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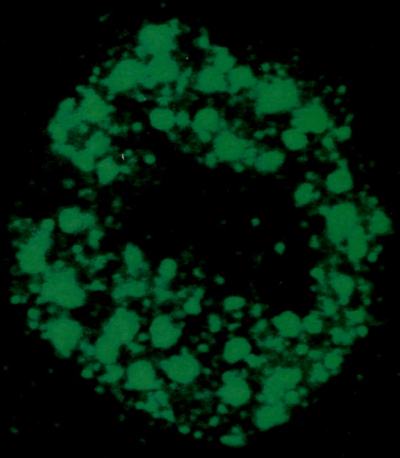

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CONTENTS/SUMMARIES

COMMENTARY

Summary: Carl Woese developed a unique research program, based on rRNA, for discerning bacterial relationships and constructing a universal tree of life. Woese's interest in the evolution of the genetic code led to him to investigate the deep roots of evolution, develop the concept of the progenote, and conceive of the *Archaea*. In so doing, he and his colleagues at the University of Illinois in Urbana revolutionized microbiology and brought the classification of microbes into an evolutionary framework. Woese also provided definitive evidence for the role of symbiosis in the evolution of the eukaryotic cell while underscoring the importance of lateral gene transfer in microbial evolution. Woese and colleagues' proposal of three fundamental domains of life was brought forward in direct conflict with the prokaryote-eukaryote dichotomy. Together with several colleagues and associates, he brought together diverse evidence to support the rRNA evidence for the fundamentally tripartite nature of life. This paper aims to provide insight into his accomplishments, how he achieved them, and his place in the history of biology.

REVIEWS

Summary: Fifty years after the discovery of the mouse *Mx1* gene, researchers are still trying to understand the molecular details of the antiviral mechanisms mediated by Mx proteins. Mx proteins are evolutionarily conserved dynamin-like large GTPases, and GTPase activity is required for their antiviral activity. The expression of *Mx* genes is controlled by type I and type III interferons. A phylogenetic analysis revealed that *Mx* genes are present in almost all vertebrates, usually in one to three copies. Mx proteins are best known for inhibiting negative-stranded RNA viruses, but they also inhibit other virus families. Recent structural analyses provide hints about the antiviral mechanisms of Mx proteins, but it is not known how they can suppress such a wide variety of viruses lacking an obvious common molecular pattern. Perhaps they interact with a (partially) symmetrical invading oligomeric structure, such as a viral ribonucleoprotein complex. Such an interaction may be of a fairly low affinity, in line with the broad target specificity of Mx proteins, yet it would be strong enough to instigate Mx oligomerization and ring assembly. Such a model is compatible with the broad "substrate" specificity of Mx proteins: depending on the size of the invading viral ribonucleoprotein complexes that need to be wrapped, the assembly process would consume the necessary amount of Mx precursor molecules. These Mx ring structures might then act as energy-consuming wrenches to disassemble the viral target structure.

Summary: *Clostridium difficile* is a Gram-positive, spore-forming organism which infects and colonizes the large intestine, produces potent toxins, triggers inflammation, and causes significant systemic complications. Treating *C. difficile* infection (CDI) has always been difficult, because the disease is both caused and resolved by antibiotic treatment. For three and a half decades, *C. difficile* has presented a treatment challenge to clinicians, and the situation took a turn for the worse about 10 years ago. An increase in epidemic outbreaks related to CDI was first noticed around 2003, and these outbreaks correlated with a sudden increase in the mortality rate of this illness. Further studies discovered that these changes in CDI epidemiology were associated with the rapid emergence of hypervirulent strains of *C. difficile*, now collectively referred to as NAP1/BI/027 strains. The discovery of new epidemic strains of *C. difficile* has provided a unique opportunity for retrospective and prospective studies that have sought to understand how these strains have essentially replaced more historical strains as a major cause of CDI. Moreover, detailed studies on the pathogenesis of NAP1/BI/027 strains are leading to new hypotheses on how this emerging strain causes severe disease and is more commonly associated with epidemics. In this review, we provide an overview of CDI, discuss critical mechanisms of *C. difficile* virulence, and explain how differences in virulence-associated factors between historical and newly emerging strains might explain the hypervirulence exhibited by this pathogen during the past decade.

