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Radiopharmaceuticalswithdendritic Scaffolds

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Abstract:

Diagnosis and therapy, in time, is very crucial for cancer treatment. Technology and screening tools use radiometals with desired properties. Emission type, associated energy, half-lives of radiometal are very crucial for radiopharmaceuticals. A chelating agent is required to hold the radiometal and for that monomeric and dendritic scaffolds are being used as chelators. For an efficient pharmaceutical, cytotoxic activity and efficient cell membrane diffusion are important criteria. Herein, a trend on using dendritic scaffold for radiopharmaceuticals is discussed.

Introduction

World Health Organization has predicted an increase of cancer patients by 2025 around 19.3 million.[1] Therefore, an effective screening tools and technologies are required for cancer diagnosis and treatment. There are several medical steps for treating a cancer patient. Depending on the state of the cancer, tools towards treating cancer include surgery, chemotherapy and radiation therapy.[2] While surgery is used to remove cancerous cells in an invasive manner, chemotherapy treat the affected cells utilising synthetic drugs. Radiotherapy is different from other two types of treatments. It involves the use of energy waves to target cancerous cells and therefore radioactive isotopes are being used as causative agents routinely in medical procedures.[3] During this process, electromagnetic radiation emits from an atom's nucleus and therefore cancerous cell targeting carriers to deliver radioactive element are extremely important. They can selectively find cancerous cell in vivo for cancer diagnosis and therapy. Various metal atoms are being used for molecular imaging and therapy.[4] These materials are two types – (a) therapeutics that emits α and β particles and being used in radionuclide-based therapy and (b) diagnostics which are β and γ-emitters and used in nuclear imaging. For nuclear medicine, popularly known as radiopharmaceuticals, availability of radiometals with desired properties such as emission types, associated energy, half-lives etc. are very crucial to treat cancer patient.[5]

Radiopharmaceuticals

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Organometallic drugs obtained from stable nonradioactive isotope have showed the way for radiometals in clinical application after the discovery of arsphenamine – an arsenic-based antimicrobial compound being used for syphilis (asexually transmitted bacterial infection).[6] Radio-therapeutic drugs are designed for precise therapeutic ionization radiation to specific diseased sites. Afterwards rapid clearance of these species from blood stream would minimize radiation damage of organs and tissues.[7]

Elemental rhenium (exists as Re-186/188) and technetium (Tc-99) are being used as diagnostic radionucleotides as these isotopes contain suitable half-life and β-emitting therapeutic properties.[8] Rhenium is consider prominent therapeutic radionuclide as it converts to $[ReO_4]^-$ over time via taking up in the thyroid and excreted renally. Using indium (^{131}In) as a control, it is shown that Re can be deposited in high dose at tumour site and therefore showed less damage on good cells during radiation.[9] Development of ^{188}Re-radiopharmaceuticles is thus subjected to get a proper business model as potentially cost-effective ^{188}Re.[10] On the other hand, technetium-99m is being used routinely as diagnostic radiopharmaceuticals due to its short half-life (around 6 hours), lost cost productivity and importantly excellent resolution of tissue imaging.[11]

Scaffold for radiopharmaceuticals

Radiopharmaceuticals preparation are feasible due to synthetic advances in organometallic chemistry. The coordination chemistry and organometallic chemistry of Tc and Re arebeing continuously explored. Tricarbonyl complexes of Re and Tc have been extensively studied following a single one-step fully aqueous based kit preparation method.[12] This preparation method offers the tricarbonyl core $[fac\text{-}M(CO)_3(H_2O)_3]^+$ (M= ^{99m}Tc, $^{186/188}$Re), which has been found (a) an inert complex as soft acid, (b)lipophilic possessing affinity towards myocardial tissue, (c) robust chemical nature under harsh conditions. These studies have also been aided by the facile synthesis andremarkable stability of $[M(CO)_3]^+$ complexes with bidentate and tridentate chelatingligands.[13] One of the common ligand, often used as prominent chelator, is H_2dedpa (N,N′-[(6-carboxylato)pyridin-2-yl)methyl]-1,2-diaminoethane). It easily forms kinetically inert complexes with certain radioisotopes, which shows excellent stability after radio labelling.[14] However, it is highly effective to permit multivalent attachment of metal ions by designing hyperbranched polymeric ligand for efficient tumour-targeting radiopharmaceuticals.[15] Among different type of polymeric macromolecules, dendrimers are synthetic nanosized (~10-20 nm) macromolecules with well-

