Advanced Drug Delivery Reviews 109 (2017) 84–101

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Gold nanoparticles for applications in cancer radiotherapy: Mechanisms and recent advancements☆

Sohyoung Her [a], David A. Jaffray [b,c,d,e,f,g], Christine Allen [a,e,g,*]

[a] Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 3M2, Canada
[b] Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
[c] Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada
[d] Department of Radiation Physics, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[e] STTARR Innovation Centre, Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[f] Techna Institute, University Health Network, Toronto, Ontario, Canada
[g] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 24 October 2015
Received in revised form 10 December 2015
Accepted 11 December 2015
Available online 19 December 2015

Keywords:
Radiosensitization
Radiation therapy
Gold nanoparticle
Mechanism
Multi-functional nanoplatform
Hypoxic radiosensitizer
Active targeting
Ion radiotherapy

ABSTRACT

Gold nanoparticles (AuNPs) have emerged as novel radiosensitizers owing to their high X-ray absorption, synthetic versatility, and unique chemical, electronic and optical properties. Multi-disciplinary research performed over the past decade has demonstrated the potential of AuNP-based radiosensitizers, and identified possible mechanisms underlying the observed radiation enhancement effects of AuNPs. Despite promising findings from pre-clinical studies, the benefits of AuNP radiosensitization have yet to successfully translate into clinical practice. In this review, we present an overview of the current state of AuNP-based radiosensitization in the context of the physical, chemical and biological modes of radiosensitization. As well, recent advancements that focus on formulation design and enable multi-modality treatment and clinical utilization are discussed, concluding with design considerations to guide the development of next generation AuNPs for clinical applications.

Contents

Abbreviations: 5′-ALA, 5′-aminolevulinic acid; Au, gold; AuNC, gold nanocapsule; AuNP, gold nanoparticle; AuNR, gold nanorod; BSA, bovine serum albumin; CT, computed tomography; DEF, dose enhancement factor; DNA, deoxyribonucleic acid; DOX, doxorubicin; DSB, double strand break; EB, external beam; EGFR, epidermal growth factor receptor; EPR, enhanced permeability retention effect; FA, folic acid; FDG, fluoro-deoxyglucose; Glu, glucose; GPM, gold-loaded polymeric micelles; GSH, glutathione; GSM, gold- and SPION-loaded polymeric micelles; HER2, human epidermal growth factor receptor 2; HGNPs, hollow gold nanoparticles; ID, injected dose; IR, ionizing radiation; kV, kilovoltage; LEE, low energy electron; LET, low energy transfer; LINAC, linear accelerator; LSPR, local surface plasmon resonance; MCTS, multi-cellular tumor spheroid; MR, magnetic resonance; MUA, mercaptoundecanoic acid; MV, megavoltage; NAC, *N*-acetyl cysteine; NIR, near-infrared; NLS, nuclear localization signal; PCL, poly(ε-caprolactone); PEG, poly(ethylene glycol); PET, positron emission tomography; PK, pharmacokinetic; PTT, photothermal therapy; RBE, relative biological effectiveness; RES, reticulo-endothelial system; rhTNF, recombinant human tumor necrosis factor alpha; RME, receptor-mediated endocytosis; RNA, ribonucleic acid; ROS, reactive oxygen species; RT, radiotherapy; SER, sensitizer enhancement ratio; SF, surviving fraction; SPION, superparamagnetic iron oxide nanoparticle; SSB, single strand break; TrxR1, thioredoxin reductase 1; Z, atomic number.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Radiotherapy for Cancer: Present and Future".

* Corresponding author at: Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Toronto, Ontario M5S 3M2, Canada.
E-mail address: cj.allen@utoronto.ca (C. Allen).

http://dx.doi.org/10.1016/j.addr.2015.12.012
0169-409X/

1. Introduction

Radiotherapy (RT), alongside surgery and chemotherapy, is one of the most effective modes of cancer treatment, with over 50% of all patients receiving RT with curative or palliative intent [1,2]. In RT, ionizing radiation (IR) is delivered to the tumor via an external beam (EB) or from an internally placed radiation source (brachytherapy). Exposure to IR causes damage to various cellular components, with the DNA being the most critical target, directly or indirectly via ionization of molecules (e.g. water) within the cells, generating a cascade of free radicals. While effective at achieving tumor control, the surrounding normal tissues are also affected by the IR. As a result, the dose of radiation administered must be limited in order to keep normal tissue toxicities at a tolerable level. Considerable improvements have been made in RT over the past few decades, with a particular emphasis on the recent technological advances that enable precision in the delivery of radiation via intensity modulation in combination with image guidance [3–7]. As well, with an increasing understanding of the molecular pathways involved in radiation response, personalized treatment approaches that utilize molecularly targeted drugs are under investigation to achieve tumor-specific targeting of IR [8,9].

