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Review Article

SOLID TUMORS: A REVIEW

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ABSTRACT

The therapeutics of tumor is largely confined upon directly encountering the tumor cells. The current cytostatic agents mainly interfere with processes involved in cell growth while the aim in immunotherapy is to make immune effector cells to selectively attack the tumor cells. A recent approach to fight tumor is to impede and interfere with its blood supply, i.e., turning off angiogenesis or neovascularisation. Drug delivery systems including polymeric carriers and colloidal carriers like liposomes, immunoliposomes, microspheres, nanoparticles are often directed against epitopes present on tumor cells and/or receptors expressed on tumor cells and carry drugs which interfere with tumor growth. In all cases, the bioactive has to cross the tumour blood vessel wall consisting of endothelial cells and basement membrane. Especially in drug delivery strategies in which polymeric, macromolecular or particulate carriers are used to increase treatment selectively, the endothelial barriers form a major obstacle.

INTRODUCTION

Over 85% of human cancers are solid tumors. The significant progress in the development of anticancer technology, there is still no common cure for patients with malignant diseases. The effectiveness of cancer therapy in solid tumors depends on adequate delivery of the therapeutic agent to tumor cells. Inadequate delivery would result in residual tumor cells, which in turn would lead to regrowth of tumors and possibly development of resistant cells. In addition, the long-standing problem of chemotherapy is the lack of tumor-specific treatments. Traditional chemotherapy relies on the premise that rapidly proliferating cancer cells are more likely to be killed by a cytotoxic agent. In reality, however, cytotoxic agents have very little or no specificity, which leads to systemic toxicity, causing undesirable severe side effects such as hair loss, damages to liver, kidney, and bone marrow. Therefore, various drug delivery protocols and systems have been explored in the last three decades[1].

Cancer chemotherapeutic agents are often administered systemically. Following a systemic administration, drug delivery to cells in solid tumors involves three processes, i.e., transport within a vessel (e.g., blood circulation), transport across vasculature walls into surrounding tissues, and transport through interstitial space within a tumor[2]. These processes are determined by the physicochemical properties of a drug or particle (e.g., molecular or particle size, diffusivity, drug binding to cellular macromolecules) and the biologic properties of a tumor [e.g., tumor vasculature, extracellular matrix components, interstitial fluid pressure (IFP), tumor cell density, tissue structure and composition]. In the last 15-20 years the role of efflux proteins and membrane transport in tumor cells was evaluated[3]. Cancer drug delivery is no longer simply wrapping the drug in new formulations for different routes of delivery. Nanotechnology, polymer chemistry and electronic engineering technologies are being brought for developing novel methods of drug delivery & their designing[4].

Various stages of tumor development (Fig. 1) can be explained as follows:

a) Tumor evolution commences when a cell (or some of likes) within a normal population sustains a genetic mutation that expands its tendency to proliferate when it would normally rest.
b) Genetically altered cell and its offspring continue to appear normal, but they reproduce excessively and lead to a condition termed to as hyperplasia. After some time (months or years) one in a million of these cells sustain additional mutation with subsequent loss of control on cell growth.
c) The offspring of this cell not only proliferate excessively but also appear abnormal in shape and in orientation. The tissue is now said to exhibit a condition termed to as dysplasia. After some time, a further mutation that alters cell behavior results.
d) The influenced and genetically altered cells turn still more abnormal in growth and appearance. If the tumor mass do not invade through any boundaries between tissues, it is termed as in situ tumor. This tumor may stay contained indefinitely however, some cells may acquire additional mutations.
e) A malignant tumor results if the genetic changes allow the tumor mass to initiate invading underlying tissue and to cast off cells into the blood or lymph. The defector cells may install new tumors loci (metastases) throughout the body.

