The use of nanotechnology in cancer management

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Drug delivery systems have provided the pharmaceutical industry a means of improving the therapeutic properties of pre-existing drugs. These systems, such as lipid- or polymer-based nanoparticles, alter the pharmacokinetics and biodistribution of the drug that is being carried. A nanoparticle is formally defined as an engineered particle in nanometer size. The inherent properties of the nanoparticle make it an ideal vector to distribute drugs. The submicron size, with diameters less than 200 nm, of the nanoparticles increases its intracellular uptake, ability to penetrate through submucosal layers and cross the blood brain barrier. Both synthetic and organic polymers have been utilized to create biodegradable nanoparticles, like the poly lactides that undergo hydrolysis upon implantation and broken down to lactic acid. The drugs are released via diffusion across the polymer matrix and through biodegradation of the polymer itself. Nanoparticles conjugated with tissue-specific ligand also allow the delivery of the drug to be more targeted, and reduce the amount of side effects. As a result, nanoparticles have the potential to increase the potency and efficacy of the drugs that are already used in practice.

Nanoparticles could vastly improve the tools we have to fight cancer through a two-fold approach: (1) early detection of cancer and (2) cancer therapeutics. The nanoparticles target the site of the cancer for both diagnostic and therapeutic purposes. The potential of nanoparticles in the field of oncology holds many promises.

NANOTECHNOLOGY FOR CANCER DIAGNOSIS

Various nanoparticles, such as iron oxide crystals, and QD semiconductor non-crystals, have shown great potential for detecting disease markers, pre-cancerous cells, fragments of viruses, specific proteins, antibodies and other disease indicators.

In the field of oncology, nanoparticles can assist to non-invasively detect tumors at an early stage, perhaps months or even years earlier than the conventional diagnostic tools would make the same diagnosis, and thus result in maximum therapeutic benefit and improve the prognosis of the patients. For instance, in breast cancer, nanomedicine can potentially use molecular imaging to accurately diagnose breast cancer when the tumor mass has only 100-1,000 cells, as opposed to the current imaging techniques like mammography, which require the detection of more than one million tumor cells for accurate clinical diagnosis.

QDs are semiconductor nanocrystals made up of 100-100,000 atoms. QDs contain electrons, which after excitation, can relax to fluorophores (molecules capable of fluorescence), allowing studies to be carried out over time. Due to all these unique characteristics, QDs can be conjugated to antibodies that have affinity for tumor-specific antigens, and they will preferentially localize to the tumor cells. The identification of the changes in cellular surface protein concentration can be an early indication of cancer. Other studies have shown that by injecting QD-labelled melanoma cells into mice, one can visualize in vivo the migration of tumor cells to the lungs on imaging. This ability to track tumor micro-metastasis can lead to greater understanding of the behavior of metastatic cancer and discovery of new treatment options.

In practice, identification of the sentinel lymph node (SLN) in breast cancer can be challenging. Currently mapping is done by using blue dye and radioisotopes. This technique obscures the surgical field and can cause radiation to the patients and health care providers. Superparamagnetic iron oxide nanoparticles allows pre-operative MRI visualization and intra-operative magnetometer-aided detection of SLNs, removing the need for harmful radioisotopes and obscuring dyes.

Nanoparticles can also make important advancements in diagnosing and imaging of brain tumors, through both preoperative and intraoperative brain mass detection, allowing for early detection of precancerous cells and improving the prognostic outcomes of cancer patients. Currently, the most widely used MRI contrast agents are based on paramagnetic gadolinium (Gd(III)). While still valuable, these ions are not without their problems. They tend to diffuse freely through a tumor and preferentially image areas where there is prominent blood-brain barrier breakdown, providing limited enhancement of the infiltrating tumor margins or areas of poorly vascularized micrometastasis. Also, the permeability of blood-tumor barrier is not homogenous, which means that the ions cannot enter all areas of the tumor equally. Furthermore, this contrast material has difficulty discriminating tumor from CNS inflammation or infections. Nanoparticles designed to preferentially target tumor areas, such as such as Ferumoxtran-10, a dextrancoated iron oxide nanoparticle, have been developed as new MRI contrast agents to avoid many of these problems and provide a wider window of opportunity for tumor imaging and enhancement.

NANOTECHNOLOGY AS CANCER THERAPEUTICS

Many conventional cancer therapeutic agents work by inducing cellular toxicity causing cancer cell death. Although cancer cells are inherently more susceptible to the effects of these agents, these agents also affect normal cells. This puts a constraint on the dosage and frequency of treatment as it inevitably causes injury to normal cells. This constraint often results in suboptimal treatment, which contributes to the persistence and recurrence of cancer after the completion of chemotherapeutic treatment. Current advances in
nanotechnology seek to resolve these therapeutic constraints by allowing for specific targeting of cancer cells helping to increase drug efficacy while limiting unwanted toxicity.

