Review Article

Advances in Bioengineering & Biomedical Science Research

Nanobiotechnology Advances in Oncology

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Abstract

Nanobiotechnology advances in cancer treatment are discussed including detailed consideration of the several drug-laden nanoparticles and the nanocarriers used to deliver them at cancerous sites. This burgeoning field is contrasted with conventional chemotherapy and its clinical advantages set forth. New directions for improving the technology are also charted, but caution is noted regarding its potential toxic effects and the correspondingly associated need for more studies.

Abbreviations

3HM= 3-helix micelles; BBB= Blood Brain Barrier; BPB= Brain Protective Barriers; END= Engineered Nano Devices; EPR= Enhanced Permeability and Retention; GBM= Glioblastoma; LPH= Lipid-coated Polymeric Hybrid; MDR= Multiple Drug Resistance; MRI= Magnetic Resonance Imaging; NBT= Nanobiotechnology; NP= Nanoparticles; PET= Positron Emission Tomography; PLGA= Poly-Lactic co-Glycolic Acid; PNP= Polymeric NP; RCT= Rational Combination Therapy; SERS= Surface-Enhanced Raman Spectroscopy; SPM= SuperParaMagnetic; T-MOC= Tumor-Microenvironment-On-Chip.

Drugs Cited: Accurin, Apoferritin, Cisplatin, Curcumin, Daunomycin, Docetaxel, Doxorubicin, Osteopontin

Introduction

Biological processes, including the ones necessary for life and those that lead to cancer, occur at the nanoscale. Accordingly, nanobiotechnology (NBT) provides us with (a) the opportunity to study and manipulate macromolecules in real-time during the earliest stages of cancer progression and thereafter; (b) the possibility of rapidly and sensitively detect cancer-related molecules, enabling us to detect molecular changes even when they occur only in a small percentage of cells; and (c) the potential to generate entirely novel and highly effective therapeutic agents. It also offers important benefits for diagnosis by providing (a) new molecular contrast agents and materials to enable an earlier and more accurate initial diagnosis as well as (b) continual monitoring of cancer patients during their treatment [1]. Further, considering that cancer therapies are currently limited to surgery, radiation or chemotherapy, or a combination thereof, which risk damage to normal tissues or incomplete eradication of the cancer, NBT offers the means to (a) target chemotherapies directly and selectively to cancerous cells and neoplasms; (b) guide in surgical resection of tumors; and (c) enhance the therapeutic efficacy of radiation-based and other treatment modalities, all of which adding up to a decreased risk to the patient and an increased probability of survival [2,3]. I will review here the several nanoparticles (NPs) designed to attack cancer including: the multi-layered shell design; the surface-enhanced Raman spectroscopy (SERS) nanotag; gelatin NPs; platelet-coated NPs; nutshells; shape-shifting engineered NPs; kinase inhibitors; bioavailability-improved NPs; lipid polmers and polymeric hybrid NPs; lipid-based surface engineering of PLGA NPs; engineered nanoscale devices; hybrid nanocrytals; and super-paramagnetic iron oxide NPs for the detection of faint cancer signals by magnetic relaxometery. I will next discuss the nanodevices utilized for the delivery of drugs to cancer sites, including protein cages; microbubbles; multi-shell hollow nanogels with responsive shell permeability; and helix micelles. I will ten contrast nanobiochemotherapy with conventional chemotherapy.

Nanoparticles against Cancer

Cancer cells are notoriously good at becoming resistant to the drugs meant to kill them. One way they do this is by rerouting their signaling networks (specifically those responsible for the cancer cells' growth), proliferation, and survival. So-called "rational combination therapy" (RCT), a multi-drug therapy, aims to attack both primary and alternative pathways, the goal being to preemptively block the cancer cell's escape route. However, because of their different chemical properties, the drugs travel to different parts of the body and enter cancer cells at different rates. For example, hydrophilic (or water-loving) drugs tend to accumulate in tissues with high water content, whereas hydrophobic (water-repellent) drugs steer clear of these tissues. Several methods are employed whereby the cytotoxic drugs are either anchored to specially designed NPs or encapsulated within such particles. Thus:

The Multi-Layered Shell Design

Since the targeted pathways are present in a variety of tumors, the NP

design adopted consists of (a) a core vesicle (filled with water and a fatty, double-layered membrane) containing both hydrophilic and hydrophobic drugs; (b) a multilayered shell; and (c) an exterior layer that targets the NPs to cancer cells and prevents them from being detected by the immune system. The purpose of the multilayered shell is to stabilize the NPs, prevent drug leakage, target the NPs to the slightly acidic environment of the tumor and minimize the NPs' interactions with non-cancerous cells.

