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TRANSENDOTHELIAL TRANSPORT OF RECEPTOR-TARGETED NANOBUBBLES INDUCED BY RECEPTOR-MEDIATED ENDOCYTOSIS IN VITRO AND IN VIVO

ACC Moderated Poster Contributions
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Background: The site-targeted nanobubbles (NBs), which are promising pharmacodelivery vehicles, hold a variety of potential applications for ultrasonic molecular imaging and/or image-guided therapeutics. However, the exact mechanism of the NBs crossing endothelium and advancing into the targeted cells is unknown. We hypothesized that receptor-mediated endocytosis, which provide a key transport pathway for macromolecules into and across cells, would be involved in the transendothelial transport of receptor-targeted NBs.

Methods: Folate-decorated NBs (F-NBs) and control NBs (C-NBs) were prepared. For tracing NBs in Vitro and in Vivo, DiO was encapsulated in the NBs as a fluorescent probe. Cellular uptake of the NBs in HeLa and A549 cells, and biodistribution of the NBs in the HeLa and A549 xenograft tumor in mice were observed. Contrast ultrasound was performed and video intensity (VI) was measured.

Results: The NBs size ranged from 160 to 500 nm. Abundance of F-NBs was noted within HeLa cells, the endocytosis of F-NBs was cut off 69.3±8.6% with the pre-treatment of folate. Rare F-NBs and C-NBs were found inside A549 cells, so were C-NBs within HeLa cells. All of those transcytosis were significantly hampered via inhibiting clathrin-/caveolae-mediated endocytosis, or macropinocytosis, but not inhibited by folate. The number of F-NBs in endothelial and tissue cells of HeLa tumor was 3.6 to 9.7-fold higher than other groups ($P<0.01$). Again, it was inhibited by the folate. Contrast-enhancement was clearly seen in HeLa tumor after F-NBs, but was not shown in other cases. The VI of HeLa tumor with F-NBs was significantly greater than other groups ($P<0.01$).

Conclusions: The receptor-mediated endocytosis is a key mechanism for F-NBs to cross the endothelium and reach the targeted cells, allowing for site-directed delivery of drugs with diagnostic and therapeutic significance.