Tumor vasculature

Tumor vasculature

Like in healthy tissues, tumor neovascularization may include angiogenesis, vasculogenesis, and intussusception. Angiogenesis represents the process of new blood vessels sprouting from existing vessels. Angiogenesis is the key event in establishment of the tumor vasculature[5]. Blood supply to tumors plays a vital role in delivering the therapeutic agents to solid tumors[3, 6]. Small tumors less than 2 mm in diameter are perfused by vasculature basically from surrounding host tissues. Growth and enlargement of tumors are accompanied by newly formed microvessels[7]. Tumor vasculature differs from the normal tissues vasculature both as functionally & morphologically. Blood vessels of tumors are generally more hetrogenous in nature, large in size with more permeability [8, 9]. There are quantitative differences in the vasculature of transplanted animal tumors and spontaneous human tumors e.g. high vascular density and better blood circulation in transplanted tumors because of absence of sinuses[10, 11]. Implanted tumor vasculature is likely to different from the spontaneous tumor i.e. the neovascularization is required to support the large number of implanted tumor cells, while the early stages of spontaneous tumors can be supported by normal vasculature supplying the adjacent normal tissues until the tumor size exceeds 2 mm in diameter, which requires few months to years of its process[7]. Most of the data available is from the vasculature of transplanted tumors. Impanted colon tumor cell lines (LS174T) which resulted in sprouts into the tumor after 3 days and establishment of microvasculature with in 10 days. Tumor vasculature which is highly heterogeneous with high density, length, diameter, vessels distribution depends on the location with in a tumor and its size[6]. Tumor vasculature was categoriezed in four regions (i) avascular necrotic region with no vasculature (ii) seminecrotic region characterized by capillaries, precapillaries and

postcapillaries extend without branching, towards the avascular necrotic region (iii) microcirculation stabilized region with many venular and driange vessels and few arteriolar vessels (iv) advance tumor region where the flow is similar to percolation in porous medium[12]. Central regions of the tumor show less density than the peripheral regions[9]. The ratio of avascular and seminecrotic regions to well-perfused regions is also a function of tumor size, i.e., larger avascular regions in larger tumors, which partly explains the lower average drug concentration in larger tumors[2,12,13]. Heterogeneity in tumor vasculature contributes to uneven drug distribution within solid tumors. Comparing the blood vasculature in transplanted rat hepatoma tumor with normal subcutaneous tissues shows large volume (50 vs 20%), surface area (70 vs 20 mm^2/mm^3) and length (36 vs 160 cm/mm^3) in tumor vessels with active neovascularization[14]. Studies show absence of vessels in the necrotic region of the tumor. The microvessels of rat colon tumors shows large diameter of capillaries (5-20 vs 5-8μm) and venules (15-70 vs 12-50μm) when compared with normal colon tissues[15]. Because of the tumor vessels diameter exceed the size of the most drug molecules (<1-2μm). The size of the tumor microvessels is not the limiting factor for drug delivery to tumors.

The unique feature of tumor microvessels is the leakiness which results from the discontinuity of the endothelium[16,17]. This unusual leaky features of tumor vessels result in increased interstitial pressure that would further restrict fresh blood flow into the tumor tissue. Thus, normalization of tumor vessels and blood supply would improve drug delivery into the tumor tissue[5]. Studies with transplanted rodent tumors shows that tumor microvessels pore size varies from 100-780nm in diameter which depends on the anatomic location of the tumor and growth of the tumor[18,20]. In comparison, microvessels in most normal tissues (with the exception of kidney and liver) are less leaky; the tight junctions between endothelial cells are usually less than 2 nm[21], whereas the pore size in postcapillary venules is larger at up to 6 nm[22,23]. Fenestrated endothelium of the kidney glomerulus and the sinusoidal endothelium of the liver and spleen show larger pore size of 40–60 nm and 150 nm, respectively[24,25].

Tumor blood flow

Microcirculation plays an important role in the growth, detection, metastasis and in the treatment of tumors i.e. angiogenesis and blood circulation supplies the nutrients and removes the waste products during tumor growth. Vehicle for the cancer cells are provided by the lymph vessels and blood to metastasize the cells to distant tissues. Drug transport was affected by the tumor blood flow through the vasculature space in a tumor. Blood flow is determined by the pressure difference between the arterial and venous blood flow and the flow resistance. Flow resistance is basically affected by the viscosity of the blood flow and the length and the diameter of the blood vessels[6]. Blood viscosity in case of tumor as compared to normal tissues is increased due to the presence of the tumor cells and large molecules like proteins and collagen which are drained from the extravascular space, which results in a greater flow resistance in tumor blood vessels. Tumor tissues also show similar arterial pressure but a lower venous pressure when compared with the normal tissues[26]. Internal region of the tumor blood vessels are veins or venuoles, while the peripheral region have few arteries or arterioles[27]. The pressure difference between the arteriole & venuole provides a driving force for blood flow which is negligible in central region of a tumor and is greater in peripheral compartment. This explain the heterogeneous blood flow with in a solid tumor, which is lower in the center but higher in periphery of tumor relative to the blood flow in the surrounding normal tissues[27-29].On the whole, the average blood flow in tumors is lower than in normal tissues[30].

