Biotechnology Advances 32 (2014) 679–692

Contents lists available at ScienceDirect

Biotechnology Advances

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

Research review paper

Interaction of stable colloidal nanoparticles with cellular membranes

Morteza Mahmoudi [a,b], Jie Meng [c], Xue Xue [c], Xing Jie Liang [c], Masoud Rahman [d], Christian Pfeiffer [e], Raimo Hartmann [e], Pilar Rivera Gil [e], Beatriz Pelaz [e], Wolfgang J. Parak [e,f], Pablo del Pino [e,f], Susana Carregal-Romero [e,g], Antonios G. Kanaras [h], Subramanian Tamil Selvan [i,j,*]

[a] Department of Nanotechnology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[c] Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanosciences and Technology of China, Beijing 100190, China
[d] Department of Chemical Engineering and Materials Science, University of California Davis, CA 95616, USA
[e] Fachbereich Physik, Philipps University of Marburg, Renthof 7, D-35037 Marburg, Germany
[f] CIC biomaGUNE, Paseo Miramón 182, 20009 San Sebastián, Spain
[g] Andalusian Center for Nanomedicine and Biotechnology (BIONAND), Andalusian Technological Park, C/Severo Ochoa, 35, 29590 Campanillas, Málaga, Spain
[h] Institute for Life Sciences, Physics and Astronomy, Faculty of Physical and Applied Sciences, University of Southampton, Highfield, Southampton SO17, 1BJ, United Kingdom
[i] A*STAR Institute of Materials Research and Engineering (IMRE), 3 Research Link, Singapore 117602, Singapore
[j] National University of Singapore, Division of Bioengineering, Faculty of Engineering, 7 Engineering Drive 1, Singapore 117576, Singapore

ARTICLE INFO

Available online 19 December 2013

Keywords:
Nanoparticle
Colloid
Cell membrane
Receptor
Protein corona
Targeted delivery

ABSTRACT

Due to their ultra-small size, inorganic nanoparticles (NPs) have distinct properties compared to the bulk form. The unique characteristics of NPs are broadly exploited in biomedical sciences in order to develop various methods of targeted drug delivery, novel biosensors and new therapeutic pathways. However, relatively little is known in the negotiation of NPs with complex biological environments. Cell membranes (CMs) in eukaryotes have dynamic structures, which is a key property for cellular responses to NPs. In this review, we discuss the current knowledge of various interactions between advanced types of NPs and CMs.

Contents

* Corresponding author at: A*STAR Institute of Materials Research and Engineering (IMRE), 3 Research Link, Singapore 117602, Singapore. Tel.: +65 6874 5249; fax: +65 6774 4657.
E-mail addresses: subramaniant@imre.a-star.edu.sg, biests@nus.edu.sg (S. Tamil Selvan).

0734-9750/$ – see front matter
http://dx.doi.org/10.1016/j.biotechadv.2013.11.012

1. Introduction

The cell membrane (CM) is a biological barrier that separates the interior of cells or organelles from the outside environment, preserving the local chemical composition and most importantly, playing an active role in the negotiation with foreign macromolecules including nanoparticles (NPs) and other biologically relevant components. It is a lipid-based sheath that envelops the cell, encloses the cytoplasm, and creates a selectively permeable barrier. The CM, also known as the plasma membrane, has a crucial significance to the life of cells (Zhang et al., 2012a). In addition, the CM of each cell type has its fingerprint characteristics, which may be used for differentiation of stem cells. More specifically, stem cells seeded on the cell-imprinted substrates (with CM topography of such mature cells) could be driven to adopt the specific shape and molecular characteristics of the CM types, which had been used as template for cell-imprinting (Mahmoudi et al., 2013a). The CM must retain molecules such as DNA, RNA, a variety of proteins and molecules that are essential for life from dissipating away, while keeping out foreign molecules that might damage or destroy the cell's contents. On the other hand, it must be selectively permeable to certain ions (such as Na^+ and K^+ for the creation of action potentials in electrically excitable cells) or organic molecules such as nutrients. In this way, the CM is involved in many important cellular processes such as signal transduction, molecular transportation, and cell communication (Anitei and Hoflack, 2012). The first interaction of NPs with cells occurs at the CM and is critically dependent on the physicochemical properties of the NPs (*e.g.* composition, size, shape, charge, surface roughness/smoothness, and surface chemistry) (Fischer and Chan, 2007; Rauch et al., 2013; Zhao et al., 2011). Importantly, the surface of NPs (*e.g.* charge, hydrophobicity, curvature, and stiffness) ultimately determines how NPs interact with physiological macromolecules from the physiological pool (largely dependent on the local bio-environment) and with the CM. The effect of protein corona on the biological fate of NPs is discussed in detail (Mahmoudi et al., 2011a).(See Table 1.)

