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Ultrasound and microbubble mediated drug delivery: acoustic pressure as determinant for uptake via membrane pores or endocytosis

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Abstract

Although promising results are achieved in ultrasound mediated drug delivery, its underlying biophysical mechanisms remain to be elucidated. Pore formation as well as endocytosis has been reported during ultrasound application. Due to the plethora of ultrasound settings used in literature, it is extremely difficult to draw conclusions on which mechanism is actually involved. To our knowledge, we are the first to show that acoustic pressure influences which route of drug uptake is addressed, by inducing different microbubble-cell interactions. To investigate this, FITC-dextrans were used as model drugs and their uptake was analyzed by flow cytometry. In fluorescence intensity plots, two subpopulations arose in cells with FITC-dextran uptake after ultrasound application, corresponding to cells having either low or high uptake. Following separation of the subpopulations by FACS sorting, confocal images indicated that the low uptake population showed endocytic uptake. The high uptake population represented uptake via pores. Moreover, the distribution of the subpopulations shifted to the high uptake population with increasing acoustic pressure. Real-time confocal recordings during ultrasound revealed that membrane deformation by microbubbles may be the trigger for endocytosis via mechanostimulation of the cytoskeleton. Pore formation was shown to be caused by microbubbles propelled towards the cell. These results provide a better insight in the role of acoustic pressure in microbubble-cell interactions and the possible consequences for drug uptake. In addition, it pinpoints the need of a more rational, microbubble behavior based choice of acoustic parameters in ultrasound mediated drug delivery experiments.

Keywords

Ultrasound, microbubbles, acoustic pressure, sonoporation, endocytosis, drug delivery