Microbial Biotech: Less Glamorous, but Effective

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Are biotechnologists so enamored of genetic manipulation that they overlook less glamorous strategies? The thought loomed up recently as I was scanning the journal *Microbiology* and spotted two nice pieces of basic microbial physiology. Both had immediate industrial implications. Yet neither owed anything to the sophisticated art of gene tinkering.

The first is by Michael Bushell and Gavin Clark at the University of Surrey, Guildford, and David Langley of Glaxo Research and Development (Greenford, U.K.). It describes a method of inducing microorganisms to produce hitherto unknown secondary metabolites, and explores the technique's potential in screening organisms for new antibiotics. Compared with present-day efforts to engineer molecular variants of natural metabolites, the research is much closer to traditional practice. Yet it is also subtly different. Such radical thinking is needed at a time when many existing antimicrobials are losing their potency with the alarming spread at drug resistance.

In the second paper, Anthony Trinci and his colleagues at the University of Manchester report a major advance in the production of the only survivor of the many single-cell protein projects that were initiated during the 1960s. The mycoprotein of *Fusarium graminearum* is already marketed in the U.K. and other European countries as Quorn, a meat substitute in a variety of pre-prepared dishes, and as a raw material for home cooking. But there is a significant drawback in its manufacturing process, which the new research promises to overcome.

The secondary metabolite report stems from Bushell's suggestion, six years ago, of a possible defect in conventional screening for antibiotic producers. He believed that the routine of limiting their growth by restricting the availability of particular nutrients (the conditions under which antibiotics typically appear) might not reveal all possible secondary metabolites if the real growth-limiting factor was oxygen.

This might seem unlikely in aerated cultures. Bushell suspected it was possible, however, in the small vessels used in screening programs, especially in actinomyte cultures with a high oxygen demand. Despite a wealth of knowledge concerning aeration efficiency in antibiotic production, little research had been conducted on oxygen limitation. In any case, the truth was impossible to determine without hard data on dissolved oxygen.

This is what Bushell and his collaborators now provide. As described in *Microbiology* (**141**:663-669), they have used a miniature electrode to measure time-dependent changes in dissolved oxygen in culture of two actinomycetes. They have found, for example, that *Saccharopolyspora erhythraea* produces erythromycin whether or not it is short of oxygen. On the contrary, *Amycolatopsis orientalis* produces vancomycin only when provided with sufficient oxygen.

The lesson is clear. Oxygen limitation can both stimulate and inhibit the formation of secondary metabolites. It's a simple discovery. Yet it has exciting potential for the detection of antibiotics that may have evaded countless screening programs in the past that did not take oxygen properly into account. Glucose limitation is the key to the paper by Tony Trinci and his colleagues. They have been supported by Marlow Foods (Marlow, U.K.) in an attempt to improve the process the company uses to make Quorn.

Quorn is a healthy eater's dream. The only snag is that the fermentation has to be halted as soon as highly branched mutants of *F. graminearum* emerge. They impair the texture and filtration of the final product, which reduces productivity.

As described in *Microbiology* (**140**:3015-3021), Tony Trinci and his colleagues have tackled the problem by the strategy, elementary in principle but sophisticated in practice, of using a chemostat. From a series of glucose-limited cultures, they have isolated variants of *F. graminearum* that are identical with the parent strain except that their highly branched mutants develop much later. Their delayed appearance could make considerable difference to the efficiency and economics of the manufacturing process.

So there you have it—two papers, one describing purely phenotypic manipulations, the other using natural mutation and selection inside a chemostat. Not a word about kilobases, YACs, or introns. In the rush to apply the shiny new technologies of molecular genetics to every single problem that presents itself, biotechnologists would be well advised not to forget that other, simpler, solutions may lie close at hand. ///