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Summary: Enteric pathogens such as *Salmonella enterica* cause significant morbidity and mortality. *S. enterica* serovars are a diverse group of pathogens that have evolved to survive in a wide range of environments and across multiple hosts. *S. enterica* serovars such as *S.* Typhi, *S.* Dublin, and *S.* Gallinarum have a restricted host range, in which they are typically associated with one or a few host species, while *S.* Enteritidis and *S.* Typhimurium have broad host ranges. This review examines how *S. enterica* has evolved through adaptation to different host environments, especially as related to the chicken host, and continues to be an important human pathogen. Several factors impact host range, and these include the acquisition of genes via horizontal gene transfer with plasmids, transposons, and phages, which can potentially expand host range, and the loss of genes or their function, which would reduce the range of hosts that the organism can infect. *S. Gallinarum*, with a limited host range, has a large number of pseudogenes in its genome compared to broader-host-range serovars. *S. enterica* serovars such as *S.* Kentucky and *S.* Heidelberg also often have plasmids that may help them colonize poultry more efficiently. The ability to colonize different hosts also involves interactions with the host's immune system and commensal organisms that are present. Thus, the factors that impact the ability of *Salmonella* to colonize a particular host species, such as chickens, are complex and multifactorial, involving the host, the pathogen, and extrinsic pressures. It is the interplay of these factors which leads to the differences in host ranges that we observe today.

Summary: Treatment of tuberculosis (TB) remains challenging, with lengthy treatment durations and complex drug regimens that are toxic and difficult to administer. Similar to the vast majority of antibiotics, drugs for *Mycobacterium tuberculosis* are directed against microbial targets. Although more effective drugs that target the bacterium may lead to faster cure of patients, it is possible that a biological limit will be reached that can be overcome only by adopting a fundamentally new treatment approach. TB regimens might be improved by including agents that target host pathways. Recent work on host-pathogen interactions, host immunity, and host-directed interventions suggests that supplementing anti-TB therapy with host modulators may lead to shorter treatment times, a reduction in lung damage caused by the disease, and a lower risk of relapse or reinfection. We undertook this review to identify molecular pathways of the host that may be amenable to modulation by small molecules for the treatment of TB. Although several approaches to augmenting standard TB treatment have been proposed, only a few have been explored in detail or advanced to preclinical and clinical studies. Our review focuses on molecular targets and inhibitory small molecules that function within the macrophage or other myeloid cells, on host inflammatory pathways, or at the level of TB-induced lung pathology.

Summary: We present a comprehensive overview of the hierarchical network of intracellular processes revolving around central nitrogen metabolism in *Escherichia coli*. The hierarchy intertwines transport, metabolism, signaling leading to posttranslational modification, and transcription. The protein components of the network include an ammonium transporter (AmtB), a glutamine transporter (GlnHPQ), two ammonium assimilation pathways (glutamine synthetase-glutamate synthase [GOGAT] and glutamate dehydrogenase), the two bifunctional enzymes adenylyl transferase/adenylyl-removing enzyme (ATase) and uridylyl transferase/uridylyl-removing enzyme (UTase), the two trimeric signal transduction proteins (GlnB and GlnK), the two-component regulatory system composed of the histidine protein kinase nitrogen regulator II (NRII) and the response nitrogen regulator I (NRI), three global transcriptional regulators called nitrogen assimilation control (Nac) protein, leucine-responsive regulatory protein (Lrp), and cyclic AMP (cAMP) receptor protein (Crp), the glutaminases, and the nitrogen-phosphotransferase system. First, the structural and molecular knowledge on these proteins is reviewed. Thereafter, the activities of the components as they engage together in transport, metabolism, signal transduction, and transcription and their regulation are discussed. Next, old and new molecular data and physiological data are put into a common perspective on integral cellular functioning, especially with the aim of resolving counterintuitive or paradoxical processes featured in nitrogen assimilation. Finally, we articulate what still remains to be discovered and what general lessons can be learned from the vast amounts of data that are available now.

Cover photograph (): *Mus musculus* Mx1 is located in the nucleus of mammalian cells and accumulates in scattered specks. HEK293T cells were transfected with pCAXL-Mx1, a mammalian expression vector encoding mouse Mx1 cDNA. Twenty-four hours later, cells were stained with anti-Mx1 polyclonal antibody followed by Alexa Fluor 488-labeled secondary antibody. Images were recorded with a Leica Sp5 AOBS confocal microscope. *(See related article on p. 551.)*