The multilayered shell can also be used to transport drugs that are not easily stored in the core, such as highly charged nucleic acids. These molecules can be spread out within different layers of the shell so that they are separated from drugs that could potentially inactivate their therapeutic effects. The exterior layer contains molecules that further target the NPs to cancer cells and help them pass through the body unnoticed by the immune system (Figure 1).

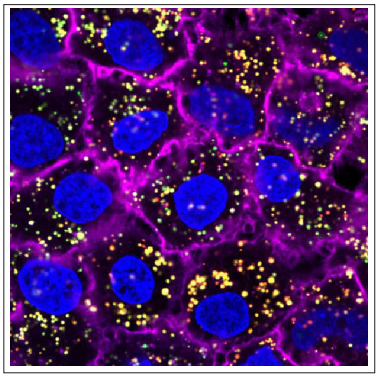

Figure 1: Nanoparticles against Cancer (From Nanotech News)

The Surface-Enhanced Raman Spectroscopy Nanotag

The surface-enhanced Raman spectroscopy (SERS) nanotag targets molecules using lasers, resulting in light scattering at different wavelengths of the electromagnetic spectrum. Because the molecules produce weak signals, gold or silver NPs are usually employed to amplify the signals, which are subsequently analyzed by a Raman spectrometer. The process is highly sensitive but fraught with challenges, including difficulties with reproducibility, signal stability and apparently a lack of quantitative information although Raman spectral quantities (line frequency center, line spectral width and four-dimensional spectral polarization vector) could theoretically provide the needed information. It has nonetheless shown significantly better properties for use in cancer detection and treatment.

The nanotag structure is comprised of a smooth inner metallic core surrounded by a spiky metallic outer shell with three-nanometer [nm] spacing. It has the following advantages: (a) it can produce a X10 times greater signal enhancement compared to smooth-shell core structures, making it possible to detect minute amounts of organic molecules, such as DNA for particular diseases; (b) a more efficient (spiky) structure generating heat that can be used to destroy cancer cells; and (c) an increased surface area that can accommodate more drugs in order to deliver a greater targeted blast to diseased cells allowing to target, image and release drugs all with one device [4].

Gelatin Nanoparticles for Delivering Multiple Drugs to the Brain

Gelatin is biocompatible, biodegradable and generally recognized as safe by the FDA. Gelatin NPs are laced with the drug *osteopontin* and administered intra-nasally along the olfactory nerve cells – a noninvasive and direct route to the brain, to reduce inflammation and prevent brain cell death. This delivery pathway bypasses the blood brain barrier (BBB). It can be most effective in delivering drugs that cannot otherwise cross the barrier and it can deliver therapeutic agents to specific regions of the brain. Once administered, the gelatin NPs target damaged brain tissue thanks to an abundance of gelatin-munching enzymes produced in injured regions. As far as is known, gelatin particles have not yet been used clinically to treat glioblastomas (GBMs).

Platelet-Coated Nanoparticles

The platelets (~100 nm in diameter) can deliver drugs to targeted sites in the body, particularly injured blood vessels, as well as organs infected by harmful bacteria. Delivered where needed, these NPs can greatly increase their therapeutic effects by directly depositing a much higher dose of medication specifically to diseased areas such as injured blood vessels and infected organs without saturating the entire body with drugs. This principle has broad implications for targeted therapy for other diseases than cancer such as neurological disorders.

