Journal of Controlled Release 276 (2018) 168

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Microchamber arrays for controlled NIR laser mediated drug delivery to single cells

Drug molecules have been encapsulated into various delivery systems, ranging from polymer micelles to microparticles. Nanoparticles have been used for intravenous injection, and microparticles have been frequently used as long-acting depot formulations. Despite extensive research in microencapsulated drug delivery systems, delivery of precise amounts of drugs into individual cells has not been easy. Traditionally, micro-pipettes have been used for placing dispersed drug delivery vehicles, or injections close to or into the cell.

In this issue, a new study is presented to address isolated cells in a spatiotemporal manner and to stimulate gene expression only in the selected cells. The work by the Frueh and Sukhorukov team shows that surface microchamber (MC) arrays, storing small hydrophilic molecules for prolonged times in subaqueous conditions, can release the loaded drug upon exposure to a near infrared (NIR) laser [1]. The MCs presented in this study are composed of biodegradable poly(lactic acid) (PLA). Gold nanoparticles are used as light harvesting agents to facilitate photothermal MC opening. The degree of photothermal heating is determined by numerical simulations utilizing optical properties of the MC and confirmed by Brownian motion measurements of laser-irradiated microparticles exhibiting similar optical properties like the MCs. The amount of bioactive small molecular cargo (doxycycline, or DOX) from local release is determined by fluorescence spectroscopy and gene expression in isolated C2C12 cells via enhanced green fluorescent protein (EGFP) biosynthesis. C2C12 cells were engineered to express the tetracycline responsive repressor (tet-R-KRAB) and activator (rtTA-2SM2) in addition to EGFP from a tetracycline responsive promoter. DOX activates EGFP expression via the tetracycline responsive promoter (Ptet) which is activated by rtTA-2SM2. Ptet is actively switched off in the absence of DOX by binding the repressor tet-R-KRAB. The opening of a MC allowed for gene expression in at least one cell, due to determined cellular sensitivity towards DOX down to 100 ng/mL. This sensitivity is enough for a locally released DOX amount in the range of pictograms. Due to a steep DOX gradient only the targeted cell was found to be affected towards DOX release. Such a high sensitivity allows for addressing not only a single cell but cellular patterns, making this study interesting for cellular engineering.

This study shows that PLA MCs can be used effectively for localized delivery to selected individual cells using a NIR-laser. The utilized PLA MCs can also be opened by high intensity focused ultrasound [2], although the resolution is not as high as by a NIR laser. In another study, PLA was additionally proven to seal MCs consisting of polyelectrolyte multilayers (PEMs), which enable a large variety of functionalization. MCs made of PEMs, however, suffer from slow (> 32 hours) production [3]. PEM-based MCs were shown to be responsive towards homogeneous low frequency and medical frequency ultrasound [4,5] indicating a large variety of release stimuli. PLA-sealed PEM MCs were shown to be responsive towards temperature, as the sealed air bubbles increased the inner pressure significantly upon temperature increase towards 80 °C [3]. To overcome the long production time of PEM-based MC production, recently, a rapid polyelectrolyte complex-based MC fabrication method based on saloplastics in combination with thermoplastics was reported [6], decreasing the production time to 1 hour. These polyelectrolyte complex-based MCs were found to be highly sensitive towards water, whereas PLA sealing, as well as investigation and utilization as sensors, is currently in progress.

Recent studies by the Frueh and Sukhorukov team are important, as it allows delivery of a predetermined amount of a drug to individual cells at the single cell level. This brings the current 2D drug delivery technology to another level for cellular engineering. While it will take more time to perfect the 2D MC array technology, its simplicity and universality makes it possible to use in diverse cells to deliver various bioactive agents, ranging from small molecular drugs to large biomolecules.

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https://doi.org/10.1016/j.jconrel.2018.03.029