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Account/Revue

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

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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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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

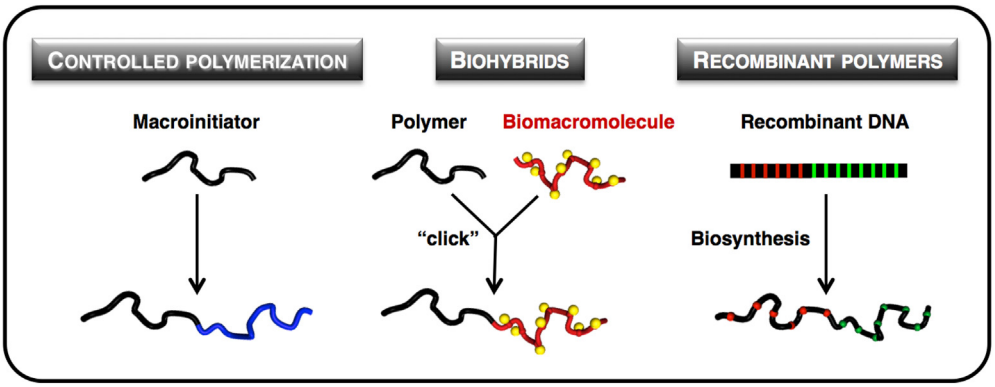

Fig. 1. Strategies to prepare bioactive block copolymers.

elegant synthetic strategy based on the controlled ring opening polymerization of norbornene-derivatives to study the balance between charge and hydrophobic interactions that are involved in CPP mechanisms [6]. The development of such synthetic tools that can facilitate establishing relevant structure–activity relationships is particularly important in the field, as bacterial resistance is becoming a huge public health concern.

In the field of drug delivery, nanoparticles resulting from the self-assembly of amphiphilic block copolymers are proving to be compelling. This field benefited from the most advanced synthetic developments. Amphiphilic and stimuli-responsive polymer nanoparticles have been designed in the last decade, using every existing controlled polymerization method. The incorporation of building blocks with tunable properties under different specific conditions (*e.g.*, pH, enzyme, temperature, magnetic field, ultrasound, X-rays) has allowed the design of many different systems capable of releasing their payload in a controlled manner [7]. Current developments mainly aim at targeting specific cells, cellular microenvironments or organs, en route to personalized medicine. Targeting properties can indeed be subsequently endowed to self-assembled polymer nanoparticles by surface grafting of biologically validated receptor-specific ligands (*e.g.,* saccharides, peptides, full antibodies or fragments, aptamers, low-molecular weight organic molecules) [8]. However, this strategy involves block copolymer synthesis, self-assembly processing and post-modification functionalization with the targeting moiety. Even though such an approach is very smart and some systems are currently in phase III clinical trials [9], one can anticipate that scalability and batch-to-batch reproducibility may become tricky when multiple functionalities have to be independently incorporated into self-assembled nanoparticles. One of the critical point is to develop synthetic methods that are precise enough to clearly enable structure–activity relationships with perfect reproducibility and useful foundation that can be transferred to any other polymer system.

3. Biohybrid macromolecules

In order to overcome the previously mentioned limitations, one particularly relevant approach consists in designing materials that encode both self-assembly and biological functionalities at the molecular level, similarly to naturally occurring molecules that form biological self-assemblies. Especially interesting are biohybrid macromolecules that combine useful features of block copolymers (*i.e.,* self-assembly propensity) with those of natural and bioactive biopolymers, such as polypeptides, proteins, polysaccharides, and glycans.

Many natural macromolecules have already been identified for their intrinsic biological activity, among which peptides and proteins represent a wide class. Polymer-peptide biohybrids can be obtained by covalently attaching biologically relevant peptides to synthetic polymer chains to form amphiphilic polymer-peptide conjugates. The latter thus possesses self-assembly properties arising from the amphiphilic character and those afforded by the peculiar nature of the polymer block, while the peptide moiety confers surface bioactivity to the resulting self-assembled micellar or vesicular structures [10]. Our group has also contributed to this area, with the design of Tat-*b*-PTMC biohybrids, featuring a biocompatible poly(trimethylene carbonate) (PTMC) polymer segment and the Tat_{47-57} sequence from HIV-1 transcription transactivator protein (TAT), with well-established cell-penetrating properties, in order to access nano-assemblies specifically dedicated to cellular internalization. Presenting a Tat-rich corona, strongly positively charged, the resulting micelles not only presented notable cell transduction ability, but also substantial toxicity. Micelles with controlled sizes and Tat surface density were designed to point out the impact of micellar engineering on the surface of nanoparticles, and to clarify their internalization mechanism [11].