Tumor blood flow measurement

Major methods used for tumor blood flow measurement include magnetic resonance imaging (MRI), positron emission tomography (PET) and droppler ultrasound imaging. For MRI, the earlier studies measured the clearance or uptake of deuterated water in tumors[55-57], but more recent studies suggest that functional gradient recalled echo MRI[58,59] and perfusion MRI[60] are as effective as the radionuclide-based techniques, both in sensitivity and specificity.

Lymphatic drainage in tumors

The major function of lymphatic system is to return the interstitial fluid to the blood circulation. Lymphatic vessels are widely distributed through out the body and become more permeable to solutes and fluid than the blood capillaries. In most normal and inflammatory tissues, macromolecules are cleared from the tissues via lymphatic system[31]. Like particles like tumor cells are deteched from the primary tumor can enter the lymph by passing between the endothelial cells of the lymphatic capillaries. An impaired lymphatic system is a characteristic of solid tumors[3].

Drug transport through tumor vasculature into the surrounding tumor tissues

Transport through blood vessels

Molecules are extravasated from blood vessels after being transported to tumor through the blood circulation. Extravasation is also associated with the fluid movement across the vasculature wall. Fluid exchange is dependent on the hydrostatic and osmotic pressure difference between the blood vessels and interstitial space. Microvascular pressure also plays an important role in determination if transvascular drug transport as well as in tumor tissues blood flow[6]. Drug transport across tumor microvascular wall is through extravasation via diffusion and/or convection through the discontinuous endothelial junctions. In comparison, transcytosis also plays a minor role[32,33]. The pore size of tumor microvessels which is 100-780 nm limits the molecules/particles distribution larger than 1μm across the tumor vasculature[18,19]. The difference in vascular permeability between tumor and normal tissues partly explains the passive tumor targeting, i.e., the tumor-selective delivery of macromolecules such as liposomes and drug-conjugated high molecular- weight polymers[24,33].

Transport through lymphatic system

Drug delivery and their retention in solid tumors are affected by the lack of lymphatic drainage i.e. defective lymphatic flow in the solid tumors decreases the clearance of high molecular weight compounds from tumor interstitium[34]. Defective lymphatic flow together with the leaky tumor blood vessels results in enhanced permeation & retention for high molecular weight compounds to the solid tumor. A phenomenon recognized as the enhanced permeability & retention (EPR) effect[34-36]. EPR effects predominant for compounds with molecular weight larger than 40 kDa, but it is negligible for smaller molecules which are readily redistribute in the blood circulation via diffusion and/or convection[36]. Study also report that EPR is also affected by the size of the tumor, having a greater EPR in small tumors, because of the greater vessel density as compared to larger tumors containing avascular region[37]. A comparison of the accumulation of radioiodinated (2-hydroxypropyl) methacrylamide copolymers with molecular weights ranging from 4.5 to 800 kDa administered intravenously to mice bearing sarcomas showed equal tumor accumulation/ retention for all copolymers at early time points (within 10 min), whereas the accumulation/retention after 6 h was significantly greater for the larger copolymers with molecular weights exceeding 50 kDa. In comparison, smaller co-polymers with molecular weights less than 40 kDa were cleared more rapidly from tumor interstitium. Hence, enhanced retention as a result of impaired lymphatic drainage is considered more important than enhanced extravasation from greater blood vessel permeability for the accumulation of high-

molecular-weight compounds in tumors[38]. Secondly the lack of lymphatic system in solid tumors increases interstitial fluid pressure (IFP) which is a major reason for limited extravasation of macromolecules in spite of leaky microvasculature in tumors. Enhanced IFP induces outward convective flow, inhibiting the transvascular transport of molecules as well as transport in tumor interstitial space[32,39,40].