Nutshells

These NPs (~120 nm in diameter) are coated with gold. They can be targeted to bond to cancerous cells by conjugated antibodies or peptides to the anopheles' surface. By irradiating the tumor with an infra-red laser, which passes through flesh without heating it, the gold is heated sufficiently to cause death to the cancer cells. It is to be noted that gold NPs strongly associate with essential blood proteins (albumin, fibrinogen, gamma-globulin, histone and insulin) and undergo conformational change upon association with the NPs [5].

Shape-Shifting Engineered Nanoparticles

NPs can also be engineered to respond to biological molecules by changing shape to gain access to diseased tissue. These shape-shifters are made of minuscule chunks of metal with strands of DNA attached to them. The targeted molecular delivery system uses modular NPs whose shape, size and chemistry can be altered by the presence of specific DNA sequences. The NPs float around harmlessly in the blood stream until a DNA strand binds to a sequence of DNA known to be a marker for cancer. When this happens, the particle changes shape, then carries out its function: target the cancer cells, expose a drug molecule to the cancerous cell and tag the cancerous cells with a signal molecule. This approach can theoretically be imbedded in personalized nanomedical treatments, further tailoring the particles to deliver drugs to specified tumors and nowhere else.

Kinase Inhibitors in Nanoparticle Formulation

Efforts to apply NBT in cancer have focused almost exclusively on the delivery of cytotoxic drugs to improve therapeutic index. There has been little consideration of molecularly targeted agents, in particular kinase inhibitors, which can also present considerable therapeutic index limitations. Examples are accurin polymeric NPs that encapsulate the clinical candidate AZD2811 (an Aurora B kinase inhibitor) using an ion-pairing approach [6]. Accurins offer several advantages, they increase biodistribution to tumor sites; provide extended release of encapsulated drug payloads; show accumulation and retention in tumors with minimal impact on bone marrow pathology; and result in lower toxicity and increased efficacy. Accurins specifically and nanotechnology in general, can increase the therapeutic index of molecularly targeted agents, including kinase inhibitors targeting cell cycle and oncogenic signal transduction pathways.

Bioavailability-Improved Nanoscale Particles and Molecules

NPs and molecules can also be developed to improve drug bioavailability, i.e., the presence of drug molecules where they are needed in the body and where they will do the most good. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. It can be achieved by employing nano-engineered devices that target the molecules and deliver drugs with cell precision.

Lipid-Polymers and Polymeric Hybrid Nanoparticles

To overcome both the dose-limiting side effects of conventional chemotherapeutic agents and the therapeutic failure incurred from multiple drug resistance (MDR), biodegradable lipid-coated polymeric hybrid nanoparticles (LPH-NPs) and polymeric nNPs (PNPs) have been designed. These form a new generation of therapeutic delivery platforms for targeted and synergistic co-delivery of drugs. They are constituted of core-shell NP structures comprising polymer cores and lipid/lipid-PEG shells. The cores and the shells exhibit complementary characteristics of both PNPs and liposomes, particularly in terms of their physical stability and biocompatibility. They exhibit superior *in vivo* cellular delivery efficacy compared to that obtained separately from PNPs and liposomes [7]. They can deliver a single drug or a combination of drugs. (They can also deliver genetic materials, vaccines and diagnostic imaging agents).

LPHs and PNPs loaded with multiple drugs have been used to treat several forms of cancer such as, for example: (a) *Docetaxel* and *Curcumin*: This combination is used to combat metastatic castration-resistant prostate cancer patients. The synergism between these two drugs was also found to overcome MDR; (b) *Doxorubicin and Curcumin*: Have been employed against osteosarcoma and (c) *Cisplatin and Curcumin*: Against cervix adenocarcinoma cell line (HeLa cells), the drug combination showed significantly higher *in vitro* cytoxicity and better *in vivo* antitumor activity than other formulations [8,9]. LPHs were more efficacious than PNPs and free drugs.

