Toxicology and Applied Pharmacology 299 (2016) 53–57

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

The concept of bio-corona in modulating the toxicity of engineered nanomaterials (ENM)

Dana Westmeier, Roland H. Stauber, Dominic Docter *

Department of Nanobiomedicine/ENT, University Medical Center of Mainz, Langenbeckstr. 1, 55101 Mainz, Germany

ARTICLE INFO

Article history:
Received 11 September 2015
Revised 5 November 2015
Accepted 16 November 2015
Available online 22 November 2015

Keywords:
Corona
Nanotoxicology
Nanomedicine

ABSTRACT

Besides the wide use of engineered nanomaterials (ENM) in technical products, their application spectrum in biotechnology and biomedicine is steadily increasing. In complex physiological environments the physico-chemical properties and the behavior of nanoparticles (NPs) are challenging to characterize. Biomolecules rapidly adsorb to the nanomaterial, leading to the formation of the protein/biomolecule corona, which critically affects the nanomaterials' (patho)biological and technical identities. This formation can trigger an immune response and affect nanoparticles' toxicity and targeting capabilities. In this review, we provide a survey of recent findings on the (protein)corona-nanoparticle interaction and discuss how the corona modulates both cytotoxicity and the immune response as well as to improve the efficacy of targeted delivery of nanocarriers.

1. Introduction

Since 2004 “nanotoxicology” has emerged an autonomous field with an explosive growth. As illustrated in Fig. 1, querying the PubMed database with the search term ‘nanotoxicology’ reveals that more than 238 reports have been published on this topic by September 2015 (in 2004 only two reports were found). Such developments are influenced by the increasing exposure of humans and the environment to nanomaterials (NM). The ability to create nanomaterial in a wide variety of different combinations concerning their chemistry, shape, size and surface properties led to the concentration of the nanotoxicological aspects regarding these NM characteristics. Although, due to their high surface energy, NMs adsorb (bio)molecules upon contact with any kind of biological environment, consequently forming the so-called (bio)molecule corona, the role of this corona in toxicological aspects has been completely neglected so far (Docter et al., 2015a; Nel et al., 2009). As the topic of this mini-review is about the “the concept of the bio-corona”, we again inquired the PubMed database with the search terms ‘nanotoxicology’ AND ‘corona’. From 2004 to 2007 we found zero reports and by September 2015 only 14 studies were published on this topic (Fig. 1). In this mini-review we will introduce you to the history and the importance of the biomolecule corona, on its impact on biomedical applications as well as its influence on the still young field of nanotoxicology.

2. The corona concept

The applications of engineered nanomaterials (ENMs) are not only increasing in technical products but also more and more in biotechnology and biomedicine (Docter et al., 2015a; Reese, 2013; Webster, 2013; Docter et al., 2015b; Setyawati et al., 2015). Thus, the ‘marriage’ of nanotechnology with biomedicine defines one of the most exciting and cross-disciplinary developments over the last decade (Reese, 2013; Webster, 2013). Nanomedicine is the field of science devoted to the medical application of ENMs. Recent years have been a surge in the development of nanomaterials as therapeutic and diagnostic agents, paralleled by major advances in the development of nano-sized delivery systems for targeted drug administration. The manipulation of ENMs' physico-chemical features opens up new horizons to rationally design a variety of clinically relevant applications like drug delivery, in vitro diagnostics, imaging nanoprobes, contrast agents and photodynamic therapy agents (Qian et al., 2008; Helou et al., 2013). Moreover, with the advent of the concept of so called ‘personalized medicine’, the field has started to grow producing a huge variety of different (multi-) functional ENMs (Muthu et al., 2014). Such developments will also lead to an increasing exposure of humans and the environment to ENMs. In this scenario, it is important to understand the interactions occurring at the interface between ENMs and biological components in order to predict the fate of (injected) ENMs. Due to their high surface energy, ENMs adsorb (bio)molecules upon contact with biological and/or abiotic environments, forming the so-called (bio)molecule corona (latin for crown) around them, transforming the bare ENM into a ENM with a biological coating (Docter et al., 2015a; Cedervall et al., 2007; Tenzer et al., 2013; Monopoli et al., 2012;

