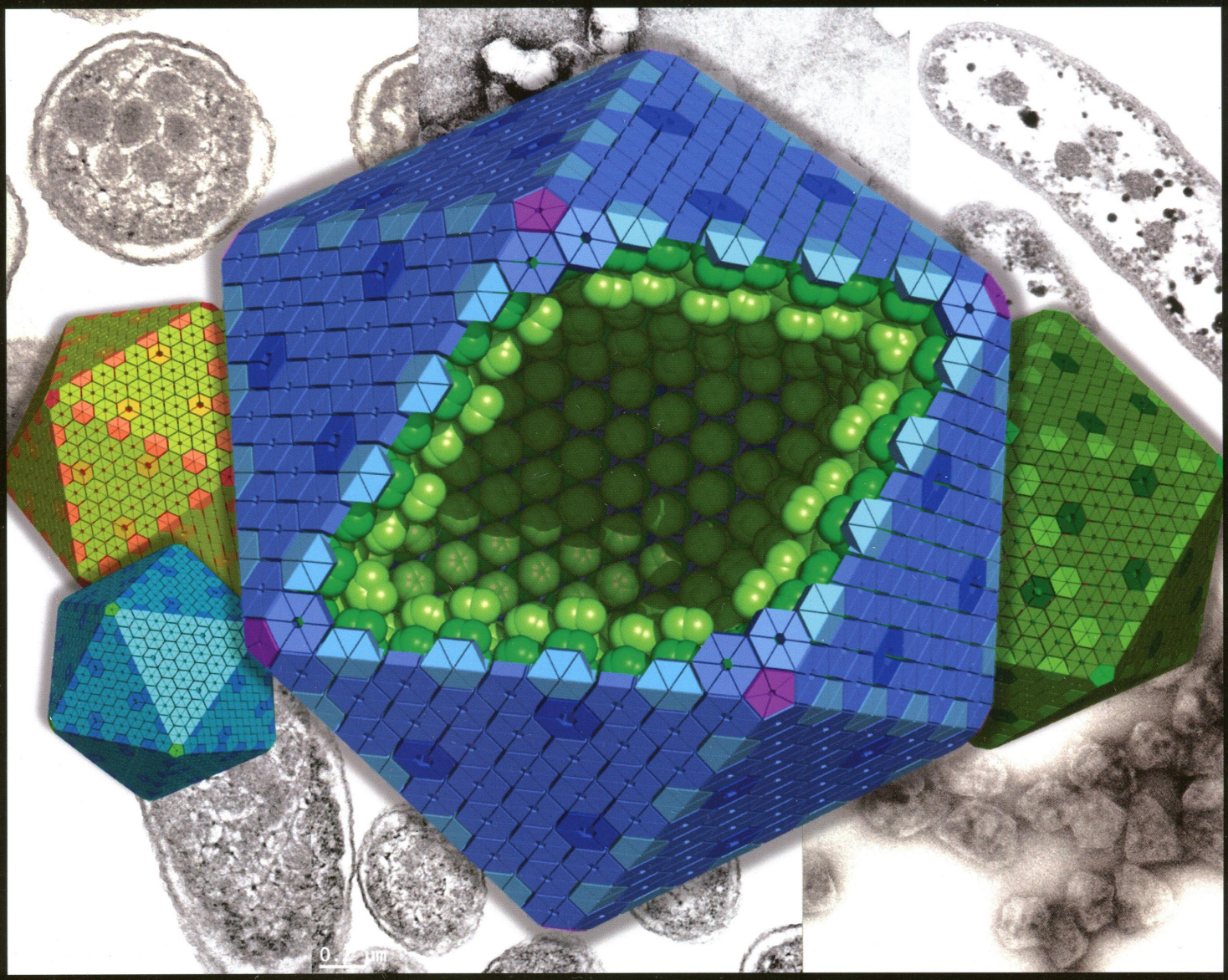
mmbr

SEPTEMBER 2014
VOL. 78, NO. 3

MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS



Published Quarterly by

AMERICAN
SOCIETY FOR
MICROBIOLOGY

MMBR
Journals.ASM.org

SEPTEMBER 2014 • VOLUME 78 • NUMBER 3

CONTENTS/SUMMARIES

REVIEWS

Summary: The aim of this review is to present the current state of knowledge on human latent tuberculosis infection (LTBI) based on clinical studies and observations, as well as experimental *in vitro* and animal models. Several key terms are defined, including "latency," "persistence," "dormancy," and "antibiotic tolerance." Dogmas prevalent in the field are critically examined based on available clinical and experimental data, including the long-held beliefs that infection is either latent or active, that LTBI represents a small population of nonreplicating, "dormant" bacilli, and that caseous granulomas are the haven for LTBI. The role of host factors, such as $CD4^+$ and $CD8^+$ T cells, T regulatory cells, tumor necrosis factor alpha (TNF-α), and gamma interferon (IFN-γ), in controlling TB infection is discussed. We also highlight microbial regulatory and metabolic pathways implicated in bacillary growth restriction and antibiotic tolerance under various physiologically relevant conditions. Finally, we pose several clinically important questions, which remain unanswered and will serve to stimulate future research on LTBI.