Transport of drug in tumor interstitial space

Small molecule transport through interstitial space mainly by diffusion, where as the large molecule is mainly transport by convection[41]. Drug diffusion depends on the diffusivity and concentration gradient where as convection depends on hydraulic conductivity and the pressure difference. While tumor has high IFP as compared to normal tissues, the net convection flow in tumor interstitium follows the outward from the core of a tumor. Drugs moves through the interstitial space to reach tumor cells located in distal to blood vessels after extravasation[2,39,42]. Distance between capillaries is dependent on the status of vascularization (e.g., vascular region vs. avascular region). Vascularization is a function of tumor size; the ratio of avascular and poorly vascularized regions to well vascularized regions increases with tumor stage, which is indicative of size[12,13]. For e.g. intercapillary distance of mammary adenocarcinoma R3230CA tumor grown in rat ovarian tissue isolated tumor have a size of 49m while stage IIb & III carcinoma of the cervix uteri in human patient have size of 304 m. The intercapillary distance in solid tumors also increases with tumor size in mouse mammary tumor and rat tumors[43].

Barriers to drug transport, accumulation and retention in tumors

Physiochemical, physiologic and biologic factors with some other factors such as tissue composition, tissue architecture and drug binding to cellular components also affect drug transport, their accumulation and retention in tumors. Solid tumors which represent dynamic system due to the time dependent development of new vasculature as well as the time dependent changes that occur in tumor cell density as a result of drug induced cell death.

Drug Binding to Cellular Macromolecules

Most of the anti cancer drugs target macromolecules like proteins and nucleic acids, with some drugs are bound extensively to intracellular and/or extracellular macromolecules. Three dimensional spheroids are basically used to study the relationship between cellular drug binding and drug penetration into solid tumors. Spheroids with some characterized of solid tumors including multicellular structures, intratumoral heterogenicity including necrotic regions and oxygen gradients and extracellular matrix. When comparing the monolayer or suspension with the spheroids, later one is more similar to in vivo tumors and used to evaluate the effectiveness of radiotherapy and chemotherapy of the drug delivered[44-47]. Various studies were performed using tumor cell spheroids which show that the drug binding affects the drug penetration and spatial distribution within the spheroids. Drugs which do not bind to the cellular macromolecules or cannot cross cell membranes readily penetrate spheroids. For e.g. drugs like 5-flurouracil, cisplatin, sucrose, inulin and monoclonal antibody against anticarcinoembryonic antigen are evenly distributed in thyroid cancer cell spheroids with in 15 minutes[48-50]. In contrast, drugs like doxorubicin, daunomycin, actinomycin, methotrexate, vinblastine and paclitaxel binds to cellular macromolecules which remain localized in the periphery of the spheroids[48,51-53]. Inspite of uneven intratumoral distribution, these high binding drugs show higher average concentrations per spheroid as compared to low binding drugs.

Extracellular matrix composition

Extracellular matrix of solid tumors is composed of macromolecules such as fibrous proteins (e.g., collagen and elastin) and polysaccharides (e.g., hyaluronan and proteoglycan). Macromolecules are basically produced by host cells and their production is regulated by tumor cells[54]. Pysiologic functions of extracellular matrix in normal tissue are to maintain homeostasis, stabilize the spatial and functional relations between cells (e.g., generating tissue cohesiveness), pose as a barrier to bacterial invasion, and regulate macromolecule transport through interstitium[55]. In tumors, the extracellular matrix proteins are a source of physical resistance to drug transport[56]. Presence of glycosaminoglycan (GAG) is associated with a lower hydraulic conductivity and a lower convective flow to interstitium, however several studies shows that GAG alone does not explain the high resistance for water and solute transport to many soft tissues. For eg. Treatment of cornea with hyaluronidase reduces the GAG contents by 75% and increases the corneal stroma conductivity by 6.5 folds.

Tumor structure and composition

Importance in tumor cell density

Diffusion through tumor interstitial space is a major mechanism of drug transport in solid tumors. Drug diffusion through in a gel structure is a function of porosity and tortuosity[57,58]. A larger fraction of interstitial space and decrease in tortuosity results in more rapid drug diffusion.

The rate of drug penetration in solid tumors and the spatial relationship among drug penetration, tumor architectures and tumor cell distribution showed the following: (a) rapid drug penetration in tumors with a lower tumor cell density and a greater fraction of interstitial space (b) drug distribution to the areas with a low epithelial cell density compared to areas with a high cell density, and (c) higher drug accumulation in xenograft tumors as a result of drug binding in tumor cells. Drug penetration in solid tumors indicate a important role of tissue composition and architecture and tumor cell density which determine the rate and extent of drug penetration and the spatial distribution in solid tumors.