* Corresponding author.
E-mail address: docter@uni-mainz.de (D. Docter).

http://dx.doi.org/10.1016/j.taap.2015.11.008
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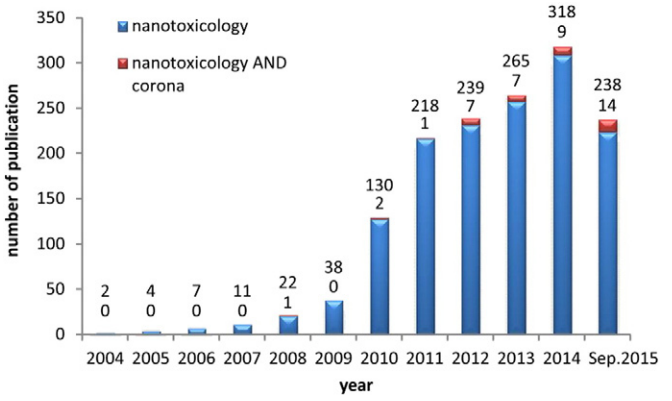

Fig. 1. Timeline of PubMed entries matching the search criteria 'nanotoxicology' and the subgroup 'nanotoxicology and corona'. Querying PubMed by using the search criteria 'nanotoxicology' reveals a constantly growing number of publications over the last ten years whereas the subgroup within this search based on the criteria 'nanotoxicology and corona' is still in its infancy. Albeit, the trend indicates that the 'corona' concerning 'nanotoxicology' represents an unresolved hot topic with high scientific relevance.

Monopoli et al., 2011). Thus, whereas the physico-chemical properties and behavior of ENMs can be engineered and controlled in technically stable, protected environments, such as technical products, this is no longer the case in complex physiological or natural environments.

Although protein adsorption onto surfaces has been known for a long time since the pioneering work by Vroman (1962), where he postulated the 'Vroman effect', a continuous flux of desorption/adsorption of proteins. This means that at any time an initially attached protein can desorb from an ENM and can be replaced by a different one with larger affinity. Thereby the protein corona composition is substantially changed, while the amount of adsorbed proteins remains at a relatively constant level. In theory, proteins, that are more abundant in the biological fluids, are the first to be adsorbed during the initial phase. Then, they are replaced by proteins of lower abundance but higher affinity, which remain around the ENM for longer times (Nel et al., 2009; Cedervall et al., 2007). The term 'protein corona' was introduced to the nanoparticle community much later in the study of Cedervall et al. (2007). Hereby, a whole field of new investigations was stimulated. Although, somehow loosely defined, the term 'hard protein corona' was coined as the (first) tightly bound layer of biomolecules with a long exchange time which represents an analytically accessible protein/biomolecule signature of an ENM in the respective environment (Docter et al., 2015b; Tenzer et al., 2013; Monopoli et al., 2012). In addition, some models further suggest that on top of this 'hard corona', a 'soft protein corona' exists, consisting of loosely associated and rapidly exchanging highly complex layers of biomolecules, not directly connected to the ENM (Monopoli et al., 2012; Walczyk et al., 2010; Walkey et al., 2014). However, since this 'soft corona' desorbs during current purification processes, its existence, analytical dissection and, particularly, its relevance for effects at the nano–bio interface remain to be fully confirmed. Therefore, as inspection of the current literature revealed that the term 'soft' versus 'hard' corona seems to mostly create more confusion than helping to describe and resolve scientific questions, we mean the hard protein corona, when referring to the protein corona. As the hard protein corona represents the effective biological identity of the ENM (Fig. 2), we will use this term throughout the review.