Lipid-Based Surface Engineered PLGA Nanoparticles

Polylactic co-glycolic acid (PLGA)-based nanocarriers are one of the most promising drug and gene delivery systems for crossing the BBB. While they offer great promise, they nevertheless present several major challenges and intrinsic drawbacks, require further engineering for clinical and research applications. These challenges include synthetic hydrophobic surface, low transfection efficiency, short circulation half-life and nonspecific tissue distribution. To overcome these problems, numerous engineering strategies have been employed with lipid-based surface functionalization of PLGA NPs showing promising results: enhancement of target specificity of the carrier, improvement of its physicochemical properties, NP-cell associations such as cellular membrane permeability, immune responses and long *in vivo* circulation half-life [10]. These challenges can be classified in three major categories: (a) First generation NPs involving strategies to facilitate travel from the injection site; (b) Second generation NPs involving BBB pre-transcytosis to enhance passage across the brain endothelial cells; and (c) Third generation NPs to achieve targeting of the impaired system cells (post-transcytosis strategies). A fusion of all or some of these strategies may be required to engineer multi-functional PLGA NPs for treating neurological disorders for which pharmaceutical treatments have been limited due to drug access to the central nervous system (CNS).

Engineered Nanoscale Devices

Engineered nanoscale devices (ENDs) are minute devices with the potential to be engineered to efficiently and more safely deliver drug treatments directly to the location of diseased cells while helping avoid harm to healthy cells that fall victim to toxic drugs administered by conventional means. Because of their diverse capabilities, nanoscale devices can contain both targeting and therapeutic agents (in both single and multi-drug approaches). They can deliver high drug levels in several situations, including anticancer drugs at the tumor site that can increase chemotherapeutic efficacy. They can also offer the opportunity to develop new approaches to therapy, including "smart" nanotherapeutics to "time" the release of any given drug or to deliver multiple drugs sequentially in a timed manner or at several locations in the body.

Hybrid Nanocrystals

A library has been developed of 800 different and uniquely shaped hybrid nanocrystals. They are formed from ordered atom clusters. They act as new tools or molecular tags enabling and aiding targeted drug delivery [11]. These new nanocrystals are multifunctional and able to be multi-tasked to do different things simultaneously. Their fabrication can be precisely controlled to create different shapes and sizes, allowing the assessment of the drug impact along its propagation path within the body.

Super-Paramagnetic Iron Oxide Nanoparticles

Nanoscale magnets offer a new way to find faint early traces of cancer in patients. They make use of magnetic relaxometry signals from superparamagnetic (SPM) iron-oxide NPs (size~25 nm) that find and attach themselves to cancerous cells. Such small cancer signals would never be detected by X-rays. Today's best cancer detection methods only catch tumors with more than 10 million cancer cells. This new approach has the potential to detect tumors with as few as 20,000 cells! The SPM NPs are enhanced with antibody proteins that target biomarker proteins produced by cancer cells. Once they bind to the cells, their range of motion is severely restricted and this restricted movement is pretty important. Upon applying an external magnetic field, the particles' dipoles will align to counteract the field. Once the dipoles face each other, the net magnetic field is essentially zero. Quantifying this relaxation phase marks the location of cancer cells. Unbound NPs will randomly reorient themselves in less than a millisecond, but because antibody-associated NP complexes that are bound to cancer cells are restricted in their movement, their magnetic relaxation is a lot slower (up to a second). Relaxometry measures this latter characteristic. This is the very principle of magnetic resonance imaging (MRI). It turns out the moments relax at a very different rate when they belong to NPs that are bound to cancer cells [12].

Nanodevices for Drug Delivery against Cancer

Miniaturized devices loaded with life-saving drugs may revolutionize chemotherapy, reducing the debilitating side effects of the therapy, making medications more effective and all the while preserving the healthy living cells (The same systems could likewise be used for delivering clot-busting drugs to the brain). Several "nano-carriages" for drug delivery have been created but many challenges remain, chief among them being how not to let the medicine act before it gets to the right place in the body. The carriers usually encapsulate drugs through long-range electrostatic interactions wherein the carrier attracts oppositely charged medicines. Other tools are available to trigger the release of drugs, for example, an external magnetic field, ultrasound waves, different pH values, etc. But, in each case,

researchers face the problem of efficiency of the drug release.

