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Editorial

Bioengineering on the Nanoscale: the Inspiration We can Draw from Endogenous Systems Interactions to Design the Nano-Bio Interface

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Nanomedicine can be described as bioengineering on the nanoscale where we seek to apply intelligent design to tackle health challenges. The last decade has seen tremendous growth in this field as studies on the various applications of nanotechnology in medicine and biotechnology form a sizeable aspect of modern day research. Biomedical applications of these nanoparticles have been reported in four major areas, namely, drug delivery, disease diagnostics, imaging and therapeutic applications. Nanoparticles can broadly be classified into two types: (a) the nano-containers, which carry and delivery drugs e.g. chitosan, silica and polymeric nanoparticles, and (b) the nano-transducers, which possess interesting physical properties e.g. magnetic iron oxide nanoparticles, fluorescent quantum dots and carbon nanotubes that are excellent electrical conductors. Whatever their functions are, they are the outcome of humans' ingenious design on the nanoscale.

Nature's intelligent design has also created a range of endogenous biomolecules that exist in the same size regime as nanoparticles. In biology, there are numerous examples of biomolecular systems that far surpass any man-made machine in terms of efficiency, precision, and complexity. Natural endogenous biomolecules such as DNA and proteins often self-assemble e.g. DNA hybridization and protein dimerization, or interact with other biomolecules in order to perform their naturally intended function. The interaction between mRNA and the protein ribosome during protein translation is one such example. Most often, these interactions between biomolecules are useful, if not critical, to the survival of the organism.

In a similar manner, nanoparticles also demonstrate a high propensity to interact with each other or with other biomolecules due to their size and high surface energy. These interactions result in phenomena termed aggregation and non-specific adsorption respectively [1]. However, unlike their natural biomolecular counterparts, these "sticky" responses are more often considered undesirable in biomedical applications as they form the root of many downstream issues plaguing the nanomedicine community. The aggregation of gold nanoparticles and quantum dots results in the loss of their optical properties, rendering them unsuitable for imaging applications [2]. Also, the self-adsorption of DNA and proteins on nanoparticles causes a loss in the structure and function of the biomolecules, resulting in a diminished biological function of the nanoparticle-biomolecular conjugation [1]. More recently, it has been shown that the non-specific adsorption of proteins on nanoparticles when placed in biological media results in the formation of a layer of protein coat termed protein corona [3,4] that subsequently leads to unwanted immune responses [5], poor targeting efficacy [6] and undesirable clearance [7]. Efforts by different research groups to minimize the formation of protein corona through strategies such as pegylation have thus far been unsuccessful in eliminating the corona completely [8].

Instead of looking at these phenomena as a nuisance, we can draw inspiration from endogenous system interactions in nature and exploit either aggregation or non-specific absorption of nanoparticles for useful biological applications. We can take advantage of the engineering that Nature has done for thousands of years and directly manipulate biological molecules. Park *et al.* demonstrated how we can exploit the non-specific absorption of proteins to enhance the efficiency of protein translation *in vitro* [9]. In their study, they conjugated DNA to gold nanoparticles. These DNA were specially designed to weakly hybridize with the mRNA of a fluorescent protein mCherry. When the entire gold nanoparticle-DNA conjugates were introduced into retic cell lysate, not only did the mRNA hybridize with the DNA, the various proteins in the retic lysate such as the ribosomes were also non-specifically adsorbed onto the gold nanoparticles. This brought the entire translation machinery to the proximity of each other to enhance the efficiency of mCherry translation. Such a technique can be extended towards the enhanced translation of other critical proteins involved in diseases such as insulin.

Non-specific adsorption of proteins can also take place when the nanoparticles are place in other biological media. In another study, Kah *et al.* formed a protein corona around gold nanorods in serum, and exploited it to perform loading and triggered release of drugs [10]. The serum albumin forms a major component of serum proteins and is a known natural transporter of small biomolecules. Therefore, the non-specific adsorption of these serum proteins onto gold nanorods enabled them to function in a manner similar to a sponge to "soak" small molecules. Two small molecules of different charges: a negatively charged DNA and a positively charged small molecule anti-cancer drug Doxorubicin were loaded onto the corona. Kah *et al.* showed that the amount of DNA and Dox loaded using the corona

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were respectively about 3 and 7 times higher than what was reported using covalent strategies to attach the molecules to gold nanorods. When the gold nanorods were irradiated by a 200 mW pulsed femtosecond laser at 790 nm (which matches the longitudinal surface plasmon of the gold nanorods), both the DNA and Dox were released in a time dependent manner. The DNA remained functional after release. The two payloads were also stably held in the protein corona with minimum leakage of DNA within the first two days, although the Dox showed a more significant burst release in the first day. This was also typical of most nanoparticulate drug delivery systems.

Cifuentes Rius *et al.* took the study further by placing the DNA loaded gold nanorods-corona (NR-Cor) into different protein solutions to demonstrate tunability of the release. They showed that by placing the NR-Cor in a solution containing proteins with high affinity of binding to the nanorods (hard corona proteins) these proteins resulted in a labile exchange with the existing proteins in the corona, leading to a more labile DNA release. On the other hand, when the NR-Cor were placed in a solution containing low affinity proteins to the nanorods (soft corona proteins), these proteins formed a different coat on the corona and retarded the DNA release instead [11]. This "blocking" technique has been shown to be effective in blood, and demonstrated that we could also exploit the non-specific adsorption of proteins to tune the release of payloads from nanoparticulate carriers in addition to loading and performing triggered release of the payloads.

The non-specific adsorption of proteins to form the protein corona around nanoparticles has also been shown to play an important role in modulating the cellular response of nanoparticles. In one such study by Kah *et al.*, the protein corona from human serum (HS) was formed on gold nanorods (NRs) passivated with four different types of amphiphilic ligands (ALs). The NR-AL-HS were introduced to human keratinocyte (HaCaT) cells, and the cellular response in terms of cell uptake, proliferation, oxidative stress and changes in gene expression were examined and compared to NR-AL in the absence of the serum corona proteins [12]. The absence of the protein corona resulted in a decrease in the cell proliferation as the concentrations of NR-AL introduced to the cells were increased. This concentration-dependence of cell proliferation was not observed in NR-AL-HS, which maintained a high level of cell proliferation throughout all concentrations. Furthermore, the presence of the protein corona on certain NR-AL was able to increase its uptake into HaCaT cells.

The few examples described above have shown how we can draw inspiration from endogenous systems to embrace the "stickiness" of nanoparticles and turn them into useful functionalities in biomedical applications. There are of course many other examples of such bioengineering on the nanoscale which can guide us towards a more rational design of nano-bio interface, paving the way for more effective sensing, therapeutic intervention and drug delivery applications in nanomedicine. To further enable discovery, we must now perhaps adopt innovative approaches to relook at certain physical phenomena from an opportunist's perspective instead of considering them as undesirable side effects. We can start by getting inspiration from Nature.

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