Efficient fabrication of a pre-invasive breast cancer model via double emulsification of Matrigel

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Pre-invasive breast cancer model

The majority of breast cancer deaths are not caused by the primary tumor, but by metastasis to other organs [1]. Because of the limitations of studying metastasis in vivo, new in vitro model systems are essential to study the process in detail. Here, we focus on our model of the earliest stage of metastasis: invasion. We present an efficient method to generate the model, using double emulsification and surfactant induced retrieval.

The key biophysical property our model captures is the heterogeneous ECM composition before invasion: Initially, cancer cells reside in a soft basement membrane before invading the fibrous and stiffer stromal ECM [2]. In our model, shown in Figure 1, MCF-7 breast cancer cells are encapsulated in Matrigel beads that mimic the basement membrane, which are then embedded in a collagen I hydrogel, mimicking the stromal ECM.

Double emulsification of Matrigel

We have successfully generated a double water-oil-water (WOW) emulsion of Matrigel using our chip with two flow-focusing junctions, by applying hydrophobic and hydrophilic coatings at different locations. Ultra thin shells are formed when the Matrigel droplet is split in the second junction, see Figure 3. Different droplet sizes can be generated as a function of flow-rate, see Figure 4.

Controlled release

By adding a small amount of water soluble surfactant, Triton X-100, the oil shell destabilizes and the beads are rