Internet Journal of Medical Update

Journal home page: http://www.akspublication.com/ijmu

Review

The Role of Nanotechnology in Molecular Imaging by using Fluorescent Quantum Dots

Dr. S. D. Dongre*[Ψ] MD and Dr. Smita Sankaye[†] MD

***Professor and Head, [†]Resident, Department of Pathology, Rural Medical College, PMT, Loni, Maharashtra, India**

(Received 09 December 2010 and accepted 19 December 2010)

ABSTRACT: Giant strides in knowledge about nanoparticles have lead to the development of sophisticated fluorescent quantum dots that have enhanced our understanding of the disease process as well as the healing mechanism following appropriate therapy. This article focuses on various aspects of fluorescent quantum dots which are now knocking at our doors to let them in to assist us in molecular imaging.

KEY WORDS: ***Nanotechnology; Molecular imaging; Fluorescent quantum dots***

INTRODUCTION

The first decade of the new millennium has paved the way for molecular imaging. Use of fluorescent quantum dots is now one of the main cornerstones of molecular imaging. Detection of biological processes at molecular level needs specialized probes. This problem was overcome when scientific advances put forth the solution in the form of fluorescent quantum dots that produce excellent contrast which enables rapid detection of changes at molecular levels.

DISCUSSION

As "nano" means one-billionth, "nanotechnology" refers to technology that deals with objects having nanoscale dimensions between 1.0 and 100.0 nm. Because of fundamental principles of quantum physics nanoscale materials have different properties than the properties of the same materials having larger dimensions[1]. Majority of research in molecular biology is taking place on a nanoscale as all biologic systems are inherently composed of nanoscale building blocks[2]. After the invention of the scanning tunneling microscope in 1981 by Binig and Rohrer[3], working on individual atoms on a surface became feasible so that nanoscale structures could be assembled into larger and more complex structures and nanoscale science grew by leaps and bounds. Combination of array technology and scanning probe microscope method has further widened the horizons. Most of the contrast agents being developed for fluorescent optical imaging are nanoassemblies that have a fluorescent reporter label and a receptor-targeting moiety on a polymer backbone[4,5]. The term *theranostics* refers to the unique combination of drug and nanocontrast. It has a bright future as it promises imaging of a protein, drug or even gene delivery system[6].

The basis of fluorescent imaging by using nanoparticles is that they exhibit luminescence. Interest in fluorescent quantum dots as an imaging tool sprang up after the discovery of green fluorescent protein in jelly fish[7].

Quantum dots score better than organic dyes and fluorescent proteins due to their higher luminescence, wide excitation with narrow emission bands, resistance to photo bleaching and high molar extinction coefficient. As the size of quantum dots is increased, the wavelength of fluorescent emission is also increased[8].

Moreover many functions can be incorporated in one nanosystem as has been demonstrated by the development of a nanosystem in which fluorescent quantum dots and pharmaceutical drugs are assembled into chitosan nanoparticles for multifunctional smart drug delivery systems[9].

The problem of occurrence of hydrophobic organic ligands following synthesis has been solved by conjugating them with a hydrophilic substance so that the solubility of quantum dots is enhanced[10]. Therefore, Bioassays and intracellular labeling

[Ψ]**Correspondence at:** Professor and Head, Department of Pathology, Rural Medical College, PMT, Loni-413736, Dt-Ahmednagar, Maharashtra, India; Email: drsdongare@gmail.com

have been possible by conjugating quantum dots with Chitosan [(CdSe-ZnS)-chitosan]. Biocompatible and biodegradable Chitosan is an obvious choice because of its hydrophilic nature.

A better alternative is to use silicon quantum dots that have a surface hydroxyl group ensuring its water solubility. Oxygen-passivation is used to stabilize its photoluminescence. Silicon quantum dots are not only less cytotoxic alternative to CdSe for bio-imaging labels[11], their initially modest yield can now be increased exponentially[12].

Heavy metal-free quantum dot bio-probes based on single phase ZnS have been prepared by selectively doping them with transition metals and halides to provide adjustable luminescence properties. Surface conjugation with folic acid enables cancer targeting[13].

The excitation and emission wavelengths of the above mentioned quantum dots lie in the visible spectrum. This hampers imaging of deeper tissues, as these wavelengths are highly absorbed by body tissue. Therefore, only superficial tissues can be seen *in vivo*. Hence while preparing fluorescent quantum dots from non fluorescent nanoparticles, the fluorophores that is being used should be such that it should both absorb as well as emit light in the near-infrared window (650–900 nm), where the absorbance of tissue is low[14].This is not so vital when using confocal microscopy, where light has to penetrate minimal tissue sections but assumes more critical stand when using fluorescence tomography, where light has to pass through substantial tissue thickness.

