C. R. Chimie 19 (2016) 143–147

Contents lists available at ScienceDirect

Comptes Rendus Chimie

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Account/Revue

Precision polymers with biological activity: Design towards self-assembly and bioactivity

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ARTICLE INFO

Article history:
Received 21 May 2015
Accepted 18 June 2015
Available online 21 January 2016

Keywords:
Self-assembly
Copolymers
Amphiphilic
Biopolymers
Bioactivity
Micelles

ABSTRACT

This short review aims at highlighting new trends in polymer science towards the design of bioactive and biofunctional materials by design. The recent development of controlled polymerization and post-modification methods together with efficient coupling strategies based on “click chemistry” approaches allows the preparation of highly precise polymer systems that combine the ability to self-assemble into well-defined and predictable structures, together with a pre-defined or molecularly encoded bioactivity (such as interaction, inhibition, recognition). Even if polymers have been used for many years in the field of biomaterials mostly because of their mechanical properties and inert character, we believe that a novel area is arising, where polymers will be at the center of innovation. Such highly precise polymer materials are believed to bring breakthrough technologies at the interface between materials science and biotechnology.

RÉSUMÉ

Cette courte revue a pour but de donner au lecteur un point de vue sur de nouvelles tendances qui émergent en science des polymères, dans le domaine des matériaux bioactifs et biofonctionnels. Les développements récents en polymérisation contrôlée, post-modification des polymères et de méthodes de couplage par « chimie click », en particulier, permettent aujourd’hui le design de polymères de précision capables de combiner dans leur structure macromoléculaire à la fois les informations pour s’auto-assembler de façon prédictible et contrôlée et des propriétés de bioactivité (interaction, inhibition, reconnaissance, etc.). Ainsi, et même si les polymères sont utilisés depuis de nombreuses années dans le domaine des biomatériaux, principalement pour leur absence de toxicité et leur furtivité, une nouvelle ère a commencé, où les polymères seront à l’origine des futures innovations de rupture à l’interface entre science des matériaux et biotechnologies.

1. Introduction

Polymers have become a major class of materials, with constant growth in their production and use over the last

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http://dx.doi.org/10.1016/j.crci.2015.06.012

few decades, mainly due to their remarkable mechanical properties, lightweight, low cost, and recycling capability. Polymer materials, that have smoothly replaced metals, ceramics, wood, *etc*. in many end products over the last fifty years, are now strategic compounds in the chemical industry. Polymers are currently found everywhere in our everyday life: *e.g.*, in the transport industry (car, aerospace, military…), in constructions, in the sport and leisure industries, in healthcare, and so on.

For many years, synthetic polymers have been obtained from the polymerization of one monomer, leading to *homopolymers*. In order to combine several properties in polymer materials, polymer mixtures can be synthesized. However, due to the strong chemical incompatibility between polymer chains, such a strategy is very limited due to the resultant macroscopic phase separation observed. *Copolymers*, resulting from the polymerization of two or more monomer units into a single chain, have been developed and have solved this problem. These can be statistical, block or grafted amongst the simplest structures. Due to continuous progress in the development of controlled polymerization methods, together with the evolvement of characterization methods down to the nanoscale and improvement of theoretical understanding, deep control of copolymers microphase separation and correlations with their macromolecular structure can now be performed. Remarkably, *block copolymers* can spontaneously self-assemble into micro- or nanostructures with controllable and predictable sizes, shapes and morphologies. As a result, block copolymers are seen nowadays as the most sophisticated polymer structures, allowing innovative approaches in materials science-related industries (*e.g.*, optics, electronics, energy, compliance) [1].

In the biomedical and biomaterials fields, due to their biocompatibility and biodegradability in the case of polyesters, polycarbonates or polypeptides for instance, polymers are widely used for many different tools, such as catheters, surgery plaques and screws, as well as scaffolds for tissue engineering or drug delivery [2]. For all these applications, their major asset is their inert behavior (stealthiness) towards the immune and reticulo-endothelial systems. However, even though polymers have already brought breakthrough technologies in medicine (*e.g.*, surgery, implants, delivery systems), allowing remarkable benefits for the patient, rather simple polymer structures have been used and developed so far. One can anticipate in a near future great improvement with more sophisticated polymers presenting integrated biological functions playing an active role in the final outcome (*e.g.*, full integration into biological tissues).

In order to progress towards this goal, a straightforward strategy in polymer design would be to explore polymers that can encode multiple functions and activity, thus mimicking natural polymers such as nucleic acids (DNA, RNAs), proteins, and glycans that are produced and used everyday in natural living systems. These are involved in a myriad of biological processes *in vivo*, in physiological or pathological circumstances, including among many others cell signaling and regulation. The level of precision in their chemical composition and structure exceeds by far what can be synthetically achieved nowadays. The latter is however critical for proper operation: for instance in the case of proteins, the control of the monomer sequence (namely the protein primary structure) is governing the protein conformation (secondary structure) and assembly (tertiary and quaternary structures) that are critical for the resulting bioactivity.

The aim of the present contribution is to highlight emerging synthetic strategies that we believe will bring significant benefit and breakthrough technologies in the biomedical or biomaterials areas. We will illustrate our thoughts with several chosen examples and do not pretend to provide the reader with an exhaustive view of this research field, but rather with a personal point of view. Our idea is especially to focus on polymer systems that have been precisely designed to interact with biological microenvironments and used to get a deeper understanding of their interaction mechanism or to establish clear structure–activity relationships. We will illustrate several synthetic approaches that are being developed in this context, including (Fig. 1): 1) synthetic polymer chemical modifications, 2) design of biohybrid macromolecules, and 3) recombinant production of bio-engineered polymers.

2. Bioactive properties *via* synthetic polymer chemical modifications

For many years, bioactive polymers were fully biocompatible such as hyaluronan widely used in regenerative medicine strategies or those presenting non-fouling or protein-repellant properties such as poly(ethylene oxide) PEO or poly(ethylene glycol) PEG used in drug delivery. The propensity of PEG polymer chains or brushes at the interface to avoid/limit adsorption of plasmatic proteins has been studied for many years. The term “pegylation” is even popularly accepted, implying the PEG conjugation as a “magic” approach to provide stealth properties to any system, which is absolutely wrong! One has not to forget the basic principles of physics beyond the effect of “pegylation” that are a high hydration rate and optimal entropic repulsion of PEG chains [3]. In the same line, aiming at designing surface–active materials, polymers with antibacterial properties have been developed. Antimicrobial polymers can provide protection against a variety of pathogenic bacteria, by analogy with their peptide analogs that are part of the innate immune system. Over the past decade, there have been significant efforts in developing antimicrobial polymers that could be used as bioactive surfaces or as intravenously administered antibiotics [4]. Li and Yang have proposed promising examples of the use of synthetically modified cell-penetrating peptides (CPPs) resulting in self-assembled nanoparticles capable of crossing the blood–brain barrier and suppress bacterial growth in infected brains [5]. However, despite considerable investment in the pharmaceutical and biotechnology industries, this strategy drudges to come true, mainly due to the lack of understanding of the underlying mechanisms involved in living systems. Learning how to program synthetic polymers with the appropriate chemical information to effectively capture the biological activity of peptides or proteins will be critical to better understand their mechanisms. For instance, Tew and coll. recently developed an