THE FIRST WORD

Going to Extremes

Can extremozymes—the metabolic currency of microbial thrill-seekers living at the edges of life—provide new answers to old questions and new sources of biotechnological innovation? Mike Adams, Francine Perler, and Robert Kelly, pioneers of this extreme research, set out what is presently known about these novel enzymes in this month's review article, "Extremozymes: Expanding the Limits of Biocatalysis."

Extremozymes are used by extremophiles—organisms from the bacteria and archaea kingdoms that live in sulfuric hot springs and volcanic vents and arctic pools—to thrive under conditions of heat, cold, pressure, pH, and salinity that would obliterate most typical temperate mesophiles. Extremophiles have gotten a lot of press lately, particularly in light of the National Science Foundation Extremozyme Workshop organized by the authors in May of last year. That, and the fact that extremophiles have such, from the viewpoint of the mesophile, bizarre lifestyles, that they are likely candidates to surplant viruses in the next round of Hollywood horror bioscripts: They take the heat. They take the cold. They take the pressure. They take over the world we took over from them.

Putting their cinematic possibilities aside, extremophiles and their products are very satisfying because they open up new ways of looking at the origins of life, of reconsidering what are the permissible boundaries of life, of looking at biochemistry and the nature of structure and stability, and of developing new technologies and applications for biocatalysis. Their place in the scientific universe has certainly changed: Fifteen years ago, this field consisted of a few researchers looking at a few enzymes from a few cranky microbes.

The most famous thermophilic enzyme is, of course, Taq, isolated first from *Thermus aquaticus*. But now that a number of extremozymes have been identified that can function at temperatures ranging from as low as the freezing point of water to at least 140° C, in saturated solutions of salt, at extremely high pressures, and in essentially nonaqueous environments, Taq is far from extreme.

How do extremophiles stay functional and stable in such harsh conditions? Can this information be applied to conventional enzymes, particularly those of biological importance, to make them more thermally stable?

The authors stress that the intrinsic basis for biological function under extreme conditions is only beginning to be addressed. Extremozymes are not yielding their secrets easily. Given extremophiles' "normal" living conditions, they are very difficult to culture, and therefore the enzymes are difficult to harvest in sufficient quantities. Sulfur-reducing hyperthermophiles create toxic and corrosive conditions, making their fermentation systems unusable for anything else. Barophiles need high-pressure vessels and reactors, making large-scale cultivation unfeasible. Thermoacidophiles often grow by oxidizing metal sulfides and elemental sulfur, creating insoluble metal oxides that foul glass surfaces and corrode metal vessels.

Besides getting enough of them, there is the considerable problem of figuring out how they do the things they do. Systematic analyses of the amino-acid sequences for analogous proteins from mesophiles and thermophiles have made few, if any, generalities clear. Structural data has also proved uncooperative: For example, the structures of some identified pyrococcal proteins are virtually identical to those of their mesophilic counterparts, yet one set of proteins is stable at high temperatures—a stability achieved, it seems, as a consequence of minor structural changes, mostly involving surface residues—while the other falls apart. This does not bode well for the straightforward conversion of mesophilic proteins into hyperthermophilic ones through recombinant techniques. But it is very exciting with respect to three-dimensional structure: If you could understand the nature of these collective surface changes, how much closer would you be to biotechnology's holy grail of de novo protein folding?

How wonderful that such far-reaching implications should come from such modest beginnings. How impossible to build into the bottom line.

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