DRUG DELIVERY

Size-dependent nano–bio interactions

In 2008, Jiang and colleagues published a Letter in *Nature Nanotechnology* (*Nat. Nanotechnol.* **3**, 145–150; 2008) where they suggested that engineered nanoparticles can actively modulate the response of targeted cells, acting themselves as therapeutic agents. This represented a stark departure from the idea that nanoparticles were simply passive agents, used to deliver drug cargos to specific targets within the body without interaction with their biological environment.

In their paper, the authors functionalized gold and silver nanoparticles of different sizes with Herceptin molecules, that targets the ErbB2 receptor overexpressed on the surface of several ovarian and breast cancer cells. Studying the interaction of such nanoparticles with SK-BR-3 cells, a type of breast cancer cells, the authors observed that the receptor-mediated cellular uptake was dependent on nanoparticle size. In particular, using fluorescence imaging to follow the endocytosis of nanoparticles with a diameter of 2 nm, 40 nm and 70 nm, they showed that 40 nm nanoparticles were the most efficiently internalized. This derived from the optimal antibody covalence that could be achieved in these nanoparticles, which in turn affected the binding avidity for ErbB2 receptors and the process of membrane wrapping leading to internalization.

Moreover, the authors also showed that when 40 nm nanoparticles were engulfed, the ErbB2 receptors that drove internalization were internalized as well, contrary to what happened when cells were treated with free Herceptin or nanoparticles outside the 40–50 nm diameter range. This has profound implications. In fact, it means that, by modifying the size of antibody-functionalized nanoparticles, the levels of membrane-bound ErbB2 can be changed. And this has direct effects on cell signalling events regulated by the membrane receptor, modulating the cellular behaviour. Indeed, compared with cells treated with the free Herceptin antibody, cells treated with 40 nm nanoparticles displayed reduced levels of proteins involved in the correct maintenance of the cell cycle, leading to cell growth inhibition and increased cell death.

Credit: Springer Nature Ltd.

In summary, this paper demonstrated that nanoparticles are not passive delivery agents, but can actively modify cell behaviour and can therefore be used to tune cellular processes. It introduced the idea that by engineering basic properties, such as size and curvature, nanoparticles could be used to stimulate specific cellular responses. The work also highlighted the importance of investigating the basic interactions between nanoparticles and biological matter, to fully harness their capabilities while curbing their toxicity. This concept has shaped research in the nanomedicine field ever since. “It is great to still see the tremendous interest in fundamental nanoparticle studies after we coined the term nano–bio interaction in the mid 2000s” says Warren Chan, lead author of the publication. “These studies are driving the design of nanotechnology for cancer, immune, and other medical applications.” Wen Jiang, first author of the paper, applied the insights gained in this work to his ensuing scientific endeavours: “This study has influenced my subsequent work on developing multivalent antibody/protein-functionalized nanoparticles for cancer immunotherapy applications.

Although our study was focusing on nano–cancer cell interactions, the same principle can be applied to and is getting renewed interests in the context of nano–immune interactions, with the emergence of cancer immunotherapy and vaccine development.”

Since 2008, significant progress has been made in nanomaterial design, resulting in the production of a large variety of smart, multifunctional nanoparticles responsive to different stimuli that can provide precise disease targeting and improved therapeutic and diagnostic outcomes — at least in preclinical studies. Progress has also been made on the fundamental understanding of nano–bio interactions. However, the sheer complexity of the task means that, thirteen years after, unravelling the basic aspects of the communication between nanomaterials and biological entities remains crucial to unlock the full potential of nanomedicine.

Chiara Pastore

Published online: 8 October 2021
<https://doi.org/10.1038/s41565-021-00996-z>