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Feature Article

"Recombinamers" as advanced materials for the post-oil age

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This work is dedicated to the memory of Prof. Antonio M. "Tony" Tamburro. His passion for science was only matched by his passion for life.

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ABSTRACT

Biotechnology offers powerful solutions to the challenges that arise during the design and development of new complex biomimetic materials to achieve specific biological responses. Recombinant DNA technologies, in particular, provide unique solutions in the biomaterials field, especially regarding the control of macromolecular architectures involving protein sequences with the aim of addressing the multiple functional requirements needed for biomaterials' applications. Here, elastin-like recombinamers are presented as an example of an extraordinary convergence of different properties that is not found in any other polymer system. These materials are highly biocompatible, stimuli-responsive, show unusual self-assembly properties and can include bioactive domains along the polypeptide chain. Applications of these engineered biomimetic polymers in nanotechnological systems, stimuli-responsive biosurfaces and tissue engineering will be discussed.

1. Introduction

Polymer science has clearly shown over several decades that macromolecules are excellent candidates for the creation of highly functional materials. As a result of the availability of thousands of different monomers and the multiple possibilities arising from their different combinations, polymer science has succeeded in producing a specific material for a particular application on many occasions, ranging from very simple materials for use as bulk commodities to highly sophisticated ones with special biomedical, engineering or nanotechnological uses. Very few other technical developments in history have shown the same rapid development and had the same deep impact on society as polymer science. The number of different technologies enabled by the existence of the appropriate polymer is amazing, and the crucial role of polymer science in the development of modern society and human well-being is unquestionable.

Most of the synthetic methodologies and the polymers we produce nowadays are, however, based exclusively on petroleum-derived chemicals. Although there is no consensus regarding how many oil reserves remain, it is clear that this resource is finite and that its price will continue to increase if we maintain our increasing rate of demand. Additionally, we would be well advised not to wait until the imminent exhaustion of our planet's oil reserves to reduce its use as a source of energy and plastics. Growing evidence that the recent increase in atmospheric CO_2 levels is causing a measurable modification of the global climate could, in the mid- to long-term, lead us to abandon, or at least drastically reduce, oil as our main source of raw materials for plastics [1]. Polymer science will therefore soon face a similar reduction in its dependence on oil to that currently being experienced by the energy sector.

Our current state of technological development and well-being cannot be maintained by sacrificing the expectations of future generations-sustainability must therefore also be a key objective in polymer science. However, we must be fully aware of the actual meaning of "sustainability". We are obliged to develop sustainable technologies that fulfill the needs of future generations. This does not mean that we must search for alternative and sustainable technological solutions, simply to maintain our current level of development. Therefore, with the degree of technical development that our grandparents enjoyed, our grandchildren will not be satisfied by a world in which polymers produced from renewable sources "only" match the performance of the "old" oil-derived plastics.

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The challenge that polymer science is currently facing must therefore be tackled from all sides. We, as polymer scientists, must develop technologies to change our current oil-dependence and unsustainability. This challenge must also be considered an opportunity to create a new polymer science which, in addition to being sustainable, will launch a technological revolution that will lead to new concepts, materials and products which will be more efficient, functional and than those we have today. Part of the aim of the present manuscript is to present evidence that this purpose is not just a utopian yearning for a better world and that some signs that this is possible may already be present.

Our level of technological development has been supported by a progressive abandonment of natural products and the extensive use of "synthetic" elements which, in terms of composition and concept, are far from being natural substances. Paradoxically, one of the most promising strategies for solving current problems is to reconsider natural products, or rather to introduce concepts imported from nature in our future synthetic materials and systems, and not only for the sake of sustainability. Thus, taking polymer science as an example, biology discovered long ago that macromolecules are the best option for obtaining highly functional materials. Relatively novel concepts in materials science such as hierarchical organization, mesoscale self-assembly or stimuli-responsiveness are common to many natural macromolecules such as proteins, nucleic acids or polysaccharides (or combinations of them). In fact, the slow but relentless process of natural selection has produced materials that show a level of functionality significantly more complex than that reached by synthetic materials. One of the best (and nicest) examples of this is the proteins. The proteins in living cells show an amazing set of capabilities in terms of functionality, ranging from the structural proteins, all of which show a significant ability to self-assemble, to the extraordinary enzymes, with their superior catalytic performance, and highly efficient molecular machines such as the flagellar rotary motor, etc. Natural proteins are usually large and very complex molecules which contain diverse specific functional groups that generate and promote self-assembly and function. Nature also makes use of different physical processes that allow directed and controlled organization from the molecular to the macroscopic level. In general, both local organization through functional chemical groups and the physical properties that give rise to order on larger scales provide the properties and functions that the biological systems require to function efficiently.

