Extreme microbes could hold the keys of a greener and healthier world

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To us humans, our planet's most extreme environments often seem to be places to offer great sceneries and beautiful landscapes. For some microbes on the other hand, these places -hot springs, high pressure, cold or hot deserts, radioactive area,...- are their home. These microorganisms are called extremophiles. Since a large portion of the extremophile world is still unfamiliar and that these organisms have surprising adaptation mechanisms, it is thought that this underexplored world and its microbial communities will have future applications in health and biotechnology.

Some of the most important compounds in pharmaceutical and biotechnology industries originated as natural products discovered from microbes. Since extreme microbes don't let themselves domesticate easily, scientists are implementing new techniques to unveil the molecular potential of these microorganisms. To find new natural products, some recent strategies used genome mining. By genome mining, we intend looking for genes of particular interest among big datasets of genetic information. Genes that are mostly looked at are the ones belonging to biosynthetic gene clusters (BGCs). BGCs represent the biosynthetic machinery to produce natural compounds. Two biomolecular families encompass most of bioactive natural products from microbes: polyketides and non-ribosomal peptides. Both have their own biosynthetic machineries and thus BGCs. Different computational tools have been developed to analyze BGCs and to find out if they could encode novel and interesting compounds (<u>1</u>). By looking at the genetic diversity of extremophiles, one can discover new BGCs and thus new potentially active natural products.

A first place in which one can look for genetic diversity among microbes is the ocean. Marine and oceanic environments are actually underexplored as resource of interesting natural products. In a recent study (2), more than 1,000 samples of sea water from all over the world were analyzed. It allowed scientists to look at more than 25,000 microbial genomes, unveiling more than 7,000 BGC families, half of which are thought to be novel. Two new biosynthetic pathways were discovered, one (phospeptin) could produce protease inhibitors while the other one (pythonamide) holds very interesting enzymes on a biotechnological point-of-view.

Hot or thermal springs are also places where to find interesting extreme microbes. Recently ($\underline{3}$), microbes from hot springs located on the ocean floor around the Kerguelen Islands were collected and their genomes analyzed. These microbes live with temperatures of more than 80°C and pH ranging up to 9. Preliminary data suggest that they are a source of various biochemical pathways, yet to be explored. Indeed, some of them could be able to oxidize carbon monoxide and might thus be used in the future as microbial fuel cells. In addition to this biotechnological application, some hot springs bacteria are already known to produce some bioactive compounds like antibiotics ($\underline{4}$).

Extremophiles are also found in cold arid environment like polar deserts. The natural compounds they produce may not only be interesting for us but also play a physiological role for their survival in their habitat. Microbial genes encoding the production of antifungal and biosurfactants were discovered in some Antarctic soil samples (<u>5</u>). These biosurfactants are thought to help these microbes in the uptake of nutrients in their nutrient-poor environment. They have many applications in various industries (food, cosmetics,...) and could replace some toxic surfactants used in the past.

There are many other places in which scientists are looking at for natural product discovery. Our planet's various microbiomes (either extreme or not) show a tremendous genetic diversity, which is still underexplored. Recent developments in genomic and bioinformatic analysis has allowed scientists to decipher the biosynthetic logic leading to the major classes of natural products. By replacing toxic or polluting processes and chemicals and by providing us with new drugs, these microbes and their compounds will help us build a greener and healthier world.

1. Medema M.H., de Rond T., Moore B.S. Mining genomes to illuminate the specialized chemistry of life. *Nature Review Genetics* **22**, 553–571 (2021).

2. Paoli L., Ruscheweyh HJ., Forneris C.C. *et al*. Biosynthetic potential of the global ocean microbiome. *Nature* **607**, 111–118 (2022).

3. Allioux M., Yvenou S., Merkel A. *et al*. Metagenome-assembled genomes reveal many novel microbial lineages in the geothermal springs of the subantarctic Kerguelen Islands. PREPRINT (Version 1) available at Research Square, 12 April 2022.

4. Mahajan G.B., Balachandran L. Sources of antibiotics: Hot springs. *Biochemical Pharmacology* **134**, 35–41 (2017).

5. Benaud N., Zhang E., van Dorst J., *et al*. Harnessing long-read amplicon sequencing to uncover NRPS and Type I PKS gene sequence diversity in polar desert soils. *FEMS Microbiology Ecology* **95**-4 (2019)