



This review exemplifies the latest progress in dendrimer-mediated targeted drug and gene delivery to cancers.

Recent advances in dendrimer-based nanovectors for tumor-targeted drug and gene delivery

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Advances in the application of nanotechnology in medicine have given rise to multifunctional smart nanocarriers that can be engineered with tunable physicochemical characteristics to deliver one or more therapeutic agent(s) safely and selectively to cancer cells, including intracellular organelle-specific targeting. Dendrimers having properties resembling biomolecules, with well-defined 3D nanopolymeric architectures, are emerging as a highly attractive class of drug and gene delivery vector. The presence of numerous peripheral functional groups on hyperbranched dendrimers affords efficient conjugation of targeting ligands and biomarkers that can recognize and bind to receptors overexpressed on cancer cells for tumor-cell-specific delivery. The present review compiles the recent advances in dendrimer-mediated drug and gene delivery to tumors by passive and active targeting principles with illustrative examples.

Margins of conventional anticancer therapy

Cancer is one of the world's most distressing diseases with no apparent cure in sight for several tumor types and millions of new cases reported every year [1]. Cancer is principally a disease of cells identified by the loss of normal cellular growth, maturation and multiplication leading to disturbance of homeostasis. The newly 'mutated' cancer cells begin multiplying uncontrollably; they can become parasitic and develop their own network of blood vessels to siphon nourishment away from the body's blood supply. The continuation of this process ultimately leads to the formation of a cancerous tumor, which in several cases becomes multidrug resistant (MDR) with the ability to proliferate and metastasize to distant organs and tissues within the body [2–4].

Cancer chemotherapy using conventional anticancer agents has been mired by several challenges such as unfavorable pharmacokinetic profiles, low aqueous solubility, narrow therapeutic index, poor membrane permeability, rapid clearance, instability, severe toxicity concerns and emergence of MDR phenotypes. These shortfalls call for exploration of advanced carrier systems that can, in part, mitigate some of the drawbacks associated with free-drug administration and

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facilitate tumor-targeted drug or gene delivery. In this regard, a wide range of organic and inorganic nanoconstructs such as polymeric nanoparticles, liposomes, polymeric micelles, dendrimers, solid-lipid nanoparticles, silica nanoparticles and carbon nanotubes with their massive structural diversity, tunable physicochemical properties and function can be utilized to enhance drug loading, protect the payload in transit and enable drug internalization in target cancer cells while limiting uptake in normal tissues and cells [5,6].

The development of smart cancer treatment approaches revolves around engineering such unique nanosystems carrying drug and gene payloads that can passively and/or actively target cancerous cells [7]. In this regard, a passive targeting approach is identified by accumulation of drug or drug-carrier system at a particular site as a result of the inherent pathophysiological, physicochemical or pharmacological factors [8–10]. However, an active targeting approach is identified by specific modification of drug or gene carriers with active ‘homing’ ligands that have high affinity for binding to a specific cell type, tissue or organ in the body [3,11–13] (Fig. 1). Several such delivery systems are currently under intense scrutiny and some have already made it into clinical phase trials, owing to their favorable preclinical outcomes [11,14]. In addition, unconventional alternatives are currently being explored for achieving better clinical responses [15–20]. In this review, we will focus our attention on the recent advances in dendrimer-based nanodelivery systems for targeted cancer therapy with examples.

Dendrimers as an emerging vista in anticancer therapy

In the current scenario, development of an ideal delivery system for cancer chemotherapy is extremely challenging for formulation

scientists as well as clinicians because of numerous limitations of anticancer agents, as noted above. In addition, gene therapy and newer molecular-target-based anticancer tactics involve use of potent but highly labile agents such as monoclonal antibodies, aptamers, siRNAs and miRNAs that are readily degraded and/or have limited stability *in vivo* [21]. More importantly, poor biodistribution and unfavorable pharmacokinetics of conventional anticancer agents lead to poor therapeutic response and adverse side effects involving healthy organs [22–24]. To overcome these limitations there is an urgent need for devising safe and effective carrier vectors that can protect the payload from degradation during transit, enhance targeting efficiency, optimize drug release profiles and reduce the adverse toxic effects caused by nontarget-organ accumulation of cytotoxic drugs. Such agents can also help tune the dosing regimen and ultimately improve patient compliance. Along these lines, several novel carrier systems are now available for anticancer therapy [25–30]. Among them, dendrimers are emerging as a favorable choice for delivery of a wide range of anticancer drugs and genes because of their unique properties such as high loading ability, appropriate nanosize, predictable release profile, favorable pharmacokinetics and targeting potentials [31] (Fig. 2).

