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Evidence that *Rickettsia prowazekii* may be susceptible to noncanonical purines

Nicholas E. Burgis
Eastern Washington University, USA

Abstract

Many biochemical pathways for cell metabolism, maintenance, and reproduction have been well conserved throughout evolution. Conservation of function for a metabolic pathway lies in conservation of amino acid residues important for function of the enzymes in that biochemical pathway. Key enzymes in the noncanonical purine (NCP) repair pathway have been highly conserved throughout evolution, and are found in all domains of life. These enzymes are important for excluding NCPs from the cellular nucleotide pools. NCPs can arise in cells from normal metabolic processes, oxidation and exogenous sources. Upon entering purine salvage pathways, or through de novo purine metabolism, NCPs can become (deoxy) ribonucleoside triphosphates ((d)NTPs). Thus NCPs can become precursors for nucleic acid synthesis, and biochemical pathways that exclude NCPs from nucleic acid precursor pools help to insure the fidelity of processes such as DNA replication and gene expression. Preliminary analysis of potential bioterrorism agents suggests that the NCP repair pathway is present in most category A and B bioterrorism agents. The exception is the causative agent of human typhus, *Rickettsia prowazekii* (RP), which lacks the three key enzymes of the NCP repair pathway. Our results indicate RP may have elevated sensitivity to NCP, relative to humans. Currently, doxycycline or chloramphenicol are successful in treatment of human typhus, however, should drug resistance develop, or the patient present hypersensitivity, alternative therapies to combat RP infections will be of value. Determining the feasibility of using NCPs as an alternate therapy to combat RP infection from bioterrorism events or natural vectors awaits experimentation.

Biography

Nicholas E. Burgis is currently an Associate Professor in the Department of Chemistry and Biochemistry at Eastern Washington University. He was trained in the fields of DNA repair and toxicology and earned his Ph.D. from The University at Albany, S.U.N.Y. with post-doctoral training at the Massachusetts Institute of Technology. His current research interests focus on understanding mechanisms of nucleotide metabolism and toxicology. Burgis currently serves as the Editor-in-Chief for the *Journal of Bioterrorism and Biodefense* and on the American Chemical Society Biochemistry Examination Committee. His research program is supported by funding from the American Heart Association and American Cancer Society.