Resurrection of 3-billion-year-old antibiotic-resistance proteins

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Scientists are reporting "laboratory resurrections" of several 2-3-billion-year-old proteins that are ancient ancestors of the enzymes that enable today's antibiotic-resistant bacteria to shrug off huge doses of penicillins, cephalosporins and other modern drugs. The achievement, reported in the *Journal of the American Chemical Society*, opens the door to a

scientific "replay" of the evolution of antibiotic resistance with an eye to finding new ways to cope with the problem.

Jose M. Sanchez-Ruiz, Eric A. Gaucher, Valeria A. Risso and colleagues explain that antibiotic resistance existed long before Alexander Fleming discovered the first antibiotic in 1928. Genes that contain instructions for making the proteins responsible for antibiotic resistance have been found in 30,000-year-old permafrost sediment and other ancient sites. Their research focused on the so-called beta-lactamases, enzymes responsible for resistance to the family of antibiotics that includes penicillin, which scientists believe originated billions of years ago.

They describe using laboratory and statistical techniques to reconstruct the sequences of beta-lactamase proteins dating to Precambrian times, 2-3 billion years ago. The team also synthesized the inferred ancestral enzymes and conducted studies on their stability, structure and function. "The availability of laboratory resurrections of Precambrian beta-lactamases opens up new possibilities in the study of the emergence of antibiotic resistance," the report states. "For instance, it should now be possible to perform laboratory replays of the molecular tape of lactamase evolution and use such replays to probe the molecular determinants of the efficiency of lactamases to adapt to different types of antibiotics." The authors also note that the extreme stability and catalytic features displayed by the 2-3-billion-year-old lactamases suggest that resurrected Precambrian proteins have utility for the biotechnology industry.

More information: Hyperstability and Substrate Promiscuity in Laboratory Resurrections of Precambrian Beta-Lactamases, *Journal of the American Chemical Society*. 2013, 135 (8), pp 2899–2902
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Abstract

We report a sequence reconstruction analysis targeting several Precambrian nodes in the evolution of class-A β-lactamases and the preparation and experimental characterization of their encoded proteins. Despite extensive sequence differences with the modern enzymes (100 amino acid differences), the proteins resurrected in the laboratory properly fold into the canonical lactamase structure. The encoded proteins from 2–3 billion years (Gyr)-old β-lactamase sequences undergo cooperative two-state thermal denaturation and display very large denaturation temperature enhancements (35 °C) relative to modern β-lactamases. They degrade different antibiotics in vitro with catalytic efficiencies comparable to that of an average modern enzyme. This enhanced substrate promiscuity is not accompanied by significant changes in the active-site region as seen in static X-ray structures, suggesting a plausible role for dynamics in the evolution of function in these proteins. Laboratory resurrections of 2–3 Gyr-old β-lactamases also endowed modern microorganisms with significant levels of resistance toward a variety of antibiotics, opening up the possibility of performing laboratory replays of the molecular tape of lactamase evolution. Overall, these results support the notions that Precambrian life was thermophilic and that proteins can evolve from substrate-promiscuous generalists into specialists during the course of natural evolution. They also highlight the biotechnological potential of laboratory resurrection of Precambrian proteins, as both high stability and enhanced promiscuity (likely contributors to high evolvability) are advantageous features in protein scaffolds for molecular design and laboratory evolution.

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