Functionalized dots for *in vivo* tumor vasculature in the infrared part of the spectrum have been developed by conjugating them with Arginine-glycine-aspartic acid (RGD) peptides that targets actively growing tumor vessels of all cancer types[15]. This is better than the conventional antibody or aptamer-mediated targeting that is specific to a particular cancer type.

Method to increase blood half-lives of nanoparticles that are otherwise foreign to the body includes PEGylation that avoids fast removal by the reticuloendothelial system. This allows larger amount of injected material to reach and bind the desired sites. PEGylation lowers cytotoxicity, exhibits a 10-fold increase in circulation half-life and does not form aggregates in the lungs[16].

Natural nanoparticles like viruses or lipoproteins evade recognition by the body's defense systems. This can be converted into fluorescent tagged quantum by modifying their surface to contain contrast generating ions and dyes[17,18] or by including inorganic nanoparticles in the core of the virus or lipoprotein[19].

Renal system can excrete nanoparticles up to 5.5 nm, while particles larger than that are mainly taken up by the reticuloendothelial system where they end up in the liver and spleen[20]. Here they are metabolized and excreted or accumulated and can potentially become toxic for the body[21].

Advantages of nanoparticulate fluorescent tagged quantum dots over single molecule-based contrast agents include[22-29]:

- Adequate contrast,
- Many types of contrast generating materials can be utilized at a time,
- Circulation time is more,
- High payloads are possible,
- Quick and efficient assemblage of components is possible,
- Multiple imaging techniques can be used for detection,
- Therapeutics can also be delivered and visualised,
- Particular cell types can also be detected and seen, or
- Promote and permit development of newer imaging systems

For imaging modalities with low sensitivity, nanoparticles bearing multiple contrast groups provide signal amplification[30]. Some nanoparticles enable deep-tissue as well as real-time evaluation diverse specimens, such as brain, heart, kidneys and lymphatic organs while leaving the tissue intact[31].

CONCLUSION

Use of fluorescent quantum dots is of immense help in visualizing early stage of disease, its progression and response to treatment. Recent advances in nanotechnology enable synthesis of a nanoparticle contrast agent possessing the required attributes for any desired application. Advances in molecular imaging, diagnostic imaging and nanotechnology must go hand in hand to reap out the best fruits from the tree of knowledge for health of the entire humanity.

REFERENCES

1. Ratner M, Ratner D. Size matters. In: Ratner M, Ratner D, eds. Nanotechnology. Upper Saddle River, NJ: Prentice Hall, 2003;11-18.
2. Freitas RA. Molecular transport and sortation. In: Freitas RA, eds. Nanomedicine. Austin, Tex: Landes Bioscience, 1999;71-92.
3. Binig G, Rohrer H. Scanning tunneling microscopy. *Helv Phys Acta*. 1982;55:726-35.
4. Weissleder R, Tung C, Mahmood U, et al. In vivo imaging of tumors with protease-activated near-infrared fluorescent probes. *Nat Biotechnol*. 1999 Apr;17(4):375-8.
5. Mahmood U, Tung CH, Tang Y, et al. Feasibility of in vivo multichannel optical imaging of gene expression: an experimental study in mice. *Radiology*. 2002 Aug;224(2):446-51.

