

Ultrasound in Cancer Treatment through Nanotechnology

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Ultrasound is an exciting theranostic modality that plays a critical role in diagnostic and treatment of various diseases [1, 2]. Owing to its non-invasive nature, acceptable safety, low cost and easy handling, ultrasonography is the second-most prescribed diagnostic modality by the clinicians after traditional x-ray radiography. Besides the diagnostic applications, ultrasound has attracted growing interest in cancer treatment. Following the thermal and mechanical interactions of acoustic waves with tissue, efficient and new approaches for cancer hyperthermia and chemotherapy have been recently suggested [3].

In recent years, with emergence of various nanoparticles and their different applications in the field of cancer, nanotechnology has presented great potentials to revolutionize conventional methods of cancer therapy and diagnosis [4, 5]. Herein, we briefly review several potential applications of ultrasound in cancer nanotechnology.

Nano-Ultrasound Hyperthermia: Ultrasound, as an external source for hyperthermia, offers some intrinsic advantages over other heating sources, such as electromagnetic waves or laser. Heat induced by ultrasound can be remotely focused to any depth inside the body. Current ultrasound based thermo-ablation procedures use high intensity focused ultrasound (HIFU) devices to induce a rapid cell death in small regions of tissue for treatment of both benign and malignant diseases. Uterine fibroids, benign prostatic hyperplasia, prostate cancer, breast cancer, brain tumors, and liver and kidney malignancies are the main diseases in which HIFU plays a critical therapeutic role. Due to small volume of ablated tissue in the focal region of a focused ultrasound field, the exposure time must be elongated to treat large

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tumors. This might rise the unwanted thermal injuries to the surrounding healthy tissues [3].

At the moment, few studies have demonstrated that various nanoparticles such as gold nanoparticles (AuNPs), magnetic nanoparticles (MNPs) and silicon nanoparticles (SiNPs) offer great sonosensitizing effects [6-8]. Expectedly, if the tumor is preferentially embedded with these nanostructures and subsequently exposed by ultrasound, selective thermal ablation of the tumor may be highly achievable. Furthermore, the power and duration of ultrasound needed to achieve enough temperature rise in ultrasound hyperthermia can be reduced in the presence of nanoparticles. Accordingly, a promising targeted hyperthermia being established through taking the intrinsic advantages of ultrasound as an energy source in combination with acoustically activated nanomaterials.

Ultrasound assisted drug delivery: Another application of ultrasound in cancer nanotechnology refers to the area of controlled drug release [9]. In conventional chemotherapy, anti-cancer drugs are systemically distributed throughout the body and do not sufficiently reach the target tissue. As a result, in order to achieve desired therapeutic dose at the target site, high concentration of drugs must be administered which is not clinically reasonable due to normal tissue complexity. An appropriate strategy to obtain adequate drug concentration at the tumor site is provided through encapsulation of drugs into nanocarriers and utilizing triggered mechanisms to facilitate drug release [10]. Pressure variation, acoustic streaming, cavitation and local hyperthermia are the main reasons which trigger or may accelerate the process of ultrasound mediated drug delivery. Today, various nanocarrier formulations such as liposomes, micelles, microbubbles have specially designed for ultrasound assisted drug delivery [11]. For example, focused ultrasound in combination with circulating microbubbles provide a noninvasive strategy for local and transient blood-brain barrier disruption to attain a targeted drug delivery in the central nervous system.

Nano-Ultrasonography: To promote the detection limit of ultrasound imaging, ultrasound enhanced-contrast agents (UECAs) that can preferentially accumulate into the target tissue and amplify the ultrasound signal have been recently developed [12]. UECAs may enhance the resolution of ultrasound images and improve lesion delineation, characterization and evaluation the response to a treatment modality. Generally, UECAs are based on gas-filled microbubble, nanobubble, hollow structure or gas-generating particles. Attaching specific ligands to the UECAs surfaces allow them to selectively bind to intravascular target and makes ultrasound molecular imaging feasible. These UECAs have optimal acoustic responses that makes a difference between ultrasonic properties and then obtained ultrasound signals of targeted and non-targeted tissue. Owing to their small size, nano-sized UECA possess enhanced tumor accumulation relative to micro-sized UECAs, due to the enhanced permeability and retention (EPR) effect. Therefore, nano-sized UECAs are thought to be elegant for tumor site detection

upon systemic delivery [13, 14].

Eventually, ultrasound in combination with cancer nanotechnology has recently yielded significant breakthrough in cancer diagnosis and therapy and seems to present more achievements so that such a combination may successfully translate into clinic in the future.