Typically, corona profiles differ significantly from the protein composition of the (biological) fluid investigated (Tenzer et al., 2013; Monopoli et al., 2012; Walkey et al., 2014; Tenzer et al., 2011). For example, although blood plasma is constituted by thousands of proteins and some of them are more abundant than others, they are not necessarily present in the protein corona of ENMs or, at least they are not necessarily the more abundant ones (Tenzer et al., 2011; Zhang et al., 2011; Martel et al., 2011). Distinct proteins will be either enriched or will display only a weak affinity for the nanoparticle surface. Furthermore, not

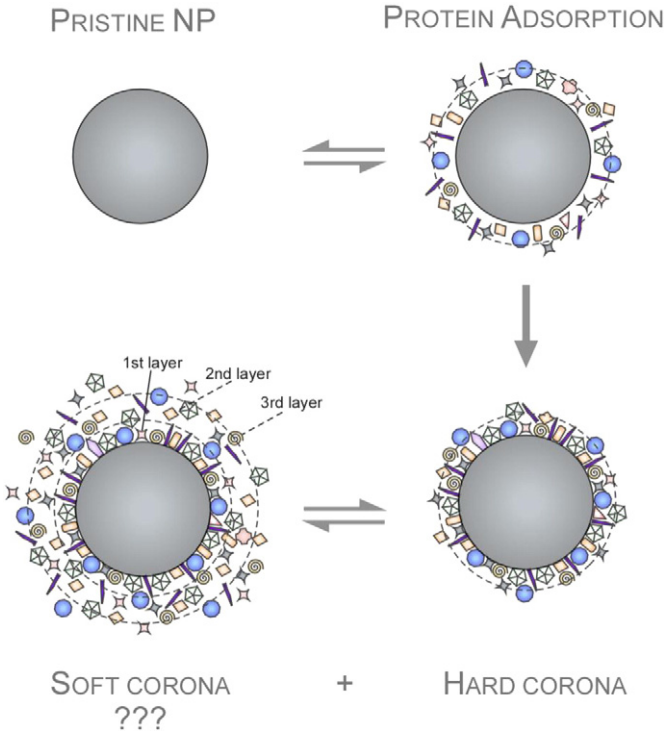

Fig. 2. Hypothetical model of protein corona formation and terminology. A highly complex protein corona is established on pristine ENMs in any biological environment. On top of this 'hard corona' the existence of a dynamic 'soft corona' of loosely associated biomolecules is also suggested but has not been proven yet. Adsorbed proteins are indicated.

only the particle material, size and the surface properties have been shown to play a role in determining the composition of the protein corona, also exposure time and the relative ratio of the physiological fluid (e.g. human or murine, plasma or serum) to the nanoparticle dispersion are critical aspects (Docter et al., 2015b; Walkey and Chan, 2012). But none of the above-mentioned factors alone is able to be used to determine the formation and composition of the biomolecule corona. The relation between the pristine ENM characteristics and the nature of the corona is far from trivial, and currently still remains impossible to predict in complex physiological environments. The scientific community is now moving from the mere evaluation of the impact of the biomolecule corona on the physical and chemical properties of ENMs to the physiological impact of the ENMs.

3. Targeting the capability of nanoparticles in the light of the biomolecule corona

Over the past decades nanocarriers were designed in the attempt to: i) increase drug bioavailability and avoid drug inactivation, which is particularly important in the case of poorly soluble compounds, or degradation by blood proteases/peptidases or nucleases (Riehemann et al., 2009); ii) minimize side effects due to a non-specific body distribution of the drug and to the high amount of drug commonly used (Ferrari, 2005), and iii) selectively deliver the payload to the affected area, thereby increasing its tissue accumulation (Bertrand et al., 2014). While the first-generation nanocarriers, such as micelles, PEGylated liposomes, and polymeric NPs, fully address the first two points by increasing the pharmacokinetics and tolerability of nano-formulate drugs (Riehemann et al., 2009; Dobrovolskaia and McNeil, 2015), the second-generation nanocarriers take advantages from active targeting strategies to tissue-specific delivery (Yang et al., 2012; Meng et al., 2013). As several receptors on the cell surface are over-expressed in diseases such as cancer (Danhier et al., 2010), these approaches are based on the functionalization of the carrier surface with active molecules,