Protein Cages

These tiny protein cages can deliver chemotherapeutic chemicals directly to cancer cells, improving treatment and lessening side effects from toxic drugs. They use *apoferritin*, the same ball of natural proteins that carries iron around in blood without letting the iron leak out. Apoferritin is made of 24 pieces that can conveniently open and close, depending on the surrounding acidity. For lung cancer, the cage's exterior is modified with a ligand (a signal triggering molecule) to render the cage particularly attractive to a common cancer cell receptor. The anticancer drug *daunomycin* was subsequently inserted into the cage. With the addition of a small amount of acid and adjusting the pH to below neutral, the protein cage slightly opened and let the drug jump inside, where it stayed until it came in contact with the cancer cell. When the ball of drugs entered the acidic environment of the cancer cell, the cage opened and delivered the drug directly. It was determined that the ligand-guided protein cages selectively penetrated and killed more than 70 percent of the cancer cells while, contrary to typical methods of drug delivery used in chemotherapy, the system did not attack healthy lung cells.

Microbubbles

Microbubbles (size ~ 1/100th of a human hair) are tiny balls of gas enclosed in an ultra-thin layer of fat and containing anti-cancer drug(s). When injected into the blood stream, upon reaching the unhealthy part of the body, the bubbles burst with ultrasound waves, releasing the drug(s) exactly where needed. Because the entire blood stream is not being flooded with the drug(s), side-effects from chemotherapy can be greatly reduced.

Multi-Shell Hollow Nanogels with Responsive Shell Permeability

Departing from the multi-layered shell design and irrespective of any electrostatic force (i.e., whether the medicines are either charged or neutral), gel nano-capsules are filled by the guest molecules, locking the molecules in the cavity and releasing them under temperature control. The carrier is surrounded by two "membranes" (or shells) of different chemical structures around a silica core which, at the end of the synthesis, will be chemically dissolved leaving only the "empty space" (cavity). The outer porous shell plays a protective (stabilizing) role and hinders aggregation of the nano-capsules, while the pores of the inner shell can open and close depending on the temperature. At the time of filling, the pores of both shells are open and the nanogel absorbs the drug molecules as a sponge. Then, the temperature changes and the pores of the inner shell close locking in the cavity and readying the drug for delivery. Subsequently, the pores will open again and the guest molecules will be released only in the places where the temperature allows (Figure 2).

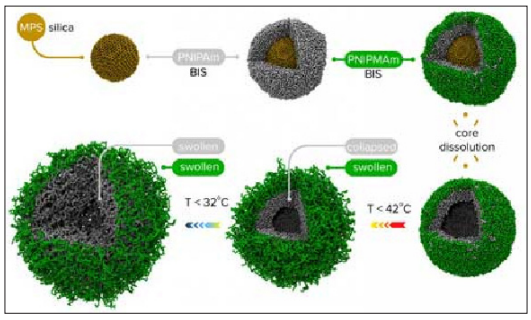

Figure 2: Multi-Shell Hollow Nanogels with Responsive Shell Permeability (From Prof. Potemkin, Moscow State University)

Helix Micelles for Brain Cancer Therapy

NBT has a fundamental role to play in the treatment of glioblastoma (GBM) or cancer of the brain. GBM is virtually inoperable, resistant to therapies and always fatal, usually within 15 months of onset. Each year, it kills approximately 15,000 people in the U.S. One of the major obstacles to treatment is the BBB, the network of blood vessels that allows essential nutrients to enter the brain but blocks the passage of other substances. What is desperately needed is a means of effectively transporting therapeutic drugs through this barrier.

Although there are FDA-approved therapeutic drugs for the treatment of GBM, these treatments have had little impact on patient survival rate because the BBB has limited the accumulation of therapeutics within the brain. Typically, GBM therapeutics are ferried across the BBB in special liposomes (size ~ 110 nm). By contrast, the 3HM nanocarriers (see below) are only about 20 nm in size. Their smaller size and unique hierarchical structure afforded the 3HM nanocarriers much greater access to rat GBM tumors than 110 nm. Copper-64 is used to label both 3HM and liposome nanocarriers for systematic PET and MRI studies to find out how a nanocarrier's size might affect the pharmacokinetics and biodistribution in rats with GBM tumors. The results not only confirmed the effectiveness of 3HM as GBM delivery vessels, they also suggest that PET and MRI imaging of NP distribution and tumor kinetics can be used to improve the future design of NPs for GBM treatment.