Summary: Humans have been increasingly recognized as being superorganisms, living in close contact with a microbiota on all their mucosal surfaces. However, most studies on the human microbiota have focused on gaining comprehensive insights into the composition of the microbiota under different health conditions (e.g., enterotypes), while there is also a need for detailed knowledge of the different molecules that mediate interactions with the host. Glycoconjugates are an interesting class of molecules for detailed studies, as they form a strain-specific barcode on the surface of bacteria, mediating specific interactions with the host. Strikingly, most glycoconjugates are synthesized by similar biosynthesis mechanisms. Bacteria can produce their major glycoconjugates by using a sequential or an *en bloc* mechanism, with both mechanistic options coexisting in many species for different macromolecules. In this review, these common themes are conceptualized and illustrated for all major classes of known bacterial glycoconjugates, with a special focus on the rather recently emergent field of glycosylated proteins. We describe the biosynthesis and importance of glycoconjugates in both pathogenic and beneficial bacteria and in both Gram-positive and -negative organisms. The focus lies on microorganisms important for human physiology. In addition, the potential for a better knowledge of bacterial glycoconjugates in the emerging field of glycoengineering and other perspectives is discussed.

Summary: The *Picornaviridae* represent a large family of small plus-strand RNA viruses that cause a bewildering array of important human and animal diseases. Morphogenesis is the least-understood step in the life cycle of these viruses, and this process is difficult to study because encapsidation is tightly coupled to genome translation and RNA replication. Although the basic steps of assembly have been known for some time, very few details are available about the mechanism and factors that regulate this process. Most of the information available has been derived from studies of enteroviruses, in particular poliovirus, where recent evidence has shown that, surprisingly, the specificity of encapsidation is governed by a viral protein-protein interaction that does not involve an RNA packaging signal. In this review, we make an attempt to summarize what is currently known about the following topics: (i) encapsidation intermediates, (ii) the specificity of encapsidation (iii), viral and cellular factors that are required for encapsidation, (iv) inhibitors of encapsidation, and (v) a model of enterovirus encapsidation. Finally, we compare some features of picornavirus morphogenesis with those of other plus-strand RNA viruses.

Summary: Bacterial microcompartments (MCPs) are sophisticated protein-based organelles used to optimize metabolic pathways. They consist of metabolic enzymes encapsulated within a protein shell, which creates an ideal environment for catalysis and facilitates the channeling of toxic/volatile intermediates to downstream enzymes. The metabolic processes that require MCPs are diverse and widely distributed and play important roles in global carbon fixation and bacterial

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Instructions to Authors are available at http://journalitas.asm.org/t/49549.

pathogenesis. The protein shells of MCPs are thought to selectively control the movement of enzyme cofactors, substrates, and products (including toxic or volatile intermediates) between the MCP interior and the cytoplasm of the cell using both passive electrostatic/steric and dynamic gated mechanisms. Evidence suggests that specialized shell proteins conduct electrons between the cytoplasm and the lumen of the MCP and/or help rebuild damaged iron-sulfur centers in the encapsulated enzymes. The MCP shell is elaborated through a family of small proteins whose structural core is known as a bacterial microcompartment (BMC) domain. BMC domain proteins oligomerize into flat, hexagonally shaped tiles, which assemble into extended protein sheets that form the facets of the shell. Shape complementarity along the edges allows different types of BMC domain proteins to form mixed sheets, while sequence variation provides functional diversification. Recent studies have also revealed targeting sequences that mediate protein encapsulation within MCPs, scaffolding proteins that organize lumen enzymes and the use of private cofactor pools (NAD/H and coenzyme A) to facilitate cofactor homeostasis. Although much remains to be learned, our growing understanding of MCPs is providing a basis for bioengineering of protein-based containers for the production of chemicals/pharmaceuticals and for use as molecular delivery vehicles.

