World Journal of Radiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4329/wjr.v5.i12.468

World J Radiol 2013 December 28; 5(12): 468-471
ISSN 1949-8470 (online)

MINIREVIEWS

Nano/microparticles and ultrasound contrast agents

Shu-Guang Zheng, Hui-Xiong Xu, Hang-Rong Chen

Shu-Guang Zheng, Hui-Xiong Xu, Department of Medical Ultrasound, Shanghai Tenth People's Hospital, Tenth People's Hospital of Tongji University, Shanghai 200072, China
Hang-Rong Chen, State Key Laboratory of High Performance Ceramic and Superfine Microstructures, Shanghai Institute of Ceramic Chinese Academy of Science, Shanghai 200050, China
Author contributions: Zheng SG, Xu HX and Chen HR conducted the literature research; Zheng SG wrote the paper; Xu HX edited and revised the paper.
Supported by National Natural Science Foundation of China, No. 81371570; Key Project from Shanghai Health Bureau, No. 20114003; Shanghai Talent Development Project from Shanghai Human Resource and Social Security Bureau, No. 2012045
Correspondence to: Hui-Xiong Xu, MD, PhD, Department of Medical Ultrasound, Shanghai Tenth People's Hospital, Tenth People's Hospital of Tongji University, No. 301 Yanchangzhong Road, Shanghai 200072, China. xuhuixiong@hotmail.com
Telephone: +86-21-66301031 Fax: +86-21-66301031
Received: July 17, 2013 Revised: October 31, 2013
Accepted: November 15, 2013
Published online: December 28, 2013

Abstract

Microbubbles have been used for many years now in clinical practice as contrast agents in ultrasound imaging. Recently, their therapeutic applications have also attracted more attention. However, the short circulation time (minutes) and relatively large size (two to ten micrometers) of currently used commercial microbubbles do not allow effective extravasation into tumor tissue, preventing efficient tumor targeting. Fortunately, more multifunctional and theranostic nanoparticles with some special advantages over the traditional microbubbles have been widely investigated and explored for biomedical applications. The way to synthesize an ideal ultrasound contrast agent based on nanoparticles in order to achieve an expected effect on contrast imaging is a key technique. Currently a number of nanomaterials, including liposomes, polymers, micelles, dendrimers, emulsions, quantum dots, solid nanoparticles *etc.*, have already been applied to pre or clinical trials. Multifunctional and theranostic nanoparticles with some special advantages, such as the tumor-targeted (passive or active), multi-mode contrast agents (magnetic resonance imaging, ultrasonography or fluorescence), carrier or enhancer of drug delivery, and combined chemo or thermal therapy *etc.*, are rapidly gaining popularity and have shown a promising application in the field of cancer treatment. In this mini review, the trends and the advances of multifunctional and theranostic nanoparticles are briefly discussed.

Key words: Ultrasound contrast agent; Microbubble; Nanoparticle; Imaging; Nanomaterial

Core tip: The theranostic nanoparticles are defined as nanoparticles with double functions (for both therapeutic and diagnostic purposes) and are commonly applied to simultaneous drug delivery and molecular imaging.

Zheng SG, Xu HX, Chen HR. Nano/microparticles and ultrasound contrast agents. *World J Radiol* 2013; 5(12): 468-471 Available from: URL: http://www.wjgnet.com/1949-8470/full/v5/i12/468.htm DOI: http://dx.doi.org/10.4329/wjr.v5.i12.468

MICROBUBBLES

Conventionally, the ultrasound contrast agents (UCAs) commercially used are microbubbles with sizes in the micrometer range, such as SonoVue®, Definity®, Luminity®, Sonazoid® *etc.*, which are mainly composed of insoluble gas (perfluorocarbons or sulfur hexafluoride) and an encapsulating shell (lipids, proteins or polymers)[1-5]. During the past decades, these UCAs were mainly used for imaging in clinical practice[2-11]. Recently, microbubbles and their associated cavitation are playing an increasingly significant role in both diagnostic and therapeutic applications of ultrasound[12]. Besides that, microbubbles have also attracted more attention as carriers and enhancers of drug and gene delivery and have been widely investigated for these applications (especially in the area of anticancer research)[13]. However, short circulation time (minutes) and relatively large size (two to ten micrometers) of currently used commercial microbubbles do not allow effective extravasation into tumor tissue (pore size of tumor endothelium is typically in the range 380-780 nm), preventing efficient tumor targeting[14,15].

