Advanced Drug Delivery Reviews 113 (2017) 97–121

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Activatable fluorescence: From small molecule to nanoparticle☆

Benjamin M. Luby [a], Danielle M. Charron [a,b], Christina M. MacLaughlin [a], Gang Zheng [a,b,c,*]

[a] Princess Margaret Cancer Centre and Techna Institute, University Health Network, Toronto, ON, Canada
[b] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada
[c] Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 15 August 2016
Accepted 27 August 2016
Available online 2 September 2016

Keywords:
Molecular imaging
Theranostics
Beacon
Smart probe
Fluorophore
Aggregation
Nanocarrier
Biosensing

ABSTRACT

Molecular imaging has emerged as an indispensable technology in the development and application of drug delivery systems. Targeted imaging agents report the presence of biomolecules, including therapeutic targets and disease biomarkers, while the biological behaviour of labelled delivery systems can be non-invasively assessed in real time. As an imaging modality, fluorescence offers additional signal specificity and dynamic information due to the inherent responsivity of fluorescence agents to interactions with other optical species and with their environment. Harnessing this responsivity is the basis of activatable fluorescence imaging, where interactions between an engineered fluorescence agent and its biological target induce a fluorogenic response. Small molecule activatable agents are frequently derivatives of common fluorophores designed to chemically react with their target. Macromolecular scale agents are useful for imaging proteins and nucleic acids, although their biological delivery can be difficult. Nanoscale activatable agents combine the responsivity of fluorophores with the unique optical and physical properties of nanomaterials. The molecular imaging application and overall complexity of biological target dictate the most advantageous fluorescence agent size scale and activation strategy.
© 2016 Elsevier B.V. All rights reserved.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Molecular Imaging".

* Corresponding author at: MaRS Centre, Princess Margaret Cancer Research Tower, Toronto, ON M5G 1L7, Canada.
E-mail address: gang.zheng@uhnres.utoronto.ca (G. Zheng).

http://dx.doi.org/10.1016/j.addr.2016.08.010
0169-409X/© 2016 Elsevier B.V. All rights reserved.

1. Introduction to fluorescence molecular imaging

Molecular biology has revolutionized our understanding of living systems and the players and mechanisms involved in health and disease. Analytical techniques for gene and protein profiling provide comprehensive snapshots of biological processes that can reveal molecular abnormalities and identify therapeutic targets and biomarkers. Complementing these static approaches is molecular imaging where biological processes are non-invasively visualized and quantitated at the cellular and subcellular level in living systems [1]. In this way, molecular imaging provides functional information on the spatial and temporal distributions of biomolecules, revealing the dynamics of disease. Molecular imaging has developed in parallel with controlled drug delivery systems. The information provided by molecular biology motivates the design of targeted drug delivery systems whose drug-target interactions and pharmacodynamics can be assessed using molecular imaging approaches [2,3]. In a clinical setting, molecular imaging is an important diagnostic tool to predict patient response to targeted therapies and to evaluate outcomes based on biomarker normalisation [4–11]. Further, integrating imaging and therapeutic capabilities into theranostic systems is a useful strategy to enable real-time tracking of drug pharmacokinetics and biodistribution [12–23]. This information aids pre-clinical drug development as well as personalizes patient management. Drug delivery systems in turn provide common technologies to support delivery of imaging agents.

Fluorescence molecular imaging is widely used in pre-clinical applications including drug discovery, delivery, and evaluation. Fluorescence imaging agents are endogenous fluorophores (e.g., tryptophan, hemoglobin), genetically expressed fluorescent proteins (e.g., green fluorescent protein), and exogenous molecular fluorophores and fluorescent nanoparticles (e.g., indocyanine green, quantum dots). Exogenously administered fluorescence agents may be conjugated to a biomolecule or incorporated into a theranostic system for the purpose of imaging its biological behaviour. They may also take the form of targeted probes that integrate a ligand (e.g., antibody [24,25], aptamer [26–28]) for interaction with a biological target, with a fluorescence agent for detection of the target in a living system [29,30]. Fluorescence imaging systems detect these exogenous agents with up to picomolar scale sensitivity in real time. Multiplexing is also possible to detect spectrally distinct fluorescence agents for simultaneous imaging of multiple biological targets or drug delivery systems. This capability is aided by the commercial availability of fluorescence agent series that are spectrally separable using standard excitation and emission filter sets (e.g., BODIPY®, IRDye®, Qdot®). Further, fluorescence imaging systems are available to image fluorescence agent biodistribution across three orders of magnitude in length scale. Macro imaging systems provide whole (small) animal biodistribution with millimetre scale resolution [31], while fluorescence agent microdistribution and subcellular localisation is imageable in ex vivo tissue sections using microscopy [32], the results of which can be correlated with conventional histopathology. Advanced fluorescence imaging techniques including in vivo microscopy [33,34], and in vitro single molecule detection have also greatly enriched our understanding of drug delivery and the complex intracellular processes involved in healthy and diseased states. From a practical standpoint, fluorescence imaging systems are relatively inexpensive, easy to operate, and do not involve the inherent safety risks of other molecular imaging modalities such as positron emission tomography or single photon emission computed tomography. These factors make fluorescence imaging an accessible technology for individual laboratories as well as centralized facilities, and have supported its popularity as a research tool.

From a clinical perspective, fluorescence molecular imaging is fundamentally limited by the poor tissue penetration depth of visible light [35]. Light propagation through tissues is attenuated by elastic scattering from refractive index differences in biological structures, and absorption by endogenous chromophores such as hemoglobin, in addition to water and fat. The optical window of 650 nm to 1000 nm defines the wavelength range across which light attenuation through biological tissues is minimal. Fluorescence agents that absorb and fluorescence in the near-infrared region of the electromagnetic spectrum enable a maximum imageable tissue depth of less than 1 cm. Light attenuation also means that two-dimensional fluorescence imaging systems give surface-weighted images, and quantitating in vivo fluorescence requires decoupling agent fluorescence from background tissue light scattering and absorption, often requiring complex software algorithms or spectral fitting procedures. This correction is performed in pre-clinical fluorescence molecular tomography systems, and handheld clinical systems implement similar approaches [36]. Clinical fluorescence imaging is therefore best suited to surface-based applications such as vulnerable plaque imaging in atherosclerosis using catheter fluorescence imaging systems [37,38], image-guided biopsy of gastrointestinal diseases using fluorescence endoscopes [39–41], non-invasive lymphatics mapping and lesion characterisation of breast cancer [21, 42], and as surgical guidance in tumour resection and lymphadenectomy [43–46].

Perhaps the most advantageous property of fluorescence agents for molecular imaging is their inherent responsivity to their environment. Fluorescence agent emission is manipulable through control of its chemical and physical interactions with biological targets. This responsivity has originated the extensive development of “activatable” fluorescence agents whose emission changes in response to the presence of a biological target [47–51]. In this review we first give an

Download English Version:

https://daneshyari.com/en/article/5519963

Download Persian Version:

https://daneshyari.com/article/5519963

Daneshyari.com