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Mechanism of Targeted Chemotherapeutic Delivery Using Ultrasound

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Abstract #1415

Ultrasound (US) is used to enhance and target delivery of drugs and genes to cancer tissues. The advantages of focused delivery to select tissues are manifold, but the exact mechanism by which US achieves these effects is not well understood. The current study further defined the role of collapse cavitation in US-induced permeabilization of cell membranes. Calcein uptake and propidium iodide (PI) staining were used to indicate cell viability.

Results

Calcein is currently used for diagnostic and therapeutic purposes. Diagnostic ultrasound utilizes the fact that ultrasound permeabilizes cell membranes and can therefore be used to monitor the permeability of internal structures. Ultrasound is used in physical therapy applications. The frequencies typically used for diagnostic purposes are greater than 5 MHz, whereas therapeutic devices are used near 20 kHz. In the current study, cavitation was used as a source of membrane perturbation. It is through the use of a pressurized chamber that the ultrasound is delivered at the target site.

Discussion

Cavitation caused by the rapid expansion and contraction of a gas bubble in the ultrasound field of view has been used for years to enhance the delivery of drugs and genes to specific tissues. Several recent studies have shown that the precise control of the cavitation process can lead to the enhancement of therapeutic delivery. These results show that there is a limited amount of cell permeabilization.

Materials and Methods

Reagents: Calcein (622.5 g/mol) (MP Biomedicals, Inc., Aurora, OH) was dissolved into 1X DPBS supplemented with 10% fetal bovine serum (Hyclone, Logan, UT). The cells were harvested during exponential growth and suspended at a concentration of 1x10⁶ cells/ml. Calcein (622.5 g/mol) (MP Biomedicals, Inc., Aurora, OH) was dissolved into 1X DPBS supplemented with 10% fetal bovine serum (Hyclone, Logan, UT). The cells were harvested during exponential growth and suspended at a concentration of 1x10⁶ cells/ml.

Cell Culture: DHD/K12 tRb rat colon cancer cells (ATCC, Bethesda, MD) were cultured at 37˚C, 5% CO₂ in DMEM (Life Technologies, Inc., Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone, Logan, UT). The cells were harvested during exponential growth and suspended at a concentration of 1x10⁶ cells/ml.

Apparatus: The chamber used for monitoring the cells was a homemade polystyrene blood chamber (20 mL). The cells were placed in the blood chamber and monitored using a fluorescence microscope. An A-100, 50 MHz, 1 MHz to 1 MHz transducer (Sonics) was used to deliver ultrasonic energy to the cells. The transducer was positioned in the center of the blood chamber, and the cells were monitored using a fluorescence microscope.

Conclusions

This research has advanced our understanding of the mechanism of ultrasound-targeted drug delivery to cancer cells. The data indicate that collapse cavitation occurs in the application of ultrasound and is the cause of membrane permeabilization. The amount of membrane permeabilization is proportional to ultrasound exposure. At the same time, the intensity and duration of the ultrasound exposure was increased, the bubble size and intensity increased, and there is a marked decrease in cell viability.

References


The data also show that there is a limited amount of cell permeabilization. This research has advanced our understanding of the mechanism of ultrasound-targeted drug delivery to cancer cells. The amount of membrane permeabilization is proportional to ultrasound exposure. At the same time, the intensity and duration of the ultrasound exposure was increased, the bubble size and intensity increased, and there is a marked decrease in cell viability.