NANOMATERIALS

Fortunately, with the development of nanotechnology, nanomaterials have also evolved and now are widely recognized as a novel type of biomaterial, with very promising applications in the field of drug delivery[13,16-21]. Currently, a number of nanomaterials, including liposomes, polymers, micelles, dendrimers, emulsions, quantum dots, solid nanoparticles *etc*., have already been applied to pre or clinical trials[22-30]. In theory, nanomaterials can overcome the aforementioned shortcomings of microbubbles due to their smaller sizes (in the nanometer range)[29,31,32]. The National Cancer Institute has defined the nanoparticle as any particle with at least one dimension under 100 nm, while in many articles, some sub-micrometer particles have also been regarded as nanoparticles[1].

The way to synthesize an ideal ultrasound contrast agent based on nanoparticles in order to achieve an expected effect on contrast imaging is a key technique. According to some recently published articles, most researchers were able to enhance the acoustic backscatter by using nanomaterial equipped with gas (perfluorocarbon), although the nanoparticle-based contrast agents for the imaging modalities discussed were in various stages of development[25-27,33-35].

The use of nanomaterials as carriers for drug delivery represents the mainstream in the field of biomedical research[29,31,36-39]. However, recently, multifunctional and theranostic nanoparticles with some special advantages, such as the tumor-targeted (passive or active), multimode contrast agents [magnetic resonance imaging (MRI), ultrasonography (US) or fluorescence], carrier or enhancer of drug delivery, and combined chemo or thermal therapy, *etc*., are rapidly gaining popularity and have shown a promising application in the field of cancer treatment[13,18-20,29,38-42].

For instance, Lammers *et al*[31] discussed the principles, pitfalls and (pre) clinical progress of drugs (including those with nanoparticles) used for tumor-targeting. Most nanoparticles can be easily functionalized with a wide variety of biomolecules or antibodies and could be used for the targeted recognition or imaging of specific tissue/organs[19,43-47]. Besides, regarding its multifunction and multimode imaging, Malvindi *et al*[48] reported a magnetic/silica nanocomposite as a dual-mode contrast agent for combined MRI and US which enables non-invasive detection of the molecular components of pathological processes through multiple-mode imaging techniques[14,48]. Wang *et al*[35] proposed that Au nanoparticle coated mesoporous silica nanocapsule-based enhancement agents can be used as an inorganic theranostic platform for contrast-intensified US imaging, combined chemotherapy and efficient high intensity focused ultrasound tumor ablation[42,45,49].

Nowadays, these kinds of nanoparticles with more novel functions are still the research focus of biomaterials and are being explored for further biomedical applications[1,14,18,20,35,43,48,50].

We hope that the information presented in this mini review will stimulate the readers' interest regarding the field of nano/microparticles and UCAs.

REFERENCES

1 **Mullin LB**, Phillips LC, Dayton PA. Nanoparticle delivery enhancement with acoustically activated microbubbles. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; **60**: 65-77 [PMID: 23287914 DOI: 10.1109/TUFFC.2013.2538]

2 **Claudon M**, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, Correas JM, Darge K, Dietrich C, D'Onofrio M, Evans DH, Filice C, Greiner L, Jäger K, Jong Nd, Leen E, Lencioni R, Lindsell D, Martegani A, Meairs S, Nolsøe C, Piscaglia F, Ricci P, Seidel G, Skjoldbye B, Solbiati L, Thorelius L, Tranquart F, Weskott HP, Whittingham T. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) - update 2008. *Ultraschall Med* 2008; **29**: 28-44 [PMID: 18270887 DOI: 10.1055/s-2007-963785]

3 **Claudon M**, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013; **39**: 187-210 [PMID: 23137926 DOI: 10.1016/j.ultrasmedbio.2012.09.002]

4 **Xu HX**. Contrast-enhanced ultrasound: The evolving applications. *World J Radiol* 2009; **1**: 15-24 [PMID: 21160717 DOI: 10.4329/wjr.v1.i1.15]

5 **Quaia E**. Microbubble ultrasound contrast agents: an update. *Eur Radiol* 2007; **17**: 1995-2008 [PMID: 17351779 DOI: 10.1007/s00330-007-0623-0]

6 **Xu HX**. Contrast-enhanced ultrasound in the biliary system: Potential uses and indications. *World J Radiol* 2009; **1**: 37-44 [PMID: 21160719 DOI: 10.4329/wjr.v1.i1.37]