One solution is represented by a new family of nanocarriers formed from the self-assembly of amphiphilic peptides and polymers, called "3HM" for coiled-coil 3-helix micelles. At only 20 nm in size and featuring a unique hierarchical structure, these new nanocarriers meet all the size and stability requirements for effectively delivering therapeutic drugs to GBM tumors. Amphiphiles are chemical compounds that feature both hydrophilic and lipophilic properties. Micelles are spherical aggregates of amphiphiles. They can cross the BBB and accumulate inside GBM tumors at nearly double the concentration rate of current FDA-approved nanocarriers (Figure 3). They have shown very good attributes for the treatment of brain cancers in terms of long circulation, deep tumor penetration and low accumulation in off-target organs such as the liver and spleen. There also is the possibility that they can be administered intravenously rather than invasively.

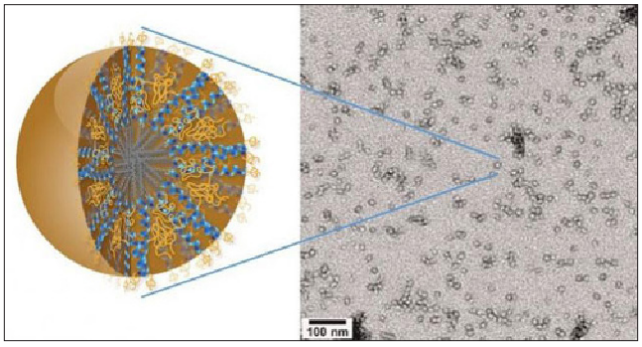

Figure 3: 3HM Nanocarriers for Effective Delivery of Therapeutic Drugs to Brain Cancer Tumors (From Dr Ting Ha, Lawrence Berkeley National Laboratory)

Nanobiochemotherapy Versus Conventional Chemotherapy

Conventional chemotherapy employs cytotoxic drugs known to kill cancer cells effectively but also healthy cells, leading to adverse side effects (nausea, neuropathy, hair-loss, fatigue and compromised

immune function). As stated earlier, NPs can be used as drug carriers for chemotherapeutics to deliver medication directly to the tumor while sparing healthy tissue. They have several advantages over conventional chemotherapy, including: (a) protecting drugs from being degraded in the body before they reach their target; (b) enhancing the absorption of drugs into tumors and into the cancerous cells themselves; (c) allowing for better control over the timing and distribution of drugs to the tissue, making it easier for oncologists to assess how well they work; and (d) preventing drugs from interacting with normal cells, thus avoiding side effects.

Active or/and Passive Targeting

Nano-sized drugs can be targeted either passively or actively, or a combination thereof. In the former case, through a process known as "enhanced permeability and retention (EPR)", because of their size and surface properties, certain NPs can escape through blood vessel walls into tissues. In addition, tumors tend to have leaky blood vessels and defective lymphatic drainage, causing NPs to accumulate in them, thereby concentrating the attached cytotoxic drugs where needed, protecting healthy tissue and greatly reducing adverse side effects. In active targeting, the molecules that bind particular cellular receptors can be attached to a NP to actively target cells expressing the receptor. Active targeting can even be used to bring drugs into the cancerous cell by inducing the cell to absorb the nanocarrier. Active targeting can be combined with passive targeting to further reduce the interaction of carried drugs with healthy tissue. Nanotechnology-enabled active or/and passive targeting can also increase the efficacy of chemotherapy, achieving greater tumor reduction with lower doses of the drug.