In physiological environments, the outer shell of NPs can be greatly modified by the adsorption of proteins, *i.e.* the protein corona, which typically will form the interface between NPs and the CM (Walkey and Chan, 2012). Thus, for a detailed study of these interactions, highly defined NPs (Rivera-Gil et al., 2013) and well characterized CMs are needed. Herein, unless otherwise specified, we will refer to different NPs, which encompass an inorganic core and a hydrophilic coating layer, purposely derivatized to avoid non-specific interactions with proteins, for instance. We also highlight the concept of typical hybrid NPs, while addressing the topic of the interaction of inorganic NPs and CMs, wherein the inorganic NPs are functionalized with biocompatible coatings and/or serum biomolecules.

1.1. Importance of the physicochemical properties of NPs and their interaction with CMs

The interaction of NPs with CMs is indispensable for many applications in imaging, diagnostics, drug delivery, and therapy. The interplay between NPs and CMs is mainly governed by the nanoengineering of the outermost hydrophilic shell of NPs. Nowadays, many synthetic routes have been established towards the design of NPs (Parak, 2011) with controlled composition, size, shape, charge, and surface functionalization (Cortie and McDonagh, 2011; Day et al., 2010; Goesmann and Feldmann, 2010; Ibanez et al., 2012; Perrault and Chan, 2009; Sau and Rogach, 2010; Xia and Halas, 2005) with excellent colloidal stability and biocompatibility (Bartczak and Kanaras, 2010; Kanaras et al., 2002; Liu et al., 2008; Zhang et al., 2011a, 2012b). However, under physiological conditions, the inorganic NP core may undergo corrosion leading to the release of toxic ions (*e.g.* due to the insufficient shielding of coating materials). Also, coatings can detach from the NP's surface. These two examples can impede the potential bioapplications of certain NPs (Pelaz et al., 2013).

The size of NPs has a significant effect on cellular interaction and uptake (Rejman et al., 2004). NPs whose sizes are smaller than the thickness of the lipid bilayer (~5 nm) may exhibit bilayer insertion, leading to the disruption of the membrane (Yang and Ma, 2010). While the size of NPs is critical for pore formation in the CM, the shape (*i.e.* aspect ratio, curvature radius, *etc.*) can also play an important role as it defines the contact surface between NPs and the CM. The properties of the organic coating of NPs (*e.g.* charge, hydrophobicity, and structure) can be also critical towards defining their interplay with CMs. Ultimately, the hydrophilic coating on NPs determines the colloidal stability and reactivity with biomacromolecules or components of the CM. A superior colloidal stability of the NPs can be achieved by different coating methods, which is highly indispensable for a variety of applications. The most common functionalization methods of NPs include the coating by biocompatible silica (Fischer and Chan, 2007; Rauch et al., 2013;

Table 1
Some delivery approaches available for NPs.

Internalization pathway[a]	Mediated by	Comments	Ref.
Using ligands	i) Cell penetrating peptides (CPP)	Up to 100-fold more uptake than equivalent "bare" NPs	Child et al. (2011), Dejardin et al. (2011), Chaudhary et al. (2013), and de la Fuente and Berry (2005).
	ii) Polycation ligands	Used typically for gene transfection	Kievit et al. (2009), Mykhaylyk et al. (2012), and Howard (2009).
	iii) Coated NPs	Endocytosis; pinocytosis (receptor independent) in macrophages	Buono et al. (2009), and Walkey et al. (2012).
Magnetofection	Magnetic fields	Magnetic force is used to pull magnetic NPs inside cells	del Pino et al. (2010), and Child et al. (2011).
Electroporation	Permeabilization of CM using electric fields	*In vitro* method for transforming cells	Lin et al. (2009).
Microinjection	Micro-needle assisted delivery	Single cell studies	Candeloro et al. (2011).
Photothermal nanoblade delivery	Polymeric imidazole	High throughput delivery into live cell cytoplasm	Lee et al. (2012).
Microfluidic device	Tubulin	Tubulin-QD conjugates delivered into the cytoplasm of HeLa cells	Xu et al. (2012).

[a] List of common techniques used for facilitating the internalization of NPs inside cells.