NANO DELIVERS BIG

a novel approach to disease therapeutics

By Sachin Patel

Nanosystems are capable of "selectively destroying tumors, providing early diagnostic information, and creating a novel platform for gene delivery and cellular repair."

Smart bombs, tracking devices, guided missiles - one would be hard pressed to find such military jargon populating the considerably tamer texts of science journals. Yet these are the phrases that pop-sci pundits are using to describe nano-scale devices – roughly 10,000 times smaller in at least one dimension than the average human hair – that are capable of selectively destroying tumors, providing early diagnostic information, and creating a novel platform for gene delivery and cellular repair. In particular, nano-scale drug delivery systems (DDS) have extended their broad-reaching arms into various sectors of therapeutic medicine, most notably cancer treatment. Whereas conventional cancer therapies are wide-acting and target-unspecific, damaging normal cells and incurring painful and detrimental side-effects, DDS have the ability to navigate the circulatory system and deliver their molecular cargo (the anti-cancer drug) directly to its biological dock (in this case, the cancer cells), amplifying the local drug payload while reducing the non-specific toxicity for the patient (1).

Receptor-mediated drug delivery

A study by Bhirde et al. shines light upon this system (2). In this study, single walled carbon nanotubes (SWNTs) were conjugated with an epidermal growth factor (EGF) ligand, a molecule which has a particular affinity to epidermal growth factor receptors present on many epithelial cells. Head and neck squamous cancer cells, which share the hallmarks of uncontrolled cell growth and proliferation characteristic of malignant cells, overexpress these receptors on the order of one thousand relative to that by healthy squamous epithelial cells. Due to the extracellular receptor-ligand interactions, the nanotube conjugate has greater proclivity towards cancerous than normal cells. In particular, cisplatin, a first-line

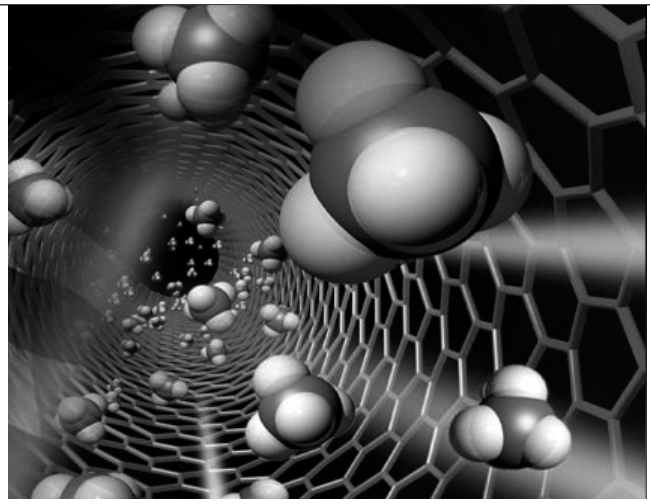

Figure 1: A graphical representation of the a carbon nanotube.

Credit:https://newsline.llnl.gov/_rev02/articles/2009/oct/10.30.09-nanotubes.php

anti-cancer drug, was conjugated to the nanotube-EGF complex, ultimately resulting in the creation of a "smart missile," which was showen to reduce tumor growth significantly *in vivo* (2).

Nanoparticle features

As outlined by Singh and Lillard, nano-drug delivery systems utilize three main delivery vehicles: nanoparticles, nanospheres, and nanocapsules (1). Possessing different properties and corresponding capabilities, each system is tailored to a specific physiological goal. Collectively, nanoparticles are described as "solid, colloidal particles," which vary in size from 10 nm to 1000 nm; naturally, the optimum size for a nanosystem would be one that maximizes drug binding, optimizes drug release and has long-term functionality in living systems, and has little to no cytotoxic effects. Methods by which drugs are linked to nanoparticles include adsorption, dissolution, entrapment, encapsulation, and covalent conjugation (1).