Nanoshells for Intra-Cellular Destruction

Moving away from conventional chemotherapeutic agents that activate normal molecular mechanisms to induce cell death, researchers are exploring ways to physically destroy cancerous cells from within. One such technology previously described (nanoshells) is being used in the laboratory to thermally destroy tumors from the inside. Nanoshells can be designed to absorb light of different frequencies, generating heat (hyperthermia). Once the cancer cells take up the nanoshells (via active targeting), near-infrared light is applied to be absorbed by the nanoshells, creating an intense heat inside the tumor and selectively killing tumor cells without disturbing neighboring healthy cells. Similarly, new targeted magnetic nanoparticles are in development that will both be visible through magnetic resonance imaging (MRI) and can also destroy cells by hyperthermia.

New Directions Urged To Improve Cancer Nanobiotechnology

Experiments with laboratory animals and efforts based on current assumptions about drug delivery have largely failed to translate into successful clinical results [13,14]. New directions are therefore urged to improve cancer NBT, including:

- Designing NPs small enough to pass through pores in blood vessels surrounding tumors but too large to pass through pores of vessels in healthy tissue;
- Fabricating "tumor-microenvironment-on-chip (T-MOC)" devices that would allow the study of the complex environment surrounding tumors and the barriers that prevent the targeted delivery of therapeutic agents. This could help solve a daunting obstacle: even if drugs are delivered to areas near the target tumor cells, the treatment is still hindered by the complex microenvironment of tumors (Figure 4). Merely killing the tumor cell would not cure the cancer because the complex environment (non-cancerous cells, blood vessel structure) supports the cancer cells;
- Developing water-soluble drugs to effectively deliver medicines. Indeed, cancer drugs need to be aqueous because the body resorbs them better, but a lot of the current chemotherapy drugs have low solubility and usually need different types of solvents to increase their solubility; and
- Evolving the treatment approach towards precision medicine that would be tailored to particular types of cancer. Recent advances in tissue engineering and microfluidic technologies present an opportunity to realize *in vitro* platforms as alternatives to animal testing. Such a major shift in research focus could play a role in developing personalized medicine (or precision medicine) tailored to a particular type of cancer and specific patients. More effective treatment might require various "priming agents" in combination with several drugs to be administered simultaneously or sequentially. Moreover, since small animal data have not been good predictors of clinical outcome, it is essential to develop *in vitro* test methods that can represent the microenvironment of human tumors [15,16].

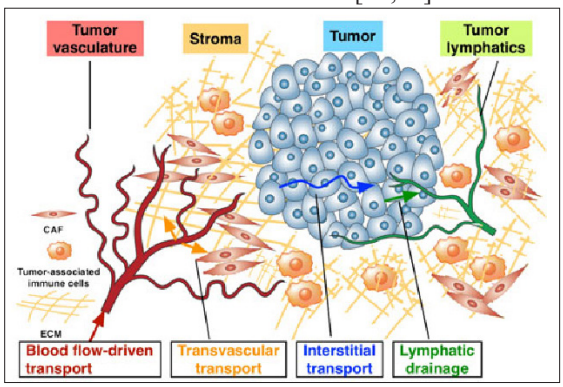

Figure 4: The Complex Microenvironment of Tumors Presents a Challenge in Developing Effective Anticancer Treatments that Attempt to Harness Nanotechnology (From Bumsoo Haan, Kinam Park and Murray Korc)

Conclusion

Nanobiotechnology offers several clinical advantages among which are the following. The nanoparticles can circulate throughout the bloodstream without being attacked by the immune system; they preferentially bind to damaged blood vessels and certain pathogens, allowing them to deliver and release their drug payloads to specific body sites; many are non-toxic as the platelet membranes are nanoparticle cores made of a biodegradable polymer that can be safely metabolized by the body; they can be packed with many small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets; they can overcome multi-drug resistance particularly after the failure of conventional chemotherapy and radiotherapy; and they enable tracking the path of chemotherapeutic drugs in real time and at the cellular level, a possibility that could revolutionize cancer care and help sort out why two patients might respond differently to the same treatment. Notwithstanding all of these clinical advantages, nanomaterials may present potential toxic effects, as was the case in the use of engineered nanoparticles and biologic microparticles in blood and their biomarker applications and the use of carbon nanomaterials (carbon fullerenes and carbon nanotubes). Investigating such potential toxic effects is of paramount importance.

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