7 **Xu HX**. Era of diagnostic and interventional ultrasound. *World J Radiol* 2011; **3**: 141-146 [PMID: 21666820 DOI: 10.4329/wjr.v3.i5.141]

8 **Xu HX**, Lu MD. The current status of contrast-enhanced ultrasound in China. *J Med Ultrason* 2010; **37**: 97-106 [DOI: 10.1007/s10396-010-0264-9]

9 **Liu GJ**, Lu MD. Diagnosis of liver cirrhosis with contrast-enhanced ultrasound. *World J Radiol* 2010; **2**: 32-36 [PMID: 21160737 DOI: 10.4329/wjr.v2.i1.32]

10 **Ignee A**, Straub B, Schuessler G, Dietrich CF. Contrast enhanced ultrasound of renal masses. *World J Radiol* 2010; **2**: 15-31 [PMID: 21160736 DOI: 10.4329/wjr.v2.i1.15]

11 **Molins IG**, Font JM, Alvaro JC, Navarro JL, Gil MF, Rodríguez CM. Contrast-enhanced ultrasound in diagnosis and characterization of focal hepatic lesions. *World J Radiol* 2010; **2**: 455-462 [PMID: 21225000 DOI: 10.4329/wjr.v2.i12.455]

12 **Stride EP**, Coussios CC. Cavitation and contrast: the use of bubbles in ultrasound imaging and therapy. *Proc Inst Mech Eng H* 2010; **224**: 171-191 [PMID: 20349814]

13 **Mohan P**, Rapoport N. Doxorubicin as a molecular nanotheranostic agent: effect of doxorubicin encapsulation in micelles or nanoemulsions on the ultrasound-mediated in-