Oligosaccharides and polysaccharides represent also an interesting class of bioactive biopolymers, even if their synthesis, purification and chemical modification are complex. Among them, chitosan, heparin and hyaluronan are the most studied [12]. Chemical modifications, mostly *via* side-chain grafting, allowed modulation of their activity and solubility, allowing the formation of self-assembled structures in some cases. Glycopolymer synthesis has also been widely developed to introduce low-molecular weight carbohydrate epitopes on polymer chains obtained by living/controlled polymerization methods [13]. Only a few studies mentioned the use of polysaccharide-block

copolymers despite their outstanding self-assembly properties. Kalin *et al.* actually envision that polysaccharide-block copolymers shall constitute an excellent alternative to polysaccharide-protein conjugates that are developed as immunizing antigens to produce carbohydrate-directed antibodies or as antigens in immunoassays [14]. More recently, efficient coupling strategies, namely "click chemistry", allowed the design of precise amphiphilic linear diblock copolymer structures with oligosaccharides. Hyaluronan has been mainly studied because of its ability to recognize CD44 glycoproteins that are involved in many diseases, including cancer and inflammation. Hyaluronan has especially been coupled to poly(γ-benzyl glutamate) *via* Huisgen cycloaddition [15] and to poly(D,L-lactide-*co*-glycolide) *via* peptide coupling [16]. In both cases, *in vitro* and *in vivo* targeting ability of the resulting nanoparticles has been demonstrated on CD44-expressing cells, together with encouraging tumor regression preclinical proofs of concept. These results, demonstrated the relevance of the concept of "self-targeting nanoparticles", implying that the targeting property is directly encoded into the polymer, by using a hydrophilic segment that has simultaneously the capacity to provide colloidal stability and to target specific cellular receptors. Such a concept can potentially be extended to any other oligosaccharides, peptides, proteins or nucleic acids that can provide at least two functions (colloidal stability and bioactivity), the bioactivity being of various nature (*e.g.*, targeting, inhibition, activation or agonist/antagonist properties for a receptor).

Nevertheless, even though such a strategy is very elegant, promising and even currently in pharmaceutical development [17], it is limited to biomolecules with sufficient hydrophilicity, that allow chemical coupling to another polymer segment using high efficient coupling strategies and retain their bioactivity after conjugation. Again, the development and optimization of such polymer-based biohybrid systems will require significant efforts in order to guarantee a perfect reproducibility due to the intrinsic polydispersity of polymer chains and possibly the biological synthons.

4. Recombinant polymers

To obviate from the previous limitations, material scientists have started in the past decade to turn towards protein-engineering techniques and to produce *de novo* protein-like polymers from recombinant methods. Mainly constituted from repeating peptide sequences, these macromolecules have received different names from their investigators such as "protein polymers", "recombinant polymers", or even "recombinamers" [18]. The principle is based on the design of an artificial gene encoding for the complete macromolecule, including structural polymeric sequences and specific peptide motifs featuring the desired biological activities (receptor binding, pH-responsive, cross-linking, enzyme-responsive motifs, *etc.*) placed at appropriate locations into the protein polymer structure. Among the significant advantages of the method are: *i*) the great freedom in material design arising from the infinite combinations of amino acid building blocks; *ii*) the monodispersity and perfect control over sequence and length in contrast with chemically synthesized polymer materials; *and iii*) the scalability to large and/or continuous batches with a perfect reproducibility. Importantly, such a precision in the polymer structure enables perfectly reliable structure–bioactivity relationship studies.

