3 THERAPEUTIC NANOPARTICLES FOR DRUG DELIVERY IN CANCER: GENERAL ASPECTS

Nanotechnology, defined as the use of materials with structural features ranging from 1 to 100 nm in size, has dramatically altered the design, use, and delivery of cancer diagnostic and therapeutic agents. Nanoscale diagnostic and therapeutic agents have been in use since the development of micellar nanocarriers and polymer–drug nanoconjugates in the mid-1950s and liposomes in the mid-1960s, whereas polymeric nanoparticles were introduced by Langer and Folkman in 1976. Since then, nanoscale constructs have been developed for the systemic delivery of agents to specific disease sites, more than 20 FDA-approved diagnostic or therapeutic nanotechnologies are in clinical use, and many others are in clinical development. Nanoparticle formulations help to overcome the issue of drug solubility, which is an essential factor for drug effectiveness. Another advantage is facilitation of drug delivery across various barriers, the most important of which is the blood–brain barrier that limits access to brain tumors. Other major advantages include targeted drug delivery, reduced toxicity because of the "enhanced permeability and retention effect" (EPR; discussed below), and facilitation of a combination of diagnostics and therapeutics for cancer.[36]

Among several nanobiotechnologies based on nanoparticles that have been used to facilitate drug delivery in cancer are polymer conjugates, liposomes, and copolymer micelles. Polymer conjugates include polymer–drug conjugates (which are macromolecular small-drug carrier systems), immunoconjugated drugs, folate receptor-targeted conjugates, and polymer-directed enzyme prodrug therapies (PDEPT).

The term "polymer therapeutics" has been coined to describe water-soluble devices that use polymers as carriers and are designed for parenteral administration. They are one of the first nanodrugs, which can be defined as nanometer-scale complexes that contain at least two components, one of which is a bioactive agent.[37]

4 POLYMER CONJUGATES: MACROMOLECULAR SMALL-DRUG CARRIER SYSTEMS

In macromolecular drug carrier systems, an active drug is covalently attached to a macromolecule, an approach that has been particularly studied in the anthracyclines.[38] These conjugates may passively target solid tumor tissues by a mechanism known as the EPR effect, which is based on the increased permeability of tumor vascular endothelium due to its poor organization (Figure 13.30). This phenomenon allows that relatively large particles loaded with an antitumor drug can extravasate and accumulate inside the interstitial space, where the drug can be released as a result of normal carrier degradation.[39] More specific targeting may be achieved by using as a part of the macromolecular component an antibody directed to a tumor antigen or a peptide whose receptors are overexpressed in tumor cells.

These conjugates do not cross cell membranes, and they need to access the intracellular space by receptor-mediated endocytosis, adsorptive endocytosis, or fluid-phase endocytosis. In these processes, the cell membrane invaginates the particle, forming an intracellular vesicle (endosome) that eventually fuses with lysosomes. The macromolecular transporter is hydrolyzed and the active drug is released as a consequence of lowered pH values at both the endosomes and lysosomes, and also as a consequence of the presence of hydrolytic enzymes in lysosomes (Figure 13.31). Some extracellular drug release may