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defined globular architecture that enables multivalent interactions with metal ions at their periphery.[16] These architectures have been used as discreet platform of efficient carriers of drug species with controlled size and biodistribution via surface functionalization. Metallodendrimers are the dendrimers functionalized with transition metals at their core, at brunches or at the brunching surface and they find application in catalysis, conductors, luminescent material etc.[17] The multivalancy of metallodendrimers allows abundance of therapeutic metals and thereby increase the bioactivity. However, low cytotoxic activity against cancel cell lines and poor cell membrane diffusion often disallowed them in clinical trials.[18]

Biocompatibility of radiopharmaceuticals

Ideal radiopharmaceuticalsshould accumulate at tumour sites due to increase in blood vessel permeability and poor lymphatic drainage, whereas they would wash from healthy cells.Amine-terminated metallodendrimers have shown some biocompatibility in gene delivery system. Poly(propylene imine) (PPI) dendrimers showed the biocompability in fifth generation dendrimers, whereas second generation dendrimer showed poor level of cell cytotoxicity.[19] On another hand, carboxylic acid-functionalized dendrimers showed no cytotoxicity and good haemolytic activity.[20] In general, cell cytotoxicity of dendritic architectures depends on the terminal functional groups, interaction between functional groups and the cell membrane. To this extent, peptide-functionalized dendrimers showed excellent biocompatibility.[21] Water soluble dendritic architecture bearing porphyrin core with terminal iminodiacetic acid group is reported to serve a diagnostic radioisotopic chelate. Biodistribution and cell imaging of the radiopharmaceuticals using these dendrimers showed the accumulation of drugs in the tumour rather than in the surrounding healthy cells.[22]PPI dendrimers with mannose or lactose functionalization at surface has been used for radiolabelling. The biodistribution of these radiopharmaceuticals showed the potential vehicles for lectin-rich organs.[23] High generation dendrimers for well-defined and site-specific radiopharmaceuticals is the focal point of cancer treatment. These drugs should have characteristics of minimum interference with dendrimer surface and receptor binding interaction during blood and tissue circulation. Increased uptake of drugs has been observed by using polyethylene glycol (PEG) as spacer group. PEG is structurally flexible and lipophilic in nature and potentially allowing forescapefrom phagocytosis by macrophage cells in the lymphatic system. Dendrimer containing folic acid group at surface and connected with

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PEG spacer is able to target-specific binding to metastatic tumour cells and has been used as potential imaging radiopharmaceuticals.[24]

Conclusion and Outlook

Target-specific dendrimers with functionalized surface and spacer group allows optimization for radiopharmaceuticals in diagnostic efficiency and treatment. Dendrimeric chelates for nuclear imaging and therapy are still an active area of research. Dendritic architectures with multivalancy and the ability to tune the ratio between macromolecule and radiometal can be exploited for efficient image quality and treatment. The nature of functional group at the periphery of dendrimer and charge distribution are essential for the synthesis of kinetically inert radiodrugs. The commercial availability of dendrimers and radio metal will produce cheaper drugs for efficient diagnosis and treatment of cancer. Utilising the diagnostic properties of radionuclides and suitable preparation method, together with enhanced permeability and retention effect, the dendrimer-based ligand will have major contribution for nanoparticle based drug delivery systems and cancer diagnosis research.

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