Conflict of Interest

None

References

1. Chiorean L, Tana C, Braden B, Caraianni C, Sparchez Z, Cui X-W, et al. Advantages and Limitations of Focal Liver Lesion Assessment with Ultrasound Contrast Agents: Comments on the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines. *Medical Principles and Practice*. 2016;**25**:399-407. doi.org/10.1159/000447670.
2. Mehrpour M, Shakeri-Zadeh A, Basir P, Jamei B, Ghaheri H, Shiran M. Effects of Low-Intensity Continuous Ultrasound on Hematological Parameters of Rats. *Journal of Biomedical Physics and Engineering*. 2016;**6**(3):195-200.
3. Beik J, Abed Z, Ghoreishi FS, Hosseini-Nami S, Mehrzadi S, Shakeri-Zadeh A, et al. Nanotechnology in hyperthermia cancer therapy: From fundamental principles to advanced applications. *J Control Release*. 2016;**235**:205-21. doi:10.1016/j.jconrel.2016.05.062. PubMed PMID: 27264551.
4. Shakeri-Zadeh A, Kamrava SK, Farhadi M, Hajikarimi Z, Maleki S, Ahmadi A. A scientific paradigm for targeted nanophotothermalolysis; the potential for nanosurgery of cancer. *Lasers Med Sci*. 2014;**29**:847-53. doi:10.1007/s10103-013-1399-x. PubMed PMID: 23917412.
5. Samadian H, Hosseini-Nami S, Kamrava SK, Ghaznavi H, Shakeri-Zadeh A. Folate-conjugated gold nanoparticle as a new nanoplatform for targeted cancer therapy. *J Cancer Res Clin Oncol*. 2016. doi: 10.1007/s00432-016-2179-3. PubMed PMID: 27209529.
6. Beik J, Abed Z, Shakeri-Zadeh A, Nourbakhsh M, Shiran MB. Evaluation of the sonosensitizing properties of nano-graphene oxide in comparison with iron oxide and gold nanoparticles. *Physica E: Low-dimensional Systems and Nanostructures*. 2016;**81**:308-14. doi.org/10.1016/j.physe.2016.03.023.
7. Shakeri-Zadeh A, Khoei S, Khoee S, Sharifi AM, Shiran MB. Combination of ultrasound and newly synthesized magnetic nanocapsules affects the temperature profile of CT26 tumors in BALB/c mice. *J Med Ultrason (2001)*. 2015;**42**:9-16. doi: 10.1007/s10396-014-0558-4. PubMed PMID: 26578485.
8. Shakeri-Zadeh A, Khoee S, Shiran M-B, Sharifi AM, Khoei S. Synergistic effects of magnetic drug targeting using a newly developed nanocapsule and tumor irradiation by ultrasound on CT26 tumors in BALB/c mice. *Journal of Materials Chemistry B*. 2015;**3**:1879-87. doi.org/10.1039/C4TB01708K.
9. Sirsi SR, Borden MA. State-of-the-art materials for ultrasound-triggered drug delivery. *Adv Drug Deliv Rev*. 2014;**72**:3-14. doi: 10.1016/j.addr.2013.12.010. PubMed PMID: 24389162. PubMed PMCID: 4041842.
10. Abed Z, Beik J, Khoee S, Khoei S, Shakeri-Zadeh A, Shiran M. Effects of Ultrasound Irradiation on the Release Profile of 5-fluorouracil from Magnetic Polylactic co-glycolic Acid Nanocapsules. *Journal of Biomedical Physics and Engineering*. 2016;**6**(3):183-194.
11. Aryal M, Arvanitis CD, Alexander PM, McDannold N. Ultrasound-mediated blood-brain barrier disruption for targeted drug delivery in the central nervous system. *Adv Drug Deliv Rev*. 2014;**72**:94-109. doi: 10.1016/j.addr.2014.01.008. PubMed PMID: 24462453. PubMed PMCID: 4041837.
12. Kiessling F, Fokong S, Bzyl J, Lederle W, Palmowski M, Lammers T. Recent advances in molecular, multimodal and theranostic ultrasound imaging. *Adv Drug Deliv Rev*. 2014;**72**:15-27. doi: 10.1016/j.addr.2013.11.013. PubMed PMID: 24316070. PubMed PMCID: 4043517.

13. Kim M, Lee JH, Kim SE, Kang SS, Tae G. Nanosized Ultrasound Enhanced-Contrast Agent for in Vivo Tumor Imaging via Intravenous Injection. *ACS Appl Mater Interfaces*. 2016;**8**:8409-18. doi: 10.1021/acsami.6b02115. PubMed PMID: 27010717.
14. Sboros V. Response of contrast agents to ultrasound. *Adv Drug Deliv Rev*. 2008;**60**:1117-36. doi: 10.1016/j.addr.2008.03.011. PubMed PMID: 18486270.