Summary: Research into the complex genetic underpinnings of the malaria parasite *Plasmodium falciparum* is entering a new era with the arrival of site-specific genome engineering. Previously restricted only to model systems but now expanded to most laboratory organisms, and even to humans for experimental gene therapy studies, this technology allows researchers to rapidly generate previously unattainable genetic modifications. This technological advance is dependent on DNA double-strand break repair (DSBR), specifically homologous recombination in the case of *Plasmodium*. Our understanding of DSBR in malaria parasites, however, is based largely on assumptions and knowledge taken from other model systems, which do not always hold true in *Plasmodium*. Here we describe the causes of double-strand breaks, the mechanisms of DSBR, and the differences between model systems and *P. falciparum*. These mechanisms drive basic parasite functions, such as meiosis, antigen diversification, and copy number variation, and allow the parasite to continually evolve in the contexts of host immune pressure and drug selection. Finally, we discuss the new technologies that leverage DSBR mechanisms to accelerate genetic investigations into this global infectious pathogen.

Summary: The concept of the minimal cell has fascinated scientists for a long time, from both fundamental and applied points of view. This broad concept encompasses extreme reductions of genomes, the last universal common ancestor (LUCA), the creation of semiartificial cells, and the design of protocells and chassis cells. Here we review these different areas of research and identify common and complementary aspects of each one. We focus on systems biology, a discipline that is greatly facilitating the classical top-down and bottom-up approaches toward minimal cells. In addition, we also review the so-called middle-out approach and its contributions to the field with mathematical and computational models. Owing to the advances in genomics technologies, much of the work in this area has been centered on minimal genomes, or rather minimal gene sets, required to sustain life. Nevertheless, a fundamental expansion has been taking place in the last few years wherein the minimal gene set is viewed as a backbone of a more complex system. Complementing genomics, progress is being made in understanding the system-wide properties at the levels of the transcriptome, proteome, and metabolome. Network modeling approaches are enabling the integration of these different omics data sets toward an understanding of the complex molecular pathways connecting genotype to phenotype. We review key concepts central to the mapping and modeling of this complexity, which is at the heart of research on minimal cells. Finally, we discuss the distinction between minimizing the number of cellular components and minimizing cellular complexity, toward an improved understanding and utilization of minimal and simpler cells.

Summary: Surface-associated microbial communities, called biofilms, are present in all environments. Although biofilms play an important positive role in a variety of ecosystems, they also have many negative effects, including biofilm-related infections in medical settings. The ability of pathogenic biofilms to survive in the presence of high concentrations of antibiotics is called "recalcitrance" and is a characteristic property of the biofilm lifestyle, leading to treatment failure and infection recurrence. This review presents our current understanding of the molecular mechanisms of biofilm recalcitrance toward antibiotics and describes how recent progress has improved our capacity to design original and efficient strategies to prevent or eradicate biofilm-related infections.

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Summary: Initially discovered in the context of immunomodulation, peptidyl-prolyl *cis/trans* isomerases (PPIases) were soon identified as enzymes catalyzing the rate-limiting protein folding step at peptidyl bonds preceding proline residues. Intense searches revealed that PPIases are a superfamily of proteins consisting of three structurally distinguishable families with representatives in every described species of prokaryote and eukaryote and, recently, even in some giant viruses. Despite the clear-cut enzymatic activity and ubiquitous distribution of PPIases, reports on solely PPIase-dependent biological roles remain scarce. Nevertheless, they have been found to be involved in a plethora of biological processes, such as gene expression, signal transduction, protein secretion, development, and tissue regeneration, underscoring their general importance. Hence, it is not surprising that PPIases have also been identified as virulence-associated proteins. The extent of contribution to virulence is highly variable and dependent on the pleiotropic roles of a single PPIase in the respective pathogen. The main objective of this review is to discuss this variety in virulence-related bacterial and protozoan PPIases as well as the involvement of host PPIases in infectious processes. Moreover, a special focus is given to *Legionella pneumophila* macrophage infectivity potentiator (Mip) and Mip-like PPIases of other pathogens, as the best-characterized virulence-related representatives of this family. Finally, the potential of PPIases as alternative drug targets and first tangible results are highlighted.

Cover photograph (Copyright © 2014, American Society for Microbiology. All Rights Reserved): Diverse bacterial microcompartments (MCPs) are beginning to be understood in terms of their various metabolic roles and their structural organization. These extraordinary polyhedral protein bodies (depicted in color as graphic art) self-assemble in a complex and optimized fashion from thousands of shell proteins and enzymes in order to allow efficient transport and sequestered metabolism of specific substrates, thereby conferring a growth advantage over other bacteria in the same environment. One example of this is the 1,2-propanediol utilization microcompartment (Pdu MCP) used by *Salmonella enterica* serovar Typhimurium in the gut. The background panels (electron micrographs taken by the indicated individuals) show Pdu MCPs in *S. enterica* (top left, bottom left, and bottom center [Thomas Bobik]), purified Pdu MCPs (top center [Chiranjit Chowdhury] and bottom right [Sharmistha Sinha]), and carboxysomes in *Halothiobacillus* (top right [Henry Aldrich]). Graphic art and image design by Sunny Chun and Todd Yeates. (*See related article on page 438.*)