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RESEARCH ARTICLE

Ultrasound-targeted microbubble destruction (UTMD): targeted nanodrug delivery in cancer

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Cavitation is a process of formation of microbubbles in the ultrasound method. These microbubbles have the potential to interact with either the normal cells or cancerous cells through developing drug delivery mechanism and targeting. This letter deals with the role and application of microbubbles formed via the cavitation process in the ultrasound method for the treatment of cancer.

Keywords: cavitation, microbubbles, ultrasound, cancerous cell and drug delivery

Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. Chemotherapy is a common treatment for a wide variety of cancer. Although it is effective against cancer cells, they also affect the normal and healthy cells since they travel throughout the body. Damage to healthy cells causes side effects. There is an immediate need for alternative methods for drug delivery. Targeted drug delivery by microbubbles in combination with ultrasound has been demonstrated as a new promising strategy for cancer. It is a non-invasive, nonhazardous, radiation-free method of drug delivery. The ultrasound-activated microbubbles increase the permeability of drugs into the target tissue. The usage of microbubbles for drug delivery is based on the observation that the rapture of microbubbles via ultrasound results in the deposition of its shell components and the increase of tissue permeability. Therefore, this method can be used to carry drugs in nano-size to the target area and deliver the drug.

TABLE 1 |

S.no.	References	Chemo drug	Microbubble
1	Liu et al., (1)	BCNU	SonoVue
2	Ting et al. (2)	BCNU	BCNU loaded MBs
3	Treat et al. (3)	Dox	Definity
4	Fei Yan et al. (4)	G Paclitaxel and Lyp-1 peptide.	The DSPC: DSPE-PEG2000: DSPE-PEG2000-biotin molar ratios were 9:0.5:0.5

Mechanism

The microbubbles are composed of a phospholipid bilayer that is approximately one or two micrometers in size, filled with a perfluorocarbon gas and air mixture, which is important to prevent the osmotically driven size changes under various conditions. Pure air-filled microbubbles would quickly dissolve, and concentrated PFC-filled microbubbles would condense into liquid droplets, resulting in microbubble collapse. The drug to be delivered along with the microbubbles is injected into the bloodstream. They travel throughout the circulation. This procedure requires ultrasound that can be produced by a transducer array fitted

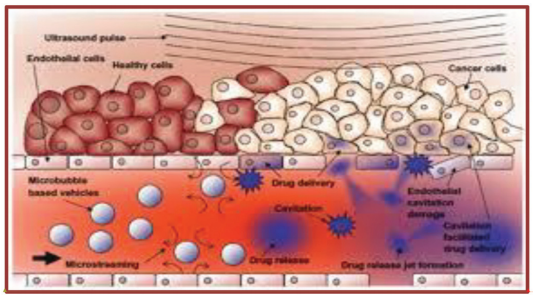

FIGURE 1 | Mechanism of microbubbles interacting with cells.

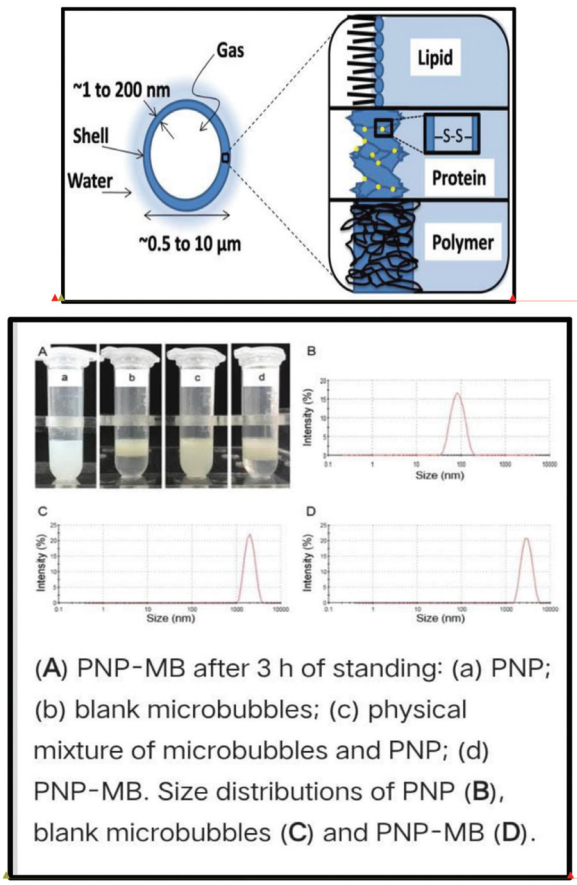

FIGURE 2 | Drug-coated microbubbles for the treatment of cancer. **(A)** PNP-MB after 3 h of standing: (a) PNP; (b) blank microbubbles; (c) physical mixture of microbubbles and PNP; (d) PNP-MB. Size distributions of PNP **(B)**, blank microbubbles **(C)**, and PNP-MB **(D)**.

around the target area. The transducers can be targeted to sonicate waves to the area of interest. Electrostatic attraction can be used to attach charged payloads to the surface of microbubbles in order to cause cancer cells to undergo apoptosis. Microbubble-ultrasound interaction results in oscillation. A shear stress is produced over the surface of the cells by oscillation against the vascular walls, which can rupture the cell membrane (**Figure 1**).

Inertial Cavitation, an occurrence that causes the microbubble to violently burst and release radial shock waves, occurs when the ultrasound interacts resonantly with the microbubble at the right frequencies. These shock waves help in efficient permeability of the drugs into the target tissue.

Importance of microbubbles in cancer treatment

Chemotherapeutic medications effectively kill cancer cells, but they can cause a variety of side effects. They cannot differentiate between healthy and cancer cells. In microbubbles, the drug is released to specific sites, thus, minimizing the drug's contact with the normal tissues. For the potential use of microbubbles in therapeutic applications, the chemical nature of the shell and its mechanical properties are crucial and require a tailored synthetic approach. An innovative formulation employed in contrast ultrasonic imaging was albumin-shelled microbubbles. Albunex was the first albumin microbubble formulation to get USFDA approval. A typical Albunex suspension contains 7 × 108 microbubbles per milliliter.

By sonicating a heated solution containing 5% (w/v) human serum albumin in the presence of gas, albumin-coated microbubbles are created. PFC gas microbubbles are created during the sonication process and are encased in a 15-nm-thick aggregated albumin shell (**Figure 2**).

Various methods

Conclusion

The use of microbubbles as a diagnostic and therapeutic tool is expanding in the field of cancer treatment. Due to the fact that the highly toxic chemotherapeutic medications are contained inside the microbubble and only released at the intended place, they might significantly lessen their side effects. The use of ultrasound to direct a microbubble in the treatment and diagnosis of cancer is a promising new method. To fully understand the method's efficacy and safety profile, more clinical studies should be required.

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