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Review

Nanostructured materials functionalized with metal complexes: In search of alternatives for administering anticancer metallodrugs

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Contents

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ABSTRACT

Nanotechnology has shown great promise in unraveling several important issues of conventional anticancer chemotherapy. Expectations project that a new generation of effective cancer therapies will be developed with enormous potential to overcome the biological, biophysical and biomedical obstacles that the human body enacts against standard chemotherapeutic treatments. Generally, nanostructures protect the entombed drug molecules from degradation in blood, allowing their safe and unimpaired delivery to specific target sites in the body. Nanostructured macromolecular systems such as curcubit[*n*]urils, cyclodextrins, liposomes, lipid nanocapsules, proteins, polynuclear organometallic compounds, carbon nanotubes, polymeric nanoparticles and ceramic materials have shown great potential in facilitating the administration of potent anticancer metallodrugs. The uniqueness of these nanostructured materials lies in their suitability for functionalization with small molecule drugs. Recently, there has been a great deal of interest among oncologists and medicinal chemists in functionalizing nanostructured materials with anticancer metallodrugs to ensure better administration. In view of these facts, the state-of-art of nanostructured materials functionalized with metallodrugs as anticancer agents is described in this review. The functionalization of several classes of metal complexes including platinum and non-platinum compounds is also addressed. Special focus is given to the co-delivery of metallodrugs within nanostructures. Toxicity of nanomaterials is discussed and the associated concerns are also highlighted. Finally, the current challenges and the future perspectives of metallodrug functionalization have been commented upon.

1. Introduction

Cancer is a genetic disease that progresses *via* a phenomenon of multistep carcinogenesis with the involvement of numerous physiological systems of the human body such as cell signaling and apoptosis. This involvement of physiological systems makes it extremely complicated to combat [1,2]. At first, cancer starts as a localized disease, but with the passage of time it may metastasize to other body sites making it difficult to be cured. Cancer is today one of the major causes of mortality; more than ten million people worldwide being diagnosed with this disease annually. Approximately 14 million new cancer cases and 8.2 million deaths were reported worldwide in 2012 [3,4]. Cancer is the second most common fatal illness after cardiovascular diseases [5]. In the USA, cancer has been a major public health issue accounting for nearly one in every four deaths. The approximations by Seigal et al. indicate that 1658,370 new cancer cases will be diagnosed in USA in 2015 with deaths of approximately 589,430 patients [6]. Huge loss of life has been reported in European countries due to increasing cancer deaths. Approximately 1359,100 cancer related deaths are predicted in Europe in 2015 [7]. In the Indian sub-continent, cancer is the second most common disease. The prevalence of cancer is predicted to increase alarmingly in developing countries to about 70% in the coming decade. The most prevalent cancers reported in the Indian population are lung, breast, colon, rectum, stomach and liver [5,8,9].

In the context of cancer, metal complexes occupy a pioneer niche in Inorganic Medicinal Chemistry because they offer multipurpose podia for drug design and development. Certain properties of metal complexes such as kinetics (ligand exchange rates) and