Carbon nanotubes

Carbon nanotubes, as used by Bhirde et al. (specifically, single-walled carbon nanotubes), are relative newcomers in the field of nanomedicine. At the apex of nanodelivery systems are polymeric nanoparticles, composed of natural and synthetic polymers. Not only are these nanoparticles stable *in vivo* and relatively easy to conjugate, but polymeric nanoparticles are also biodegradable and pose less of a health hazard in living systems. Arguably, the most important and overlooked caveat in nanoparticle synthesis concerns its pharmacokinetics - whether it induces cellular apoptosis or is acutely cytotoxic. As described in the core example of the EGF-guided, carbon nanotube longboat drug delivery system, nanoparticles concentrate preferentially "to tumors, inflammatory sites, and at antigen sampling sites" by the naturally enhanced permeability of the vasculature at these regions (2). After localization at such points, nanoparticles unload their drug cargos, molecular labels, or other diagnostic markers. Hence, nanoparticles are considered revolutionary not simply by virtue of drug localization, but also by their optimal drug release and functionality. Free drugs, when travelling in the circulatory system unbound to any scaffolds, are incredibly susceptible to nuclease and protease breakdown (which degrades the higher-order specific structures of the drug) before the drug even reaches its target site, rendering it impotent. While conjugated to a carbon nanotube, for example, the drug becomes shielded by the biological inertness of the structurally-fixed carbon backbone of the nanotube. Moreover, free drugs, much like free radicals in the body, are active threats to normal tissue. Understandably, physicians must regulate the amount of cytotoxic drug in the body such that side effects to normal tissues do not cause morbidity or mortality. Due to their novel features, drug delivery vehicles can allow for target specificity through localization of the nanotubes, which would allow ncrease in the amount of delivered drugs due to the decreased risk of fatal side effects (1).

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Other modes of drug delivery

Some other forms of targeted drug delivery vehicles include liposomes, which embrace the idea of drug encapsulation. According to Singh, such systems use "contact-facilitated drug delivery" - being endocytosed into the cell via lipid-lipid exchanges with the target cell membrane. Other DDS, such as hydrogels and dendrimers, exploit different forms of drug uptake, but drug payload is generally dependent only on the surface area (or volume) of the respective systems. One of the main attractions of carbon nanotubes has been their ability to carry a number of different types of drugs. Why is this property of special biological importance? Consider a patient who has head and neck squamous cell cancer A, which consists of genetically different populations of squamous cells, which we will call a, a', a", and so forth. Assume population a is killed by drugs X and Y, a' is resistant to X, and a" is resistant to Y. A doctor using conventional cancer therapies would be forced to compromise dosage in order to accommodate the wider arsenal of drugs. Carbon nanotubes, however, allow for multiple drug conjugation (1). For example, a single nanotube may carry drug X and drug Y in comparable amounts and then deliver that to the target sites, thus ensuring that all three populations, a, a', and a", are killed.

Credit: Bhirde, A., Gutkind, J.S., Rusling, J.F. (2009

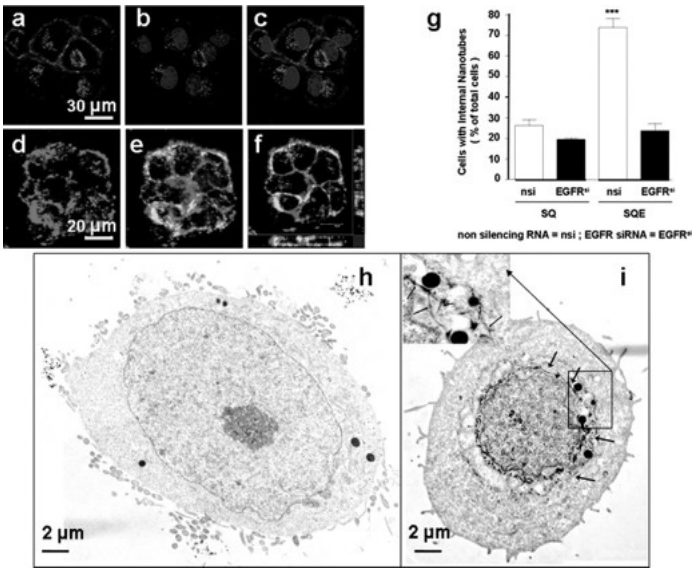

Figure 2: An *in vivo* representation of the localization of carbon nanotubes on the perinuclear envelope, revealing a possible endocytotic mechanism of entry.

