EDITORIAL

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Industrial microbiology. A new challenge

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Together with metallurgical processes, microbiology is the technological and scientific field that has been used from ancient times both to improve living conditions and to increase survival opportunities by transforming risks into challenges. After humans became sedentary, and agriculture began to transform food availability, acquiring new materials that either never existed before (metallurgy) or existed at very low levels (microbiology) became the impetus for a new human activity: industry. Industry has been usually defined as the art and ability to transform raw materials into new and useful products. Food was most likely one of the first products that humans tried to ensure. While agriculture gave humans the possibility of having enough food, weather and climatic conditions limited its year-round availability. Thus, the challenge was being able to maintain sufficient food stocks in good condition throughout the year, until the next harvest. Microbiology was involved in this process by chance and, as a result (probably after hundreds of failed attempts), bread, cheese, wine and beer have been consumed for thousands of years. In fact, yeast was used to produce beer in Sumeria before 7000 BC, and Assyrians already produced wine in 3500 BC. These beverages are obtained through the action of microorganisms, and the final products can be stored for longer periods than the original raw materials. Two main characteristics defined early industrial processes: (i) They appeared after a coincidental observation (i.e. the fermentation of sugar present in fruits or grains to yield alcohol), which human societies then gradually learnt to control and to make more profitable. (ii) Although processes derived from these observations were optimized and became increasingly profitable, knowledge of them was a result of experience, and the reasons why, e.g., fruit must turned into wine or milk turned into cheese, were not known.

Such was the state-of-the-art until the second half of the nineteenth century, when two events marked the beginning of industrial microbiology: (i) The scientific phenomena responsible for early industrial processes started to be understood and well known. Around 1860, Pasteur discovered the major role of yeast in the food and beverage industries. As a result, he has been considered the father of modern microbiology. The idea that microorganisms were living material that could be used as elementary chemical reactors became widely accepted. Thus, industrial microbiologists could address the same concepts as engineering chemists (especially energy and mass balances). (ii) The capability to control and make these processes much more profitable (including the use of more efficient microbial species or strains) increased. This capability derived from the recognition that the conditions at which microbial "machines" give an optimal yield are controlled, external ones (pH, temperature, pressure, feed flow) that do not affect the machine itself: the microorganisms used grow also naturally in the environment. Furthermore, all the processes focus on maintaining the status quo, trying to avoid variations that might affect the yield. Even today, some of the regulations for whisky and wine production are related to the need to use endogamic yeast. Therefore, mutation, degradation or contamination of the working microbial species are risks to be avoided.

That had been the situation until a few decades ago, and is the core of classic industrial microbiology [3]. Microbial processes are involved in food, pharmaceutical, fine-chemical, cosmetic, energy and new-material industries. It has been estimated that these processes move currently more than US$ 70 billion worldwide [1]. The replacement of petroleum-based fuels by yeast fermentation-obtained ethanol (bioethanol) will mean a new revolution in the energy market and it will fulfill environmental requirements. For several reasons, microbiological processes with industrial applications are usually much more advantageous than any other industrial processes, accounting for the strong continued interest in this field. First, the specific ability of a given microorganism to produce a particular molecule can be exploited. This molecule can be a secondary metabolite or, more directly, a by-product of microbial metabolism. While chemical industrial processes may yield the same product, the process is often more complex, involving more pathway steps, and/or mixed with some undesirable byproducts. Second, the molecules obtained from microorganisms are synthesized under mild

conditions, resulting in less energy and equipment costs compared with chemical synthetic processes. Nevertheless, industrial microbiology still has some limitations, due to the need of having the working microorganism fully operative and protected against mutation, other microbial contaminants, competitors, and environmental changes.

During the last few decades, molecular biology and subsequently genetic engineering have contributed to a better understanding of both the ultimate mechanisms involved in industrial microbial processes and the main conditions influencing them. For the first time, it has been possible to modify selectively and efficiently these microbiological machines; their natural abilities have been improved or new ones derived from other organisms (either microbes or even plants) have been added to them. As a consequence, these living machines have turned out to be more productive and more resistant against changes, and can thus be used for other new biochemical reactions.

Over the last 20 years, new or more efficient industrial processes involving microorganisms have been launched, yielding purer, less expensive products or substances not available using classical chemical methods. In general, it is now possible to: (i) convert secondary reactions into main metabolic pathways; (ii) optimize productions and yields; (iii) change the original metabolic pathways to allow the use of less expensive raw materials, or to obtain previously unknown molecules; and (iv) use the enantiomeric properties of enzymes to obtain new chiral molecules. The long list of products obtained by these methods increases every year, and many industrial areas are involved. The products most commonly obtained in industrial microbiology include:

- Pharmaceutical proteins (human interferon, epidermal growth factor and hemoglobin, antigens for hepatitis-B virus, stabilizers for erythropoietin and human chorionic gonadotropin) obtained from microorganisms such as *Saccharomyces cerevisiae*, *Pichia pastoris*, *Hansenula polymorpha* or *Agrobacterium tumefaciens*.
- Recombinant enzymes for industrial processes obtained from microorganisms. The industrial enzyme market for non-therapeutic uses, such as food, detergents, textiles, leather, pulp and paper industry reached US $2 billion in 2000 [2]. Microbial lipases are of special interest because of their stability in organic solvents and their lack of a requirement for cofactors, their broad substrate specificity and their high enantioselectivity. Lipolase™ from Novozyme, launched in 1994, is the first recombinant lipase; it was obtained by cloning the *Thermomyces lanuginosus* (formerly *Humicula lanuginosa*) lipase gene into the *Aspergillus orzyae* genome [4].
- Antibiotics, including biosynthetic penicillin V and natural penicillin G. Of the 12,000 antibiotics known in 1995, more than 20% can be produced by filamentous fungi. Biosynthetic and semisynthetic penicillins and cefalosporins have a market reaching US $15,4 billion.
- Inmunosuppresive agents, including cyclosporin A, obtained from *Tolypocladium nivenum,* or mycophenolate mofetil, from several *Penicillium* species.
- Hypocholesterolemic agents including lovastatin, obtained from *Aspergillus terreus*, and pravastatin, from *Penicillium citrium*, which have a market of US $15 billion.
- Antitumoral agents such as taxol, first discovered in plants but later transferred to and produced by *Taxomyces andreanae*; in 2000 it comprised 10% of total sales for Bristol Myers-Squibb, reaching US $1 billion [5].
- Mycotoxins including adrenalin inhibitors, estrogens and anabolic agents for cattle and sheep, or gibberellins used in brewing and malting industries.
- Pigments, including the carotenoid astaxanthin from *Phaffia rhodozyma*, and β-carotenoid from *Blakeslea trispora*, used in food and textile industries.
- Polyunsaturated fatty acids, including γ-linoleic acid from *Mucor circinelloides,* and arachidonic acid from *Mortierella isabellina*.

This voyage is only at its beginnings, and many challenges still face us. For example, the technology suitable to synthesize all these molecules in a less expensive, more efficient way, using carbon dioxide as the carbon source, water as the electron acceptor, and sunlight as the driving energy, is needed. Many scientists have tried to solve this equation for years, unaware that such a process namely, photosynthesis, already exists and has been used by photosynthetic organisms (many microorganisms and all plants) for millions of years. As a final example, the previously mentioned switch from petroleum-based fuels to bioethanol will mean a new revolution in the energy market, and will change significantly international commercial relationships. Nevertheless, this is only the first step towards the final goal: the hydrogen-based battery. Microbiology will no doubt take part in this task as well.

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