Nevertheless, the basis for all of this amazing functionality displayed by natural proteins seems to be based on one simple concept, namely a complex and completely defined primary structure. Protein biosynthesis in living cells occurs with an absolute control of the amino-acid sequence, from the first amino acid to the last, with a complete absence of randomness. Indeed, the need for such absolute control becomes dramatically apparent in some genetic disorders where the lack or substitution of just one amino acid in the protein leads to a complete loss of the original function, which can have dramatic consequences in patients with sickle cell anemia, phenylketonuria and cystic fibrosis [2]. If we want to create truly functional materials, we must therefore find a way to synthesise complex and completely defined macromolecules. This task, which is currently too difficult for even our most sophisticated chemical methods, occurs routinely in all living cells. One further characteristic of protein biosynthesis should be highlighted at this point, namely that the machinery for protein biosynthesis is extraordinarily flexible. Ribosomes are able to process and produce practically any amino-acid sequence stored in the information elements known as genes, which means that the flexibility of this process is essentially absolute. From a practical point of view, if we can therefore somehow control the information that genes deliver into the machinery, we can also control the biosynthesis process itself.

This idea also has remarkable precedents. In the last few years, significant effort has been dedicated to replacing petrochemical-based chemical processes with biological methods using renewable resources. Thus, fermentation processes for the production of biological monomers have been improved by numerous studies involving the metabolic engineering of microorganisms and the directed development of enzymes. Such microorganisms have been widely exploited for medical, agricultural, food and industrial applications. In addition, they have been engineered to produce recombinant proteins, amino acids and chemicals for use as drugs and biofuels [3,4]. For example, various monomers have been produced via different biological pathways, depending on the microorganism, from substrates such as succinic acid, lactic acid or some diols [5]. This process involves the whole metabolic and regulatory network together with fermentation, recuperation and subsequent purification processes.

The development of new technologies has made it possible to follow protein expression in cells and tissues through proteomics and it has allowed researchers to engineer proteins with new functions that lead to extraordinary technical applications. Nature has designed proteins with specific functional properties, such as the ability to self-assemble, recognition specificity or monodispersity, and scientists are now starting to exploit and enhance these properties in protein-based materials. Genetic and protein engineering provide us with the tools to precisely produce numerous protein-based polymers far above the current capabilities of synthetic polymer chemistry. These techniques allow us to synthesize protein chains with absolute control over their molecular mass, composition, sequence and stereochemistry. This is a key drawback of conventional chemical synthesis, where any increase in the complexity of the final molecule unavoidably leads to an almost exponential increase in the time and cost of the synthesis.

The use of recombinant DNA technologies to obtain protein-based polymers with total control of the randomness of the polymer sequence permits us to design the required functionalities of the final biomaterial in a highly precise manner. The success of engineered protein polymers in material applications will, however, depend on being able to obtain materials with specified physical and chemical properties. As an example of these approaches, we show here how elastin-like polymers (ELPs) play an important role in the synthesis of advanced materials, with a particular emphasis on biomedical and nanotechnological uses.

1.1. Genetic engineering of protein-based macromolecules

In the last few years, the application of powerful molecular biological methods has allowed the design and synthesis of new advanced materials almost at will. The use of the 20 naturally occurring amino acids in the design and production of genetically engineered functional protein-based macromolecules with specific or multifunctional properties offers practically infinite possibilities and a significant number of advantages. First, DNA technologies allow the introduction of tailored synthetic genes into the genetic make-up of a microorganism, plant or other organisms which induces the production of its encoded protein-based polymer as a recombinant protein [6,7]. These macromolecules offer the possibility to obtain materials with some of the complex properties found in natural proteins in combination with functions of particular technological interest that are not displayed in living organisms. Secondly, the degree of control and complexity attained by genetic engineering is clearly superior to that achieved by conventional chemical synthesis. These polymers, for example, are strictly monodisperse and can be obtained with molecular weights