Dendrimers are nanosized (1–100 nm) globular macromolecules with a unique architecture consisting of three distinct domains: a central core, a hyperbranched mantle and a corona with peripheral reactive functional groups [32]. Dendrimers can be conveniently fabricated by convergent or divergent synthesis [33,34]. The high level of control over the synthesis of dendritic architecture makes dendrimers a nearly perfect (spherical)

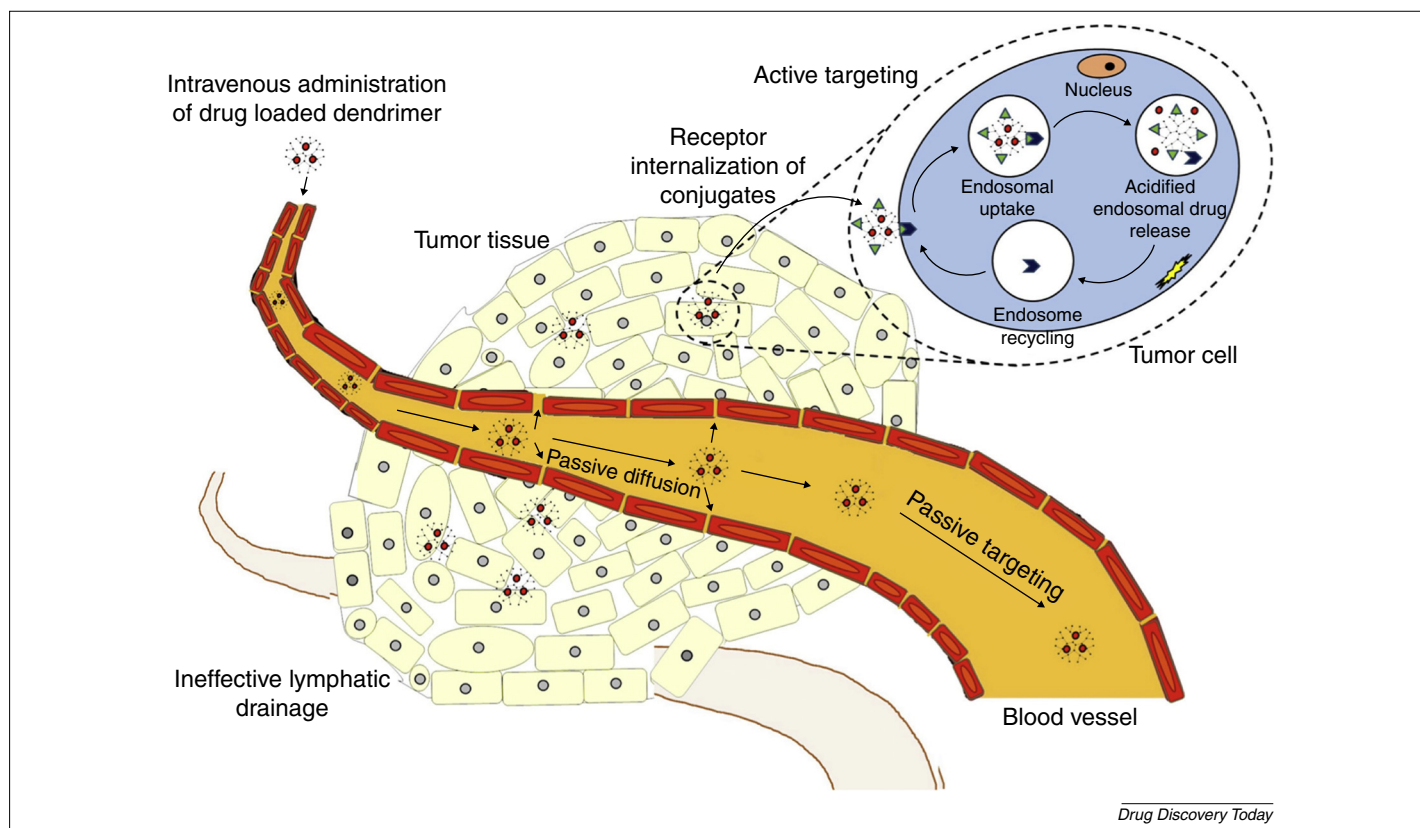


FIGURE 1

Dendrimer-mediated active and passive targeting approaches.

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