tracellular delivery and nuclear trafficking. *Mol Pharm* 2010; **7**: 1959-1973 [PMID: 20957997 DOI: 10.1021/mp100269f]
14 **Casciaro S**, Soloperto G, Greco A, Casciaro E, Franchini R, Conversano F. Effectiveness of functionalized nanosystems for multimodal molecular sensing and imaging in medicine. *IEEE Sens J* 2013; **6**: 2305-2312 [DOI: 10.1109/JSEN.2013.2252164]
15 **Maeda H**, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release* 2000; **65**: 271-284 [PMID: 10699287]
16 **Suzuki R**, Oda Y, Utoguchi N, Namai E, Taira Y, Okada N, Kadowaki N, Kodama T, Tachibana K, Maruyama K. A novel strategy utilizing ultrasound for antigen delivery in dendritic cell-based cancer immunotherapy. *J Control Release* 2009; **133**: 198-205 [PMID: 19000727 DOI: 10.1016/j.jconrel.2008.10.015]
17 **Petros RA**, DeSimone JM. Strategies in the design of nanoparticles for therapeutic applications. *Nat Rev Drug Discov* 2010; **9**: 615-627 [PMID: 20616808 DOI: 10.1038/nrd2591]
18 **Janib SM**, Moses AS, MacKay JA. Imaging and drug delivery using theranostic nanoparticles. *Adv Drug Deliv Rev* 2010; **62**: 1052-1063 [PMID: 20709124 DOI: 10.1016/j.addr.2010.08.004]
19 **Byrne JD**, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Adv Drug Deliv Rev* 2008; **60**: 1615-1626 [PMID: 18840489 DOI: 10.1016/j.addr.2008.08.005]
20 **Chen Y**, Chen H, Zeng D, Tian Y, Chen F, Feng J, Shi J. Core/shell structured hollow mesoporous nanocapsules: a potential platform for simultaneous cell imaging and anticancer drug delivery. *ACS Nano* 2010; **4**: 6001-6013 [PMID: 20815402 DOI: 10.1021/nn1015117]
21 **De Jong WH**, Borm PJ. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine* 2008; **3**: 133-149 [PMID: 18686775]
22 **Nie S**, Xing Y, Kim GJ, Simons JW. Nanotechnology applications in cancer. *Annu Rev Biomed Eng* 2007; **9**: 257-288 [PMID: 17439359 DOI: 10.1146/annurev.bioeng.9.060906.152025]
23 **Kratz F**. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. *J Control Release* 2008; **132**: 171-183 [PMID: 18582981 DOI: 10.1016/j.jconrel.2008.05.010]
24 **Torchilin VP**. Recent advances with liposomes as pharmaceutical carriers. *Nat Rev Drug Discov* 2005; **4**: 145-160 [PMID: 15688077 DOI: 10.1038/nrd1632]
25 **Chung MF**, Chen KJ, Liang HF, Liao ZX, Chia WT, Xia Y, Sung HW. A liposomal system capable of generating CO2 bubbles to induce transient cavitation, lysosomal rupturing, and cell necrosis. *Angew Chem Int Ed Engl* 2012; **51**: 10089-10093 [PMID: 22952023 DOI: 10.1002/anie.201205482]
26 **Wang X**, Chen H, Chen Y, Ma M, Zhang K, Li F, Zheng Y, Zeng D, Wang Q, Shi J. Perfluorohexane-encapsulated mesoporous silica nanocapsules as enhancement agents for highly efficient high intensity focused ultrasound (HIFU). *Adv Mater* 2012; **24**: 785-791 [PMID: 22223403 DOI: 10.1002/adma.201104033]
27 **Kang E**, Min HS, Lee J, Han MH, Ahn HJ, Yoon IC, Choi K, Kim K, Park K, Kwon IC. Nanobubbles from gas-generating polymeric nanoparticles: ultrasound imaging of living subjects. *Angew Chem Int Ed Engl* 2010; **49**: 524-528 [PMID: 20013828 DOI: 10.1002/anie.200903841]
28 **Wang L**, Shi J, Zhang H, Li H, Gao Y, Wang Z, Wang H, Li L, Zhang C, Chen C, Zhang Z, Zhang Y. Synergistic anticancer effect of RNAi and photothermal therapy mediated by functionalized single-walled carbon nanotubes. *Biomaterials* 2013; **34**: 262-274 [PMID: 23046752 DOI: 10.1016/j.biomaterials.2012.09.037]
29 **Eifler AC**, Thaxton CS. Nanoparticle therapeutics: FDA approval, clinical trials, regulatory pathways, and case study. *Methods Mol Biol* 2011; **726**: 325-338 [PMID: 21424459 DOI: 10.1007/978-1-61779-052-2_21]
30 **Chen H**, Li B, Ren X, Li S, Ma Y, Cui S, Gu Y. Multifunctional near-infrared-emitting nano-conjugates based on gold clusters for tumor imaging and therapy. *Biomaterials* 2012; **33**: 8461-8476 [PMID: 22951103 DOI: 10.1016/j.biomaterials.2012.08.034]
31 **Lammers T**, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. *J Control Release* 2012; **161**: 175-187 [PMID: 21945285 DOI: 10.1016/j.jconrel.2011.09.063]
32 **Allen TM**, Cullis PR. Drug delivery systems: entering the mainstream. *Science* 2004; **303**: 1818-1822 [PMID: 15031496 DOI: 10.1126/science.1095833]
33 **Liberman A**, Martinez HP, Ta CN, Barback CV, Mattrey RF, Kono Y, Blair SL, Trogler WC, Kummel AC, Wu Z. Hollow silica and silica-boron nano/microparticles for contrast-enhanced ultrasound to detect small tumors. *Biomaterials* 2012; **33**: 5124-5129 [PMID: 22498299 DOI: 10.1016/j.biomaterials.2012.03.066]
34 **Yang F**, Chen P, He W, Gu N, Zhang X, Fang K, Zhang Y, Sun J, Tong J. Bubble microreactors triggered by an alternating magnetic field as diagnostic and therapeutic delivery devices. *Small* 2010; **6**: 1300-1305 [PMID: 20486225 DOI: 10.1002/smll.201000173]
35 **Wang X**, Chen H, Zheng Y, Ma M, Chen Y, Zhang K, Zeng D, Shi J. Au-nanoparticle coated mesoporous silica nanocapsule-based multifunctional platform for ultrasound mediated imaging, cytoclasis and tumor ablation. *Biomaterials* 2013; **34**: 2057-2068 [PMID: 23246067 DOI: 10.1016/j.biomaterials.2012.11.044]
36 **Wang AZ**, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. *Annu Rev Med* 2012; **63**: 185-198 [PMID: 21888516 DOI: 10.1146/annurev-med-040210-162544]
37 **Egusquiaguirre SP**, Igartua M, Hernández RM, Pedraz JL. Nanoparticle delivery systems for cancer therapy: advances in clinical and preclinical research. *Clin Transl Oncol* 2012; **14**: 83-93 [PMID: 22301396 DOI: 10.1007/s12094-012-0766-6]
38 **Chen Y**, Chen H, Guo L, He Q, Chen F, Zhou J, Feng J, Shi J. Hollow/rattle-type mesoporous nanostructures by a structural difference-based selective etching strategy. *ACS Nano* 2010; **4**: 529-539 [PMID: 20041633 DOI: 10.1021/nn901398j]
39 **Chen Y**, Chen H, Zhang S, Chen F, Zhang L, Zhang J, Zhu M, Wu H, Guo L, Feng J, Shi J. Multifunctional Mesoporous Nanoellipsoids for Biological Bimodal Imaging and Magnetically Targeted Delivery of Anticancer Drugs. *Adv Funct Mater* 2011; **21**: 270-278 [DOI: 10.1002/adfm.201001495]
40 **Rapoport N**, Gao Z, Kennedy A. Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy. *J Natl Cancer Inst* 2007; **99**: 1095-1106 [PMID: 17623798]
41 **Popović Z**, Liu W, Chauhan VP, Lee J, Wong C, Greytak AB, Insin N, Nocera DG, Fukumura D, Jain RK, Bawendi MG. A nanoparticle size series for in vivo fluorescence imaging. *Angew Chem Int Ed Engl* 2010; **49**: 8649-8652 [PMID: 20886481 DOI: 10.1002/anie.201003142]
42 **Wang ZY**, Song J, Zhang DS. Nanosized As2O3/Fe2O3 complexes combined with magnetic fluid hyperthermia selectively target liver cancer cells. *World J Gastroenterol* 2009; **15**: 2995-3002 [PMID: 19554652]
43 **Behnke T**, Mathejczyk JE, Brehm R, Würth C, Gomes FR, Dullin C, Napp J, Alves F, Resch-Genger U. Target-specific nanoparticles containing a broad band emissive NIR dye for the sensitive detection and characterization of tumor development. *Biomaterials* 2013; **34**: 160-170 [PMID: 23072943 DOI: 10.1016/j.biomaterials.2012.09.028]
44 **Liu J**, Li J, Rosol TJ, Pan X, Voorhees JL. Biodegradable nanoparticles for targeted ultrasound imaging of breast cancer cells in vitro. *Phys Med Biol* 2007; **52**: 4739-4747 [PMID: 17671332]
45 **Sheeran PS**, Luois SH, Mullin LB, Matsunaga TO, Dayton