Over the last decade, several classes of recombinant polymers have been developed and studied, mostly elastin-like polypeptides (ELPs), silk and silk-like proteins (SLPs) and combination thereof, namely silk-elastin-like protein polymers (SELPs), with the aim of designing bioactive nanoparticles and hydrogels [19]. With the specific aim of developing drug delivery systems, most recombinant polymers studied are based on the pentapeptide repeat [-VPGXG-] derived from the hydrophobic domain of elastin. These ELPs indeed present a unique *lower critical solution temperature* (*LCST*, also designated as ITT or T_t) that has a dual benefit: firstly, the *LCST* constitutes a means to control the self-assembly process, a critical issue when working with peptide and protein-materials; secondly, the *LCST* greatly facilitates isolation and purification of the protein product out of the protein lysate soup. Since the first diblock ELP, featuring consecutive hydrophilic and lipophilic blocks, self-assembled into nanometer-sized micelles described by Conticello and coworkers [20], significant advances have been made. Comprehensive studies on ELP block copolymer design have evidenced critical parameters (hydrophilic-to-hydrophobic block ratio, copolymer size, distribution of polar and apolar regions along the polymer chain, cross-linking) to obtain stable monodisperse core-shell nanoparticles [21]. Temperature responsiveness has been identified as a hallmark to trigger site-specific targeting and accumulation of ELPs both *in vitro* and *in vivo* [22]. The possibility to increase material complexity and to display bioactive peptide motifs onto the surface of ELP nanoparticles has also been demonstrated. Chilkoti and coll. for instance described a recombinant diblock ELP preceded by the $\alpha_v\beta_3$ integrin-targeting linear GRGDS sequence turning from a low-avidity state as an unimer into a multivalent high-avidity ligand above its critical micelle temperature (*CMT*) [23]. Using ELPs as drug carriers, high molecular weight hydrophilic ELPs have also been conjugated at their C-terminal end to hydrophobic doxorubicin derivatives, inducing self-assembly into a drug-rich core surrounded by a soluble protein corona. *In vivo*, the drug-nanoparticle formulation had a fourfold higher maximum tolerated dose (MTD) than doxorubicin and induced nearly complete tumor regression after a single systemic dose [24].

5. Conclusions

En route for highly functional biomaterials and nanodevices, amphiphilic block copolymer structures are gaining in complexity and precision in their macromolecular structure. In addition to their intrinsic self-assembly properties, they may include stimuli-responsiveness possibly in addition to relevant biological functions. In order to be used as model systems for the establishment of structure–bioactivity relationships, they however suffer from some deviation in their chain-to-chain structure and molar masses. If not necessarily an issue for the final

purpose, there is still a critical need to develop perfect polymer structures during the development stages, for better understanding and rational design. The recent progress in precision and sequence-controlled polymerization methods may be an interesting approach, even though limited so far to certain synthetic monomers [25]. DNA technologies and DNA-templating polymerization methods can also present a high level of precision [26], but are requiring the design of specific templates and monomers with some limitations. The latest development – and certainly one of the most promising and realistic for future research and technology transfer – involves the production of protein-like polymers by protein engineering. Recombinant DNA techniques allow fine-tuning of amino acid positioning within the final polymer product, thereby enabling the incorporation of specific biological properties (including degradation), in addition to imparting intrinsic biocompatibility. We foresee that protein-polymer materials, with greater potential to echo the functional complexity of native proteins, are prone to substitute for traditional, synthetic polymers, highly regarded in the last-century. Their biocompatibility and biodegradability into natural metabolites (amino acids) are obvious advantages towards biomedical applications. As recombinant protein polymers do not require specific complex post-translational modifications, their large scale-production can be performed in *E. coli* at a lower cost considering material's complexity in contrast with most recombinant proteins currently used in the clinics (antibodies) that require mammalian cell cultures. The perfect batch-to-batch reproducibility of the material structure obtained by such a process is also a key parameter for future clinical and industrial developments. As for every technological breakthrough, this approach mainly concerns the design of high value-added materials. The potential impact is profound for biomedical applications particularly in the area of drug delivery, but also in biomaterials, tissue engineering and regenerative medicine. We have no doubt that the published literature in this domain, which has matured dramatically in the last 5 years, will continue to exhibit tremendous growth in the next few years involving a wide range of scientific communities from polymer science to colloidal science.

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