



Cover story

Nanoparticle properties affecting nuclear targeting in cancer and normal cells



With the advent of nanotechnology came the promise of new targeted drug delivery systems. These systems are expected to be capable of delivering their therapeutic payload directly to their site of action. The latter offered new horizons for cancer therapy in particular, promising to deliver chemotherapeutics specifically to the tumor site, reducing side effects, therapeutic dose and patient expense. Such potential has led to even greater ambition, where scientists have developed a plethora of cancer targeted nanoparticles that are expected to effectively treat tumors. Unfortunately, the fact that very few cancer nano-based drugs have actually made it to the market clearly shows the magnitude of difficulties in translating the technology to clinics. The initial ambition accompanied with unlimited potential has hit the wall with a series of failures of nanoparticle formulations in clinical studies. The initial assumptions of improved drug delivery to tumors by nanoparticles and targeted cancer therapy by modification of the nanoparticle surface with a ligand or antibody still remain as assumptions. More than two decades of testing has not been able to verify such assumptions. Delivering a drug to its target tissue is a challenging task. It is even harder to specifically deliver it to its target cell, or more specifically its target organelle inside the target cell, in particular the nucleus for most chemotherapeutics. This topic was reviewed in a recent issue of this journal [1].

Due to the aberrant nature of cancer, it is quite possible for nanoparticles that under normal conditions are capable of reaching their target to fail to do so in cancer. Unfortunately, this issue has not been well addressed. The uncommon differences between normal and cancer cells are not taken into consideration, particularly those that occur in the nucleus and intracellular trafficking mechanisms. The paper by Tammam et al. [2] published in this issue examined intracellular trafficking. The authors prepared nuclear targeted small and large chitosan nanoparticles with a high, intermediate and low density of a nuclear localization signal (NLS) and tested their nuclear delivery efficiency in cancer and non-cancer cells. In all the cell lines tested, unmodified small nanoparticles showed better nuclear localization than similar nanoparticles modified with a NLS, indicating that nanoparticles do not utilize the classical nuclear import mechanism for nuclear entry. On the other hand, larger nanoparticles require a NLS for nuclear targeting. Interestingly, large nanoparticles with a low-intermediate NLS density showed better nuclear delivery than those with higher densities in A549 lung cancer cells, HEK 293 cells, primary human fibroblasts, L929 fibroblasts but not in glioma 261. In glioma 261, unmodified large nanoparticles successfully targeted the nucleus, whereas large nanoparticles with a low-intermediate NLS density failed to do so in glioma. The authors then demonstrated that this was attributed to an underlying impairment in the classical nuclear import

pathway in glioma [2]. These results indicate that for nanoparticle use in cancer, it is of utmost importance to test the nuclear allocation and intracellular trafficking of nanoparticles in the exact cancer model and to trace the underlying reason for the aberrant intracellular NP trafficking. Furthermore, this paper demonstrates the importance of careful nanoparticle optimization for targeted drug delivery. A difference in the density of NLS of the same nanoparticles influence whether they will end up in the nucleus or the cytoplasm.

The study by Tammam et al. [2] is important. It not only describes the mechanisms of nanoparticle trafficking inside cancer cells, but also provides design criteria for others developing formulations for combination therapy. For example, Wu et al. in this issue [3] discusses supramolecular nanoassemblies for co-delivery of siRNA and doxorubicin to treat multidrug-resistant breast cancer. The target locations inside the cancer cells for the two active agents may be different, and this may lower the overall efficacy. The work by Tammam et al. provides a new insight into designing nanoparticle formulations with careful consideration of the case specific variables. It highlights the important attributes of nanoparticle-based drug delivery system design, particularly pertaining to fine tuning for active nuclear targeting. It is important to note that the (uncontrolled) inclusion of a targeting ligand on a nanoparticle surface does not necessarily improve delivery to the target cell/organelle. More importantly, nanoparticles optimized for targeted drug delivery for a specific drug in specific cells may not be useful for delivery of other drugs in other cells. The information described in the Tammam's work explains, at least partially, why the data of certain nanoparticles could not be reproduced for other drugs, and clinical studies.

References

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