PA. Design of ultrasonically-activatable nanoparticles using low boiling point perfluorocarbons. *Biomaterials* 2012; **33**: 3262-3269 [PMID: 22289265 DOI: 10.1016/j.biomaterials.2012.01.021]
46 **Brannon-Peppas L**, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. *Adv Drug Deliv Rev* 2004; **56**: 1649-1659 [PMID: 15350294]
47 **Veiseh O**, Gunn JW, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. *Adv Drug Deliv Rev* 2010; **62**: 284-304 [PMID: 19909778 DOI: 10.1016/j.addr.2009.11.002]
48 **Malvindi MA**, Greco A, Conversano F, Figuerola A, Corti M, Bonora M, Lascialfari A, Doumari HA, Moscardini M, Cingolani R, Gigli G, Casciaro S, Pellegrino T, Ragusa A. Magnetic/Silica Nanocomposites as Dual-Mode Contrast Agents for Combined Magnetic Resonance Imaging and Ultrasonography. *Adv Funct Mater* 2011; **21**: 2548-2555 [DOI: 10.1002/adfm.201100031]
49 **Wei H**, Huang J, Yang J, Zhang X, Lin L, Xue E, Chen Z. Ultrasound exposure improves the targeted therapy effects of galactosylated docetaxel nanoparticles on hepatocellular carcinoma xenografts. *PLoS One* 2013; **8**: e58133 [PMID: 23469265 DOI: 10.1371/journal.pone.0058133]
50 **Dai LC**, Yao X, Wang X, Niu SQ, Zhou LF, Fu FF, Yang SX, Ping JL. In vitro and in vivo suppression of hepatocellular carcinoma growth by midkine-antisense oligonucleotide-loaded nanoparticles. *World J Gastroenterol* 2009; **15**: 1966-1972 [PMID: 19399928]

P- Reviewers: Martins WP, Tsalafoutas I **S- Editor**: Wen LL
L- Editor: Roemmele A **E- Editor**: Liu SQ

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com