Biotechnology Advances 32 (2014) 952–970

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Bionanoconjugation for Proteomics applications — An overview

João Pinto da Costa [a,1], Rui Oliveira-Silva [a,1], Ana Luísa Daniel-da-Silva [b,*], Rui Vitorino [a,*]

[a] Mass Spectrometry Centre, QOPNA, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
[b] CICECO, Aveiro Institute of Nanotechnology, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 15 March 2014
Accepted 26 April 2014
Available online 22 May 2014

Keywords:
Nanoproteomics
Bioconjugates
Nanoparticles and nanomaterials

ABSTRACT

Formed as an interdisciplinary domain on the basis of Human Genome Project, Proteomics aims at the large-scale study of proteins. The enthusiasm that resulted from obtaining the complete human genetic information has, however, been chastened by the realization that this information contributes little to the comprehension and knowledge of the expressed proteins. In the wake of this realization, the Human Proteome Project (HUPO) was founded, which is a global, collaborative initiative, aiming at the complete characterization of the proteins of all protein-coding genes. Nonetheless, the rapid detection of these molecules in complex biological samples under conditions considered to be of clinical relevance is extremely difficult, requiring the development of very sensitive, robust, reproducible and high throughput platforms. Nanoproteomics has emerged as a feasible, promising option, offering short assay times, low sample consumption, ultralow detection and high throughput capacity. Additionally, the successful synthesis of biomolecules and nanoparticle hybrids yields systems which often exhibit new or improved features. Herein, we overview the recent advances in bioconjugation at the nanolevel and, specifically, their application in Proteomics, discussing not only the merits and prospects of Proteomics, but also present day limitations.

Contents

* Corresponding authors at: Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal. Tel.: +351 234 370 700.
E-mail addresses: ana.luisa@ua.pt (A.L. Daniel-da-Silva), rvitorino@ua.pt (R. Vitorino).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.biotechadv.2014.04.013
0734-9750/

Introduction

Within Nanotechnology, a new field of research has emerged that has drawn increasing interest in the past few years. Nanobiotechnology — or Bionanotechnology — can be defined as a field standing at the intersection between nanomaterials and biotechnology (Bagchi et al., 2012; Gazit, 2007), and, generally, it is considered as having two basic goals (Sapsford et al., 2013): a) using the intrinsic properties — such as catalytic, structural and specific binding properties — of biomolecules in the assembly of hybrid materials that show new or improved characteristics and b) the utilization of the unique properties of the nanomaterials (NMs) within a biological setting, such as using nanoparticles (NPs) for in vivo imaging (Gonçalves et al., 2012) or localized drug delivery (Hartmann et al., 2013). In Table 1, we provide an overview of some of the nanobioconjugates already developed. It should be noted, however, that, due to the recent explosion of interest in these compounds, such description could not but be invidious. Magnetic nanoparticles (MNPs), such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are the most commonly used nanomaterials, offering controllable size and the ability to be externally manipulated (Santhosh and Ulrih, 2013). For example, Bystrzejewski and co-workers successfully controlled the diameter and magnetic properties of carbon-encapsulated iron nanoparticles (Bystrzejewski et al., 2013) while Li et al. (2007b) were able to coat Fe_3O_4 particles with alumina by controlling the formation thin carbon layers resorting to the hydrothermal reaction of glucose. Additionally, such particles can be easily functionalized with other components. For instance, different poly(amino acids) have been used for the direct surface modification of MNPs aiming at the synthesis of functional magnetic resonance (MR) probes (Yang et al., 2013). With the same goal in sight, polymers, such as polyethylene amine and polyethylene glycol, have also used for the coating of iron oxide nanoparticles (Schweiger et al., 2011). The team led by Somsook described the development of an enhanced catalyst for the selective oxidation of benzyl alcohol by using MNPs with organometallic compounds (Kamonsatikul et al., 2012). Antibodies (Rosen et al., 2012) and enzymes (Kumar et al., 2012) have also been used in the modification of magnetic nanoparticles, showing potential clinical relevance in cancer theranostics. This versatility has opened the window for the application of MNPs in the fields of proteomics and peptidomics (Agrawal et al., 2013; Ray et al., 2011; Tyan et al., 2013). Although MNPs are the most commonly used type of NPs in bioconjugation, other particles have also been explored for this purpose, namely, gold nanoparticles, due to their optical properties and enhanced capability in adsorbing biomolecules (Lee et al., 2014).

In this review, we intend to give an updated overview of the different types of bioconjugation at the nanoscale that have been developed, as well as their potential applications in numerous fields of research. Simultaneously, we will attempt to give a comprehensive outline of the limitations of such methodologies, while also looking at the future prospects for this emerging technology.