Nano-toxicity

Indeed, carbon nanotubes have heralded a new age in nanomedicine, owing to their remarkable versatility and stability in biological systems. Composed of one or more sheets of graphene, and with the ability to be molded to specific dimensions, carbon nanotubes are not only being increasingly used in the electrical and structural engineering sectors, but also in the bioengineering sector for drug delivery purposes, as we have reviewed here. With the discovery of protein/DNA/molecular probe-binding methods, carbon nanotubes present a wealth of opportunities for disease therapy and biological imaging, among other goals. However, their cytotoxicity and biodistribution *in vivo*, important concerns in the transition from bench to bedside, are not fully understood. Recently published toxicological data on carbon nanotubes suggest that they behave in a similar fashion to asbestos fibers, clogging the fine arterial networks and capillary beds in the lungs and inducing respiratory irritation and, when exposed longer, mesothelioma (3). Moreover, pathological evidence suggests that the lungs of mice that have inhaled a high quantity of nanotubes bear certain similarities to those of coal miners - with the pulmonary vessels clogged by the nanotube bundles. Such microscale aggregation is the result of substantial Van der Waals interactions between charged nanotubes' surfaces. Finding a molecule or surfactant that would disrupt such chemical interactions but not their biological properties is of great importance (3,4).

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PEG-conjugated delivery systems

Polyethylene glycol, a polymer of ethylene oxide, has been touted as one such molecule that addresses both the concerns of clumping and cytotoxicity. Liu et al. demonstrated that functionalization of SWNTs with branched polyethylene glycol (PEG) chains results in longer circulation, reduced toxicity, and more effective clearance - though how this affects the SWCNTs' surface-binding capabilities remains unknown (4). Furthermore, the linear covalent linkage of PEG to SWCNTs' surfaces not only makes the hydrophobic nanotubes more soluble but also increases their hydrodynamic size and reduces their immunogenicity. For these reasons, PEG has become one of the more attractive molecules for drug conjugation (4).

Conclusion

Carbon nanotubes, and nanoparticles in general, have numerous medical applications, ranging from early diagnosis to effective intervention. Moreover, mini-structures such as these could one day become mini-machines capable of fixing damaged cells or organs, or even removing malignant, metastatic cells. These particles could ultimately prove to be the nano-sized solutions we seek to the mighty medical problems we currently face. H

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References

1.Singh, R., Lillard, J.W. (2009). Nanoparticle-based targeted drug delivery. Experimental Molecular Pathology, 86(3), 215-23.

2. Bhirde, A., Gutkind, J.S., Rusling, J.F. (2009) Targeted Killing of Cancer Cells in Vivo and in Vitro with EGF-Directed Carbon Nanotube-Based Drug Delivery. ACS Nano, 3(2), 307-316.

3. Schipper, M., Ratchford, N., Davis, C., Kam, N.W.S., Chu, P., Liu, Z., Sun, X., Dai, H., & Gambhir, S. (2008). A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice. Nature Nanotechnology, 3(3), 216-221.

4. Liu, Z., Chen, K., Davis, C., Sherlock, S., Cao, Q., Chen, X., Dai, H. (2008). Drug delivery with carbon nanotubes for in vivo cancer treatment. Cancer Research, 68(16), 6652-60.

5. Airgir, A. et al. (2008) Head and neck cancer. The Lancet, 371, 1695-1709.

6. Moses, M., Brem, H. & Langer, R. (2003). Advancing the field of drug delivery: Taking aim at cancer. Cancer Cell, 4, 337-341.