In summary, drug transport through interstitial space, similar to drug transport via blood circulation, is a major mode of drug distribution or delivery throughout a solid tumor. Hence, the relative importance of the transport through the interstitial space is likely to be greater in poorly vascularized tumors with reduced drug transport via blood circulation, as compared to highly vascularized tumors.

Dynamic changes in tumors

Angiogenesis

Angiogenesis or development is a dynamic process[7]. During the initial growth phase (1-2mm in diameter), tumor cells obtain oxygen and nutrients from the blood supply of the surrounding normal tissues. Angiogenesis is required for further growth of tumor beyond the microscopic stage with new blood vessels sprouting from the mature blood vessels from the surrounding normal tissues grow toward tumor cells. In tumors blood vessels are morphologically different from blood vessels in tumor tissues. Maintenance of these new vessels requires the presence of growth factors, bFGF was the first to induce angiogenesis in normal tissues. VEGF is a major inducer of tumor angiogenesis[59]. Drug supply to tumors is dynamic process which changes with time and microenvironment of the tumor.

Apoptosis

Drug induced cell death is called as apoptosis which is mainly the mechanism of anticancer drugs. It is a controlled physiologic process which occur biochemically and morphologically distinct manner and leads to cell death. Apoptosis involves sequence of events including from cell shrinkage, increased cytoplasmic density, chromatic condensation and segregation into sharply circumscribed masses and the formation of membrane bound surface apoptotic bodies[60]. Apoptotic cells are phagocytosed from the midst of living tissues by neighboring cells or macrophages without eliciting an inflammatory

reaction. Role of apoptosis in drug delivery to tumors were experimented using histocultures system. It was shown that drug induced apoptosis leads to decreased tumor cell density and expanded interstitial space, resulted in enhanced rate of drug penetration to the inner layers of the solid tumors[61-63]. Further results shows 30% apoptotic cell fraction was sufficient to enhance drug transport, while about 7 % cell fraction is not enough for enhanced drug transport[64-66]. Transport of highly protein bound drug to solid tumor which is dynamic process and determined by the drug effect.

Anticancer drugs can induce necrosis in addition with apoptosis. Whether a drug induces apoptosis or necrosis, which is dependent on intensity of the initial drug induced insult, with necrosis occurring at higher intensity[67-68]. Although both apoptosis and necrosis produces cell death and reduces tumor cell density, but there is an intense differences in the nature of cell death by these two processes. Apoptosis occurs in an orderly fashion and does not elicit inflammation, whereas necrotic cell death is accompanied by extensive inflammation. Finally, apoptosis induction typically requires lower drug concentrations and is therefore more readily attainable as a result of clinically relevant doses[67].

Experimental approaches to improve drug delivery to tumors

Enhancement of drug delivery by altering tumor blood flow

Several strategies to enhance tumor blood flow, including physical and pharmacologic methods. These approaches depend on the existing vasculature, which improves the drug delivery to vascular regions of tumors but will not improve the delivery to avascular regions. Local hyperthermia enhances the delivery of radioimmunoconjugate and monoclonal antibody in animals[69] and human patients[70], presumably through an initial increase in tumor blood flow. Hence, enhanced drug delivery by local hyperthermia results from factors other than increased blood flow. The ability of vasopressors to increase tumor blood flow was tested with angiotensin II and adrenergic vasopressors, it is shown that former was effective, whereas adrenergic vasopressors (e.g., epinephrine and methoxamine) were not effective[71-72]. At a systemic blood pressure between 100 and 150 mm Hg, angiotensin II enhances tumor blood flow without changing the blood flow of normal organs such as liver, brain, and bone marrow. The selective increase in tumor blood flow results from the loss of autoregulation of blood flow and homeostasis in tumor blood vessels[142], presumably because tumor blood vessels lack both smooth muscle cells surrounding the endothelial cells and angiotensin II receptors[71].

Enhancement of drug retention in tumors

Enhanced Permeation and retention effect was evaluated as a passive tumor targeting approach to deliver macromolecules. Tumor targeting with some macromolecules such as polymeric drug conjugate {e.g., poly(styrene-co-maleic acidhalf- n-butylate)-conjugated neocarzinostatin[34,73] and PK1[N-(2-hydroxypropyl)-methacrylamide copolymer doxorubicin]} , proteins[34,74], liposomes[75], and nanoaprticleshave been demonstrated. Some of these compounds are currently in clinical evaluation[75].