6. Del Vecchio S, Zanneti A, Fonti R, et al. Nuclear imaging in cancer theranostics. *Q J Nucl Med Mol Imaging*. 2007 Jun;51(2):152-63.
7. Leon R, Petroff PM, Leonard D, et al. Spatially resolved visible luminescence of self-assembled semiconductor quantum dots. *Science*. 1995 Mar;267(5206);1966-8.
8. Michalet X, Pinaud FF, Bentolila LA, et al. Quantum dots for live cells, in vivo imaging, and diagnostics. *Science*. 2005 Jan;307(5709):538-44.
9. Li L, Chen D, Zhang Y, et al. Magnetic and fluorescent multifunctional chitosan nanoparticles as a smart drug delivery system. *Nanotechnology.* 2007;18(40):405102.
10. Nie Q, Tan WB, Zhang Y. Synthesis and characterization of monodisperse chitosan nanoparticles with embedded quantum dots. *Nanotechnology*. 2006;17(1):140-4.
11. Fujioka K, Hiruoka M, Sato K, et al. Luminescent passive-oxidized silicon quantum dots as biological staining labels and their cytotoxicity effects at high concentration. *Nanotechnology*. 2008;19(41):415102.
12. Shinoda K, Yanagisawa S, Sato K, et al. Stability of nanocrystalline silicon particles in solution. *J Cryst Growth*. 2006;288(1):84-6.
13. Manzoor K, Johny S, Thomas D, et al. Bio-conjugated luminescent quantum dots of doped ZnS: a cyto-friendly system for targeted cancer imaging. *Nanotechnology*. 2009 Feb;20(6):06510213. Epub 2009 Jan 14.
14. Sosnovik D, Weissleder R. Magnetic resonance and fluorescence based molecular imaging technologies. Prog *Drug Res.* 2005;62:83-115.
15. Hu R, Yong KT, Roy I, et al. Functionalized near-infrared quantum dots for in vivo tumor vasculature imaging. *Nanotechnology*. 2010 Apr;21(14):145105. Epub 2010 Mar 16.
16. Otsuka H, Nagasaki Y, Kataoka K. PEGylated nanoparticles for biological and pharmaceutical applications. *Adv Drug Deliv Rev.* 2003 Feb;55(3):403-19.
17. Anderson EA, Isaacman S, Peabody DS, et al. Viral nanoparticles donning a paramagnetic coat: conjugation of MRI contrast agents to the MS2 capsid. *Nano Lett*. 2006 Jan;6(6):1160-4.
18. Cormode DP, Mulder WJM, Fisher EA, et al. Modified lipoproteins as contrast agents for molecular imaging. *Future Lipidol*. 2007;2:587-90.
19. Huang X, Bronstein LM, Retrum J, et al. Self-assembled virus-like particles with magnetic cores. *Nano Lett.* 2007 Aug;7(8):2407-16.
20. Choi HS, Liu W, Misra P, et al. Renal clearance of quantum dots. *Nat Biotechnol*. 2007 Oct;25(10):1165-70.
21. van Schooneveld MM, Vucic E, Koole R, et al. Improved biocompatibility and pharmacokinetics of silica nanoparticles by means of a lipid coating: a multimodality investigation. *Nano Lett*. 2008 Aug;8(8):2517-25.
22. Medintz IL, Uyeda HT, Goldman ER, et al. Quantum dot bioconjugates for imaging, labelling and sensing. *Nat Mater.* 2005 Jun;4(6):435-46.
23. Nahrendorf M, Zhang H, Hembrador S, et al. Nanoparticle PET-CT imaging of macrophages in inflammatory atherosclerosis. *Circulation.* 2008 Jan;117(3):379-87.
24. Klibanov AL, Maruyama K, Torchilin VP, et al. Amphipatic polyethyleneglycols effectively prolong the circulation time of liposomes. *FEBS Lett.* 1990 Jul;268(1):235-8.
25. Allen TM, Hansen C, Martin F, et al. Liposomes containing synthetic lipid derivatives of poly(ethylene glycol) show prolonged circulation half-lives in vivo. *Biochim Biophys Acta*. 1991 Jul;1066(1):29-36.
26. Schmieder AH, Winter PM, Caruthers SD, et al. Molecular MR imaging of melanoma angiogenesis with alpha(nu)beta(3)-targeted paramagnetic nanoparticles. *Magn Reson Med.* 2005 Mar;53(3):621-7.
27. Winter PM, Neubauer AM, Caruthers SD, et al. Endothelial alpha(v)beta3 integrin-targeted fumagillin nanoparticles inhibit angiogenesis in atherosclerosis. Arterioscler *Thromb Vasc Biol*. 2006 Sep;26(9):2103-9.
28. Amirbekian V, Lipinski MJ, Briley-Saebo KC et al. Detecting and assessing macrophages in vivo to evaluate atherosclerosis noninvasively using molecular MRI. *Proc Natl Acad Sci U S A*. 2007 Jan;104(3):961-6.
29. Durr NJ, Larson T, Smith DK, et al. Two-photon luminescence imaging of cancer cells using molecularly targeted gold nanorods. *Nano Lett.* 2007 Apr;7(4):941-5.
30. Debbage P, Jaschke W Molecular imaging with nanoparticles: giant roles for dwarf actors. *Histochem Cell Biol*. 2008 Nov;130(5):845-75.
31. Sandros MG, Behrendt M, Maysinger D, et al. InGaP@ZnS-enriched chitosan nanoparticles: a versatile fluorescent probe for deep-tissue imaging. *Advanced Functional Materials*. 2007 Dec;17(18):3724-30.