant organisms.

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Summary: Long-chain-length hydrophobic acyl residues play a vital role in a multitude of essential biological structures and processes. They build the inner hydrophobic layers of biological membranes, are converted to intracellular storage compounds, and are used to modify protein properties or function as membrane anchors, to name only a few functions. Acyl thioesters are transferred by acyltransferases or transacylases to a variety of different substrates or are polymerized to lipophilic storage compounds. Lipases represent another important enzyme class dealing with fatty acyl chains; however, they cannot be regarded as acyltransferases in the strict sense. This review provides a detailed survey of the wide spectrum of bacterial acyltransferases and compares different enzyme families in regard to their catalytic mechanisms. On the basis of their studied or assumed mechanisms, most of the acyl-transferring enzymes can be divided into two groups. The majority of enzymes discussed in this review employ a conserved acyltransferase motif with an invariant histidine residue, followed by an acidic amino acid residue, and their catalytic mechanism is characterized by a noncovalent transition state. In contrast to that, lipases rely on completely different mechanism which employs a catalytic triad and functions via the formation of covalent intermediates. This is, for example, similar to the mechanism which has been suggested for polyester synthases. Consequently, although the presented enzyme types neither share homology nor have a common three-dimensional structure, and although they deal with greatly varying molecule structures, this variety is not reflected in their mechanisms, all of which rely on a catalytically active histidine residue.

Cover photograph (Copyright 2013, American Society for Microbiology. All Rights Reserved.): (Top row, leftmost column) Molecular structure of the heterodimeric form of reverse transcriptase (RT) composed of p51 (blue) and p66 (purple) subunits (from the Molecular Modeling Database [MMDB], accession number 49500). (Top row, second column) Wide-field deconvolution microscopy image of HeLa cells. eEF1A1 was detected using a mouse monoclonal antibody. Nuclei were stained with DAPI (4′,6-diamidino-2-phenylindole). (Top row, third column) Schematic representation of the vesicular stomatitis virus (VSV) transcriptase complex. (Second row, leftmost column) Proximity ligation assay (PLA) between eEF1A and RT in HIV-1-infected cells was performed using a mouse monoclonal antibody to RT in conjunction with a rabbit antibody to eEF1A. Nuclei were stained with DAPI. (Second row, second column) Molecular schematic of a model structure for human eEF1A1. (Adapted from Soares et al., PLoS One **4:**e6315, 2009.) (Second row, third column) PLA between eEF1G and RT in HIV-1-infected cells was performed using a mouse monoclonal antibody to HIV-1 RT protein in conjunction with a rabbit antibody to eEF1G. Nuclei were stained with DAPI. (Bottom row, leftmost column) Molecular schematic of EF-Tu (yellow) and EF-Ts (magenta) overlaid with a surface representation of the β-subunit (labeled βS). (Reprinted from Kidmose et al., Proc. Natl. Acad. Sci. U. S. A. **107:** 10884–10889, 2010, with permission.) (Bottom row, second column) PLA between eEF1G and RT in HIV-1-infected cells was performed using a mouse monoclonal antibody to RT protein in conjunction with a rabbit antibody to eEF1G with a FITC-labeled probe. Nuclei were stained with DAPI. (Bottom row, third column) The stem-loop structure at the 3′ untranslated region (UTR) of tombusvirus genomic RNA. The highlighted nucleotides GGGCU (red), termed the replication silencer element, that can bind to the 3′ end of the genome (AGCCC; green), is a proposed eEF1A binding site. (Design of this image was by Vincent Cutillas.) (*See related article on p. 253.*)