Enhanced drug delivery by modulating vascular and interstitial pressure

Greater microvascular pressure (MVP) results in an increase in transvascular fluid filtration, i.e., convection flow across the vascular wall, and in turn, enhances transvascular drug transport to tumors[32]. A lower interstitial fluid pressure (IFP) results in the same effects. Hence, a larger difference between MVP and IFP may result in a greater convective flow and fluid extravasation and thereby enhance the delivery of macromolecules. In general, either decreasing IFP or increasing MVP may enhance drug delivery to solid tumors. Some other factors like physical, chemical and pharmacologic approach including heat, radiation, photodynamic therapy, mannitol (osmotic agents), nicotinamide, dexamethasone (corticosteroids),

pentoxifylline, and tumor necrosis factor- (TNF-_) were used to lower IFP[76]. It shows that these approaches can reduce IFP sufficiently to enhance drug delivery and transport in solid tumors.

Enhancement of drug delivery using apoptosis-inducing pretreatment

Drug transport in tumor interstitium increases with expansion of interstitial space and reduction in tumor cell density. The use of apoptosis inducing pretreatment (i.e. paclitaxel & Doxorubicin) to increase the tumor transport of highly protein-bound drugs. These highly protein bound drugs are also efficient in inducing apoptosis. In vitro studies with histocultures of xenograft and human patient tumors & in vivo studies in tumor-bearing animals shows the tissue priming with these drugs enhances the rate and extent of drug delivery and eliminates the steep drug concentration gradient between the periphery and the core of solid tumors. Hence, the finding that tissue priming improves drug delivery and distribution suggests that interstitial space plays a more important role in drug delivery than MVP or IFP.

Selected delivery systems

Liposomes

Liposomes are perhaps the best vehicle for cancer drug delivery, which are capable of increasing the drug concentration in solid tumors and/or limiting drug exposure to critical target sites such as bone marrow and myocardium. In year 2000, European Agency for the Evaluation of Medicinal Products (EMEA) has approved a liposomal formulation of doxorubicin of approx 190 nm in size for the treatment of metastatic breast cancer. Macrophage deposition of I.V. administered liposomes was markedly minimized either by bilayer or surface modification[77]. Long circulating liposomes have the capability to deliver between 3 and 10 times more drug to solid tumor compared with the drug administered in free form. There are several other approaches that exploit active targeting of long circulating liposomes to tumor cells, where receptor mediated endocytosis which bypass tumor cell multidrug efflux pumps. These strategies utilize tumor specific monoclonal antibodies or their internalizing epitopes or ligands such as transferrin & folic acid, which are attached to the distal end of the polyethylene glycol (PEG) chains expressed on the surface of the long circulating liposomes (table1).

Polymeric Nanoparticles

Abraxane ™ is the only example of a regulatory approved (FDA, US) nanoparticles formulations for I.V. drug delivery in cancer patients which is a albumin nanoparticles encapsulated paclitaxel with a mean diameter of 130 nm for metastatic breast cancer. This formulation overcomes poor solubility of paclitaxel in the blood and allows patients to receive 50% more paclitaxel per dose over a 30 min period[78]. Nanoparticles assembled from synthetic polymers have received attention in cancer drug delivery[79].

Table 1: Various Drug Delivery Systems for Tumor

• Liposomes for antitumor drugs, immunoliposomes, stealth liposomes, tumor-selective targeted drug delivery via folate-peg liposomes, hyperthermia and liposomal drug delivery, liposome-mediated oligonucleotide delivery, lipid-coated microbubbles as a delivery vehicle for Taxol, use of thermosensitive liposomes and localized hyperthermia, photodynamic therapy for chemosensitization
• Microspheres as drug delivery systems in tumor therapy, subcutaneous injection of microspheres carrying antitumor drugs, magnetic targeted microparticle technology, nanoparticles for delivery of antitumor drugs, chemoembolization, antitumor drugs bound to carbon particles,

nanoerythrosomes, albumin-based drug carriers

- Monoclonal antibodies, bispecific antibody fusion protein, radio-immunoconjugates, drug immunoconjugates, immunotoxins, combined use of MoAbs and cytokines, humanized MoAbs, two-step targeting using a bispecific antibody, single-chain antibody-binding protein technology
- Ultrasonic activated drug carrying micelles, tumor-activated pro-drug therapy, site-specific delivery and light-activation of antitumour proteins
- Targeting antitumor drugs to tumor blood vessels, peptides targeted against integrin cell adhesion proteins, drugs to induce clotting in tumor vessels, vascular targeting agents, cytoporter
- Antineoplastic drug implants into tumours, polyethylene glycol technology, pressure-induced filtration of drugs across vessels to the tumour, use of vitamins as carriers for antitumour agents, delivery across the blood-brain barrier, chemotherapeutic agents incorporated in biodegradable polymer wafers, boron neutron capture therapy, tumour necrosis therapy (TNT), iontophoretic delivery into subcutaneous tumours

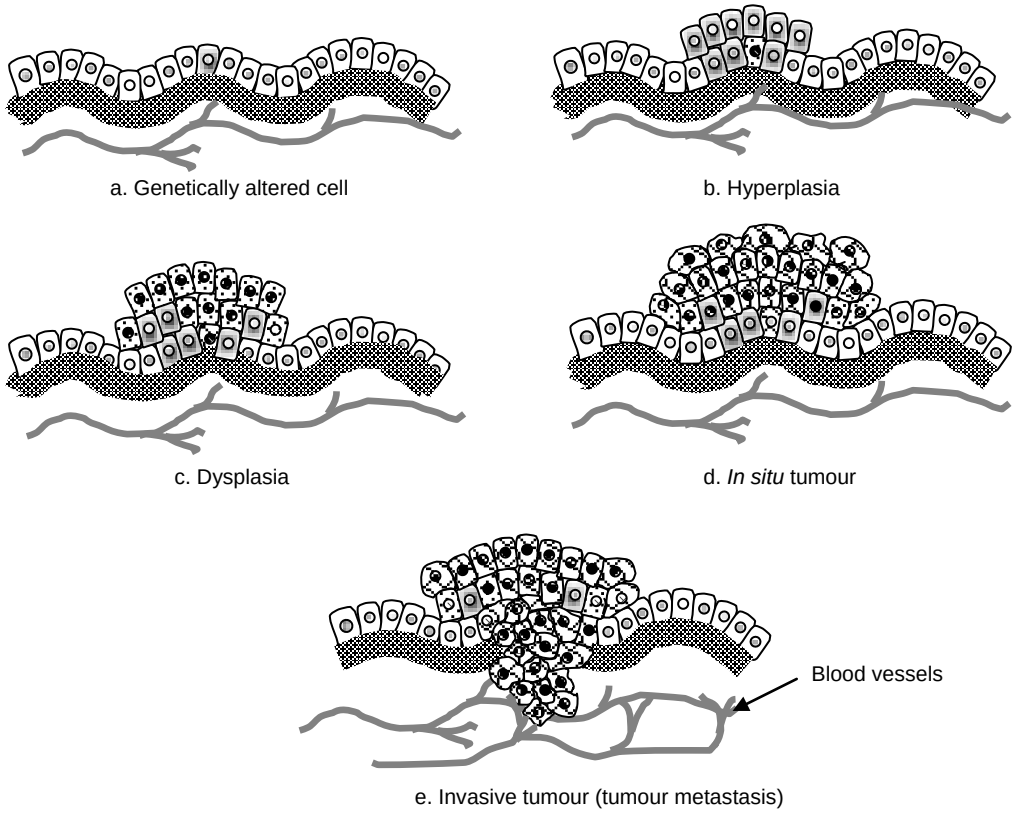

Fig. 1: Mechanisms and stages of tumor development

CONCLUSION

The innovation in research field on the targeted drug delivery would be a shift from "receptor to nucleus" reflecting a desire to construct defined pathway linking the end points of different regulatory cellular events. However, for basic and technical reasons, research efforts have been focused overwhelmingly on receptor/ligand or transcription factor/DNA interactions. In the future, targeted drug-delivery systems may also prove particularly valuable to enable the use of a drug that seems to be ineffective or toxic, if delivered systemically [e.g., neural growth factor (which need to cross blood-brain barrier) or vaccines (which need to be taken up by antigen presenting cells)].

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