Nanotechnology, which offers a number of unique features suited for applications in oncology, has also emerged as a promising strategy to enhance radiotherapeutic efficacy. By exploiting the enhanced permeability and retention (EPR) effect, the preferential accumulation of nanoparticles in the tumor may lead to (1) improved contrast enhancement for image-guided RT, (2) tumor-specific delivery of chemotherapeutic agents for combined chemo-RT, and (3) an increased local dose of radiation using particles with high atomic numbers (Z). Among various nano-platforms investigated for radiotherapeutic applications, gold nanoparticles (AuNPs) have been most extensively studied due to their high X-ray absorption coefficient, as well as the ease of synthetic

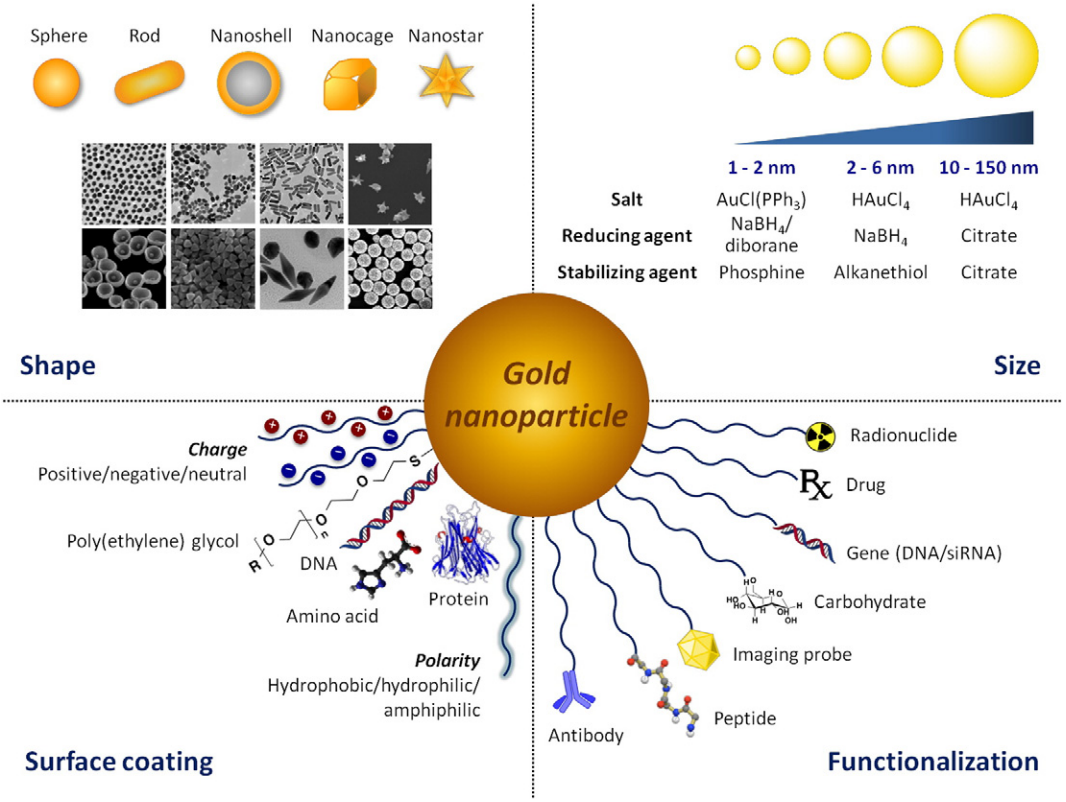

Fig. 1. The synthetic versatility of AuNPs. AuNPs offer a unique platform for straightforward manipulation of particle size, shape, surface coating and functionalization, enabling fine-tuning of particle properties. Adapted with permission from [10–15].