Cancer specific nanoparticle directed drug delivery takes advantage of cancer physiology by both a passive and active drug delivery mechanism. In the passive drug delivery mechanism, nanoparticles are selectively concentrated at the site of the tumour by the enhanced permeability and retention effect (EPR).\(^{14}\) The EPR works due to the inherent faulty physiology of fast growing tumour. It is known that tumours require angiogenesis for continued growth. However, the growth of these new blood vessels is disorganized and leaky due to enlarged junctions between endothelial cells as well as deficiencies in the underlying basement membrane.\(^{15}\) While normal endothelium junctions are typically 5 to 10 nm in size,\(^ {13}\) gaps between the leaky endothelium of the tumour are significantly larger and range from 100 to 750 nm.\(^ {16}\) Concurrently, the disorganized growth of the tumour also results in formation of a disorganized lymphatic network.\(^ {18}\) The leaky vasculature and the lack of a lymphatic network result in the accumulation of nanoparticles in the cancer interstitium, passively concentrating drug at the site of the tumour.\(^ {14}\) Novel nanoparticle chemotherapy, Doxil (a pegylated liposomal doxorubicin nanoparticle), takes advantage of the EPR. In vitro experiments have shown Doxil to have a 10-fold increase of doxorubicin concentration (the chemotherapeutic drug (or payload)) within the tumour compared with conventional doxorubicin administration.\(^ {17}\) Although clinical trials comparing Doxil and conventional doxorubicin administration have shown no statistical improvement in survival (overall and disease free), Doxil was nevertheless shown to significantly decrease the risk of cardiotoxic effects of doxorubicin use (a significant side-effect limiting dosage and usage).\(^ {17}\) It should be noted that the pegylation procedure helps the nanoparticle escape from macrophage detection\(^ {14}\), while the liposomal core structure helps protect the bound doxorubicin to achieve a significantly longer half-life than free doxorubicin also contributing to the increased concentration of drug seen at the site of tumour.\(^ {17,18}\)

The active drug delivery mechanism works by targeting specific receptors preferentially expressed on the tumour cell. For example, folate receptors are preferentially expressed in some cancer phenotypes while showing limited expression in normal tissue.\(^ {19}\) Experimental findings in mouse models comparing conventional paclitaxel (given as free drug) with a heparin-folate-taxol (heparin as carrier molecule and folate as targeting molecule) showed the folate-directed nanoparticles to have more potent activity against tumour growth.\(^ {12}\) Another example is the transferrin receptor. In vitro studies using MCF-7 (human breast cancer cell line) comparing transferrin-conjugated paclitaxel-loaded nanoparticles treatment versus free paclitaxel showed the transferrin-conjugated paclitaxel treatment to have greater inhibitory effect on cell growth.\(^ {20}\)

Although drugs can be delivered to the tumour, another significant impediment remains due to chemotherapeutic drug resistance. The most studied cause of resistance is the membrane associated protein p-glycoprotein (p-gp).\(^ {21}\) The p-gp is expressed in a number of cell types in the body and functions to effectively pump chemotherapeutic agents out of the cell, conferring resistance. Nanoparticle drug design could sidestep this impediment by a number of possible mechanisms. One such mechanism is to co-administer a p-gp antagonist along with the therapeutic drug, thus inhibiting the p-gp function.\(^ {21}\) Clinical trials evaluating various potential antagonistic agents have shown disappointing results thus far, though new compounds continue to be discovered with improved binding specificity to p-gp.\(^ {21}\) Another mechanism could rely on receptor mediated endocytosis and subsequent endosomes formation as means for gaining access to the cell cytoplasm, which could effectively mask the nanoparticle until a high concentration of therapeutic drug is released to reach therapeutic effect, essentially overwhelming the p-gp.\(^ {12}\) In vitro and in vivo mouse models have shown that drug resistance can be overcome through this mechanism.\(^ {21}\)

Nanoparticle as a means for drug delivery offers many unique benefits in the treatment of cancer compared to other targeted drug therapies proposed such as antibody-drug conjugates. Firstly, nanoparticles could carry a significantly larger drug payload per ligand-receptor binding event compared to antibody-drug conjugates as well as being more versatile in the type of drug its able to carry since drugs are stored within the nanoparticle, with limited exposure to environment, while the type and number of drugs conjugated to an antibody could significantly affect its kinetics and biodistribution.\(^ {18}\) Secondly, nanoparticles are large enough to target multiple ligands allowing for multivalient binding and selectivity enhancement. Therefore, nanoparticles can use multiple weak ligand interactions to greatly increase the pool of cancer binding targets whereas single ligand recognition offered by antibody- conjugates require strong affinity to be effective.\(^ {22}\) Thirdly, nanoparticle design could allow the rate of release of the drug to be tailored for the drug of action. For example, topoisomerase I inhibitors such as the camptothecin-based drugs are reversible inhibitors of the enzyme, and therefore, have better efficacy if exposure of drug is prolonged.\(^ {23}\) Lastly, nanoparticles could allow for the co-localization of different types of agents to work synergistically within the target cell to increase drug efficacy.\(^ {22}\)

CONCLUSION

Nanoparticles holds new promise as means for earlier detection and better treatment of cancer. Imagine a future where nanoparticles can help detect cancer before it even has a chance to manifest, and selectively destroy cancer cells while leaving the normal cells unharmed. Cancer, in such a circumstance, could become a highly manageable condition. However, despite our current research there is much we still do not understand. Nanoparticles offer a new avenue to tackle these challenges. More research is needed in this promising and dynamic field of cancer therapeutics.

REFERENCES