Concepts and early steps

Before proceeding, however, it is important to define what constitutes a "nanobioconjugate". Perhaps one of the first successful uses of such particles in modern days was described by Fawell et al. (1994). In their work, the authors cross-linked *Tat* peptides to β-galactosidase, horseradish peroxidase, RNase A, and domain III of *Pseudomonas* exotoxin A (PE). By monitoring the uptake colorimetrically or by cytotoxicity, they showed that *Tat* chimeras were effective on all cell types tested, with uptake occurring in all cells. This work evidenced that *Tat*-mediated uptake could allow for the therapeutic delivery of macromolecules previously thought to be impermeable to living cells. However, the first scientifically described nanobioconjugate is assigned to Helcher, who, in 1718, described the use of boiled starch in gold colloids for enhancing their stability (Helcher, 1718). It is possible, then, to define a nanobioconjugate as a nanomaterial at the submicrometer level that is deliberately interfaced with a biological molecule (or fraction of a biomolecule). Spasford and colleagues further defined a nanobioconjugate as being intentionally produced at the nanoscale, showing discrete functional or structural parts arrayed on its surface or internally (Sapsford et al., 2013) and displaying unique properties or compositions that may not occur in the same material in the bulk scale (Kreyling et al., 2010). Although this definition is consistent with the vast work carried out and summarized in Table 1, what constitutes a NM has been the subject of much debate (Joachim, 2005; Kreyling et al., 2010). Initially, it was considered as a NM any intentionally produced material with at least one dimension <100 nm. Recently, agencies have proposed more generally accepted definitions and terminology, sustaining, however, the upper limit of 100 nm in at least one of the dimensions (ASTM, 2006; ISO, 2008, 2011). Nonetheless, it should be noted that this upper limit is not valid for all NMs (Sapsford et al., 2013). Others consider that novel size-dependent properties alone, rather than particle size, should be the primary criterion in any definition of NPs (Auffan et al., 2009; Skocaj et al., 2011). Such definitions should be carefully considered, as there are regulations and legal restrictions that must be respected (Brayner et al., 2012; EPA, 2010; SCENIHR, 2010). For the purpose of this review, we will consider as nanomaterials any intentionally produced material with at least one dimension inferior or close to 100 nm.

General applications of nanomaterials

The innate properties of nanomaterials, and, in particular, nanoparticles, make them especially suited to be used as biomolecular composites. They exhibit unique size-dependent physical, electronic, optical and chemical properties (Sapsford et al., 2013) that can contribute to the resulting conjugate. These include the size-tunable photoluminescence of quantum dots (Zhang et al., 2013c), the Plasmon resonance of gold nanoparticles (Chen et al., 2014), the electrical and mechanical properties of carbon NMs (Zhang et al., 2013a) or the enhanced magnetic moment and catalytic properties of magnetite core–shell NPs (Amarjargal et al., 2013). Nanoparticles also exhibit high surface-to-volume ratios, providing a high reactive surface available for the display of multiple biological components at their surface. These *biologicals* can potentially be different and, thus, may contribute to enhanced multifunctionality (Sapsford et al., 2013). NPs have also been described as carriers for insoluble materials, including drugs (Guo and Huang, 2014) and radioactive isotopes (Di Pasqua et al., 2013), acting as shields and avoiding chemical and/or photodegradation of such compounds. However, the opposite may be also intended: NPs have been designed to undergo gradual degradation in vivo, usually intended for the controlled localized release of drugs (Brannon-Peppas and Blanchette, 2012; Elzoghby et al., 2012; Panyam and Labhasetwar, 2012). As Sapsford et al. (2013) highlight, when considered cumulatively, such properties make nanoparticles an interesting and promising platform for the development of theranostic agents, i. e., designed bionanoconjugates capable of numerous tasks, such as active sensing (Szymanski and Porter, 2013), diagnostics (Sukhanova et al., 2012), tumor-targeting (Conde et al., 2013), and drug (Elzoghby et al., 2012) or image contrast agent (Mi et al., 2014) delivery. As the properties of these materials are better understood and their synthesis methodologies are improved — tackling numerous issues for large scale production, such as the control of particle size and growth (Thorat and Dalvi, 2012) — the vast scope of applications of NMs and their bioconjugates will surely increase.

Nanomaterials are particularly interesting for proteomics applications, as they exhibit ideal characteristics affecting, namely, biocatalytic reactions, such as mass transfer resistance, effective enzyme loading and large surface area (Cipolatti et al., 2014).