Abbreviations: 16HBE, human bronchial epithelial; 2008, human ovarian carcinoma; 4T1, breast carcinoma; 8505C, human thyroid carcinoma; A253, human submandibular tumor cell line; A2780, human ovarian carcinoma; A2780cisR, cisplatin resistant human ovarian carcinoma; A549, adenocarcinomic human alveolar basal epithelial cells; A549R, cisplatin resistant human adenocarcinomic alveolar basal epithelial cells; AIDS, acquired immuno deficiency syndrome; AsPC-1, human pancreas adenocarcinoma ascites metastasis cell line; Au@GSH, glutathione-stabilized gold nanoparticles; B16, mouse melanoma; Bax, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2 gene; BEAS-2B, normal human bronchial epithelium; C13, human cisplatin-resistant ovarian carcinoma; C57BL/6, inbred strain of laboratory mouse; C6, glioma cells; CNTs, carbon nanotubes; CT26, mouse colon carcinoma; Cu–NCs, copper nanoclusters; Dendrimer-DACHPt, dendrimer-linked diaminocyclohexyl platinum (II); DLD-1, human colon carcinoma; DMSO, dimethyl sulphoxide; DNA, deoxyribonucleic acid; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DOTAP, 1,2-dioleyl-3-trimethylammoniumpropane chloride; Dppz, dipyridophenazine; DSPE-Peg2K, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene glycol)-2000]; DU-145, human prostate carcinoma; EPR, enhanced permeability and retention; Fem-x, human malignant melanoma; H22, murine hepatocellular carcinoma cell line; H460, human non-small cell lung carcinoma; HCT116, human colon carcinoma; HCT-15, human colon carcinoma; HEK-293, human normal embryonic kidney cells; HeLa, human cervical carcinoma; HepG2, human hepatocellular carcinoma; HIV, human immuno deficiency virus; HMS, hexagonal mesoporous silica; HS27, human skin fibroblast cell line; HSA, human serum albumin; HT-29, human colon carcinoma; IC50, half maximum inhibitory concentration; JNK, jun-amino-terminal kinase; K562, human myelogenous leukemia; KB, mouth epidermal carcinoma cells; kDa, kilo Dalton; KP1019, indazolium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)]; L1210, mouse leukemia; L540, Hodgkin's disease-derived cell line; LDH, layered double hydroxide; LLC, Lewis lung carcinoma; LNCs, lipid nanocapsules; LSPR, localized surface plasmon resonance; MA148, ovarian carcinoma cell line; MCF-7, human breast carcinoma; MCM-41, mobil composition of matter no. 41; MDA-MB-231, human breast carcinoma; MDR, multiple drug resistance; mM, millimolar; mPEG-*b*-P(LA-*co*-MCC), monomethoxy poly(ethyleneglycol)-block-poly(l-lactide-*co*-2-methyl-2-carboxyl-propylene carbonate); MPEG-*b*-PCL-*b*-PLL, monomethoxy (polyethylene glycol)-poly(d,l-lactide-*co*-glycolide)-poly(l-lysine); MPEG-PGA, methoxypolyethylene glycol-block-poly(glutamic acid); MPS, matrix metalloproteinases; MRI, magnetic resonance imaging; MSN-Pt, mesoporous silica nanoparticulated platinum; MSNs, mesoporous silica nanoparticles; MSU-2, Michigan State University Silica type 2; MWCNTs, multi-walled carbon nanotubes; NAMI-A, new anti-tumor metastasis inhibitor-A; NCI-ADR/RES, adriamycin resistant breast cancer cell line; NCI-H1299, human non-small cell lung carcinoma cell line; NCI-H596, human non-small cell lung carcinoma cell line; NCPs, nanoscale coordination polymers; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIH3T3, mouse embryo fibroblast cell line; NIR PL, near infra-red photoluminescence; nm, nanometer; NMOFs, nanoscale metal–organic frameworks; NPs, nanoparticles; Nrp-1, neuropilin-1; NSCLC, non-small cell lung carcinoma; OSC-19, oral squamous cell carcinoma; OVCAR-3, human ovarian carcinoma cells; OVCAR8, human ovarian carcinoma cells; P388, mouse leukemia; PBMC, peripheral blood mononuclear cells; PC-3, human prostatic carcinoma; PDT, photodynamic therapy; PEG/PLA, polyethyleneglycol/polylactic acid; PEG, poly(ethylene glycol); PEITC, phenethyl isothiocyanate; P-gp, P-glycoprotein; PLGA, poly(lactic-*co*-glycolic acid; PLGA-PEG, poly(D,L-lactic-*co*-glycolic acid)-block-poly(ethylene glycol); PMCs, polymer–metal complexes; POPC, 1-palmitoyl-2-oleoyl-snglycero-3-phosphocholine; RAFT, reversible addition-fragmentation chain transfer; RBCs, red blood cells.; RBITC-SiO_2, rhodamine B isothiocyanate doped silica-coated nanoparticles; RES, reticuloendothelial system; RG2, rat glioma 2 cell line; RNA, ribonucleic acid; ROS, reactive oxygen species; RuIICp, ruthenium(II) cyclopentadienyl complex; RuPMC, polylactide ruthenium cyclopentadienyl complex; SBA-15, Santa Barbara amorphous type material-15; SCLC, small-cell lung cancer; siRNAs, small interfering ribonucleic acids; SK-hep-1, human liver adenocarcinoma; SK-N-SH, human caucasian neuroblastoma; SKOV-3, human ovarian carcinoma cell line; SWCNTs, single-walled carbon nanotubes; SWNHs, single-walled carbon nanohorns; U373, human glioblastoma cell line; U87, epithelial-like human glioblastoma-astrocytoma; WiDr, human colon carcinoma; β-CN, β-casein; μM, micromolar.