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Cancer targeted therapeutics: From molecules to drug delivery vehicles

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ABSTRACT

The pitfall of all chemotherapeutics lies in drug resistance and the severe side effects experienced by patients. One way to reduce the off-target effects of chemotherapy on healthy tissues is to alter the biodistribution of drug. This can be achieved in two ways: Passive targeting utilizes shape, size, and surface chemistry to increase particle circulation and tumor accumulation. Active targeting employs either chemical moieties (e.g. peptides, sugars, aptamers, antibodies) to selectively bind to cell membranes or responsive elements (e.g. ultrasound, magnetism, light) to deliver its cargo within a local region. This article will focus on the systemic administration of anti-cancer agents and their ability to home to tumors and, if relevant, distant metastatic sites.

1. Introduction

With the injection of mustine into a patient suffering from non-Hodgkin's lymphoma in 1946 (see Scheme 1), the era of chemotherapy began whereby cancer could be treated by chemical agents [1]. Chemotherapeutics are designed to kill rapidly dividing cancer cells but also effect the cells of the skin, hair, gastrointestinal tract, and bone marrow. The pitfall of all chemotherapeutics lies in drug resistance and the severe side effects experienced by patients, including myelopenia, mucositis (linked to gastrointestinal toxicity), cardiotoxicity, and alopecia [2].

One way to reduce the off-target effects of chemotherapy on healthy tissues is to alter the biodistribution of drug (see Table 1). This can be achieved in two ways: Passive targeting utilizes shape, size, and surface chemistry to increase particle circulation and tumor accumulation. Active targeting employs either chemical moieties (e.g. peptides, sugars, aptamers, antibodies) to selectively bind to cell membranes or responsive elements (e.g. ultrasound, magnetism, light) to deliver its cargo within a local region [3]. This article will focus on the systemic administration of anti-cancer agents and their ability to home to tumors and, if relevant, distant metastatic sites.

2. Pharmacologic targeting

Pharmacological agents that act only on the diseased cells are ideal. Chemotherapeutics were initially designed to eradicate rapidly proliferating cancer cells. These agents can be designed to affect different aspects of the mitosis process. Alkylating agents, like mustine and cisplatin, covalently bind DNA and prevent DNA replication. Antimetabolites, like gemcitabine and 5-fluoruoracil (5-Fu), resemble nucleobases and can be incorporated into the cell's DNA, inhibiting enzymes involved in DNA synthesis or signaling DNA damage. Antimicrotubules, which include the family of taxanes, polymerize microtubules, arresting mitosis. Topoisomerase inhibitors affect DNA unwinding and result in DNA cleavage. Antibiotics, like the anthracyclines, intercalate within DNA.

Drug molecules can also inhibit specific receptor pathways. For example, folate inhibitors, such as methotrexate, were originally designed to bind the folate receptor on acute lymphoblastic leukemia (ALL) cells [61]. Tamoxifen competes with naturally-occurring estrogen for binding to the estrogen receptor to inhibit estrogen-mediated breast cancer growth, known as anti-hormonal therapy [14]. The tyrosine kinase inhibitor imatinib (Gleevec®) prevents phosphorylation of BCR-ABL in chronic myelogenous leukemia cells [62]. A second generation BCR-ABL tyrosine kinase inhibitor (nilotinib) was developed to overcome resistance to imatinib. Nevertheless, most chemotherapeutic agents affect healthy cells, which results in side effects that limit the dose of drug. Additionally, the dense structure of the tumor interstitial matrix acts as a tortuous, viscous, and steric barrier to diffusion of these agents [63].

3. Passive targeting

3.1. Enhanced permeability and retention (EPR) effect

Solid tumors arise due to the uncontrolled proliferation of a single cell. Solid tumors may exhibit a necrotic core due to nutrient transport limitations. In response, tumors elevate levels of vascular permeability factors such as vascular endothelial growth factor (VEGF), bradykinin, nitric oxide, peroxynitrite, and matrix metalloproteinases [21]. Differences in

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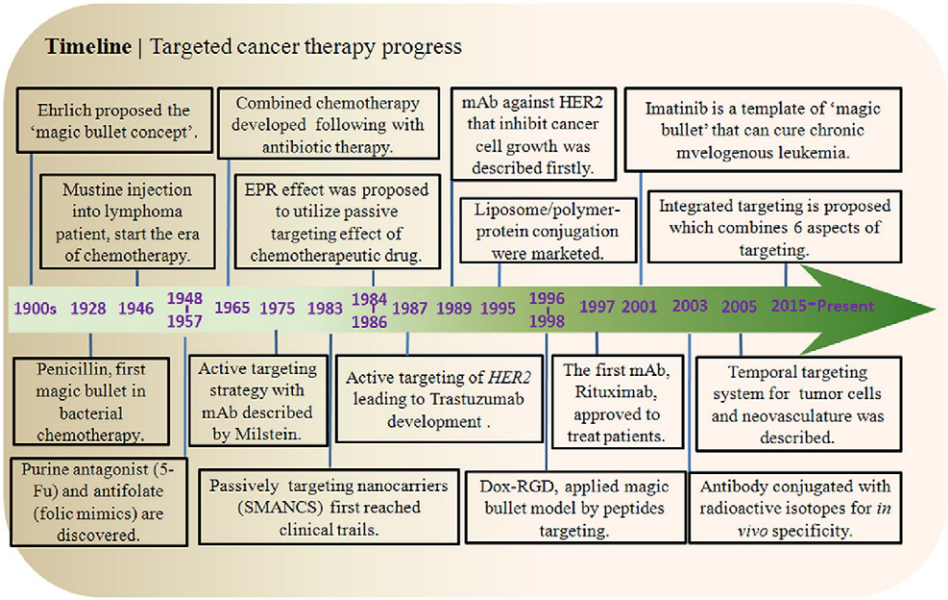

Scheme 1.

blood flow in tumors relative to normal tissues was first reported in the 1960s [64]. In 1984, the pathophysiological basis of the SMANC macromolecular drug carrier was described by Maeda et al. [65]. Two years later, the term enhanced permeability and retention (EPR) effect of macromolecules and lipids in solid tumors was coined, which is often used to describe passive delivery of anti-cancer drugs to tumors [66,67]. In tumor pathology, angiogenesis, or new blood vessel formation, results in abnormally constructed vessels with large vascular fenestrae (as large as 600 nm) and impaired lymphatic drainage [68]. As a result, particles less than 200 nm preferentially accumulate in the tumor interstitium [69]. The liver (~107 nm) [70], kidney (~5 nm) [71,72], and spleen (~110 nm) also exhibit large fenestrae, which allow chemotherapeutic nanoparticle accumulation and toxicity [73]. Additionally, phagocytosis of particles by monocytes in the liver and spleen (e.g., Kupffer cells in the liver) also contributes to the accumulation of particles in the reticuloendothelial system.

In comparison to delivery via a bolus intravenous injection, chemotherapeutics encapsulated within nanoparticles exhibit higher tumor accumulation and toxicity. Animal studies suggest that the EPR can lead to a more than 10–100-fold increase in nanoparticle accumulation within tumors compared with the use of free drugs [74]. Liposomal doxorubicin (DOXIL®) is widely used to treat ovarian cancer and Kaposi's sarcoma (more than 300,000 patients treated annually). Its preferential biodistribution protects patients from the cardiotoxicity of the unencapsulated doxorubicin [75]. Passive targeting also benefits from extended circulation time; Doxil utilizes a polyethylene glycol (PEG) coating to minimize protein and immune cell interactions. PEG brushes, between 2 and 5 kDa in length and 0.64–0.96 PEG molecular/nm^2 surface density are used widely for this purpose [57].

In addition to a favorable biodistribution, nanoparticles encapsulate and protect poorly soluble and toxic anti-cancer agents, which can improve the therapeutic index (ratio of the lethal dose for 50% of the population to the minimally effective dose for 50% of the population, or LD_{50}/ED_{50}) [76]. Thus, nanoparticles can act as "Trojan horses" whereby they conceal a toxic agent within a benign vessel. Common features of nanoparticles that are exploited in targeted drug delivery are the surface-to-volume ratio, size, shape, encapsulation efficiency, and surface chemistry. These physicochemical parameters can affect the overall blood circulation kinetics, the extravasation processes and intratumoral diffusion; however, directly measuring the influence of each specific characteristic on the EPR is difficult.

3.2. Composition

Many different materials are used in the construction of nanocarriers for the purpose of localizing chemotherapeutics within tumors via the EPR effect (Fig. 1). These materials include: nanogold [77], semiconductors [78], porous silica [79], iron oxide [80], carbon (nanotubes [81], graphene [82], nanodiamond [83]), lipids (liposome [84], exosome [85]), polymers [86], dendrimers [87], proteins (albumin, antibody) [88], cyclodextrins [89], carbohydrates [90], and the combination or conjugation among them (Fig. 1). Each material has unique structural properties. For example, polymeric nanoparticles are solid, amorphous matrices; liposomes are bilayer spheres encapsulating an aqueous or gas volume, and some inorganic structures have crystalline lattices that can adsorb or emit light; while, silicon nanoparticles have directional scattering [91]. How each particle is synthesized also affects drug loading and stability. Although each material is different, their in vivo behaviors (e.g., circulation time, protein interaction, immunogenicity, uptake, and distribution.) are often dictated by their size, shape, and charge.

3.3. Size

Size is perhaps the most well studied property in relation to nanoparticle transport. Several important in vivo functions of particles depend on particle size: circulation time, protein absorption, biodistribution, extravasation, immunogenicity, internalization, intracellular trafficking, payload delivery, and degradation (reviewed in [92,93]). As mentioned previously, carriers can extravasate through gaps in the peritumoral tissue, in a size-dependent manner. Experiments using liposomes of different mean sizes suggest that the threshold vesicle size for extravasation into tumors is 400 nm [94]. However, the compromised lymphatic drainage cannot properly efflux fluid or carriers, resulting in an elevated interstitial fluid pressure that diminishes the driving force for convective interstitial transport [63]. In mice xenograft models, when the kinetics of intratumoral accumulation were studied over 30 min, smaller macromolecules (40- to 70-kDa dextrans, 11.2 to 14.6 nm in diameter) penetrated 15 μm from the vessel wall; while, 2 MDa dextran (~50 nm) were found 5 μm from the vessel wall [95]. This accumulation was transitory as smaller molecules rapidly diffused back into the vascular compartment. Larger nanocarriers are