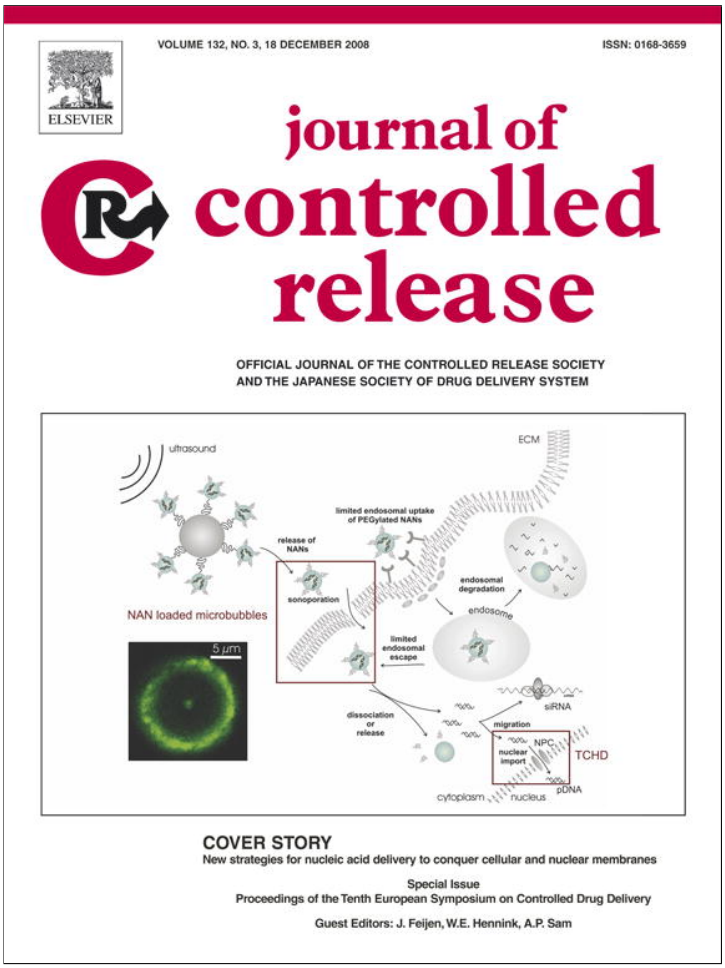

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Cover Story

Ultrasound-activatable drug-loaded microbubbles for intracellular targeting

Efficient intracellular delivery of various drugs, especially high molecular weight drugs such as genes and proteins, has been extremely difficult. A paper in this issue, by the research team of Niek Sanders and Stefaan De Smedt, presents an innovative approach for intracellular delivery of nucleic acids [1]. In this approach free nucleic acids can gain access to the cell's cytoplasm via short-living membrane perforations that occur during the ultrasound-mediated implosion of microbubbles. Ultrasound-assisted gene delivery has been utilized before, but it required a large amount of nucleic acids to overcome two limitations: (i) massive degradation of the unprotected nucleic acids by nucleases, and (ii) not enough molecules entering the cells before the membrane perforations close again. The authors designed a new ultrasound-responsive microbubble that alleviates these two limitations. The microbubble consists of a lipid-stabilized gas core to which nucleic acid-containing nanoparticles are attached. The nanoparticles protect the nucleic acids against nucleases. Exposure of the microbubbles to ultrasound results in their implosion, causing the release of a 'cloud' of the nanoparticles which are instantaneously propelled, probably via the membrane perforations, into the nearby cells. These nanoparticle-grafted microbubbles act like cluster bombs that 'detonate' by exposing them to ultrasound.

The efficiency of gene expression or gene silencing is much higher when a gene or siRNA is linked to microbubbles than the unprotected counterpart. Free nanoparticles without microbubbles are not able to transfect cells on their own. This indicates that ultrasound can be used for time-controlled, as well as space-controlled, gene expression or gene silencing. Obviously, application of the microbubbles is not limited to gene or siRNA delivery. Indeed, the microbubble approach may also open new opportunities for targeted delivery of other drugs including low molecular weight chemotherapeutics and protein drugs. Instead of nanoparticles, other delivery vehicles, such as liposomes or polymer micelles, can be attached to microbubbles to develop clinically useful formulations. Because the genes and protein can be delivered into the cells through transiently formed cell membrane perforations, they are expected to bypass detrimental endosomes.

Reference

[1] Ine Lentacker, Roosmarijn E. Vandenbroucke, Bart Lucas, Joseph Demeester, Stefaan C. De Smedt, Niek N. Sanders, New strategies for nucleic acid delivery to conquer cellular and nuclear membranes, J. Control. Release 132 (2008) 279–288, doi:10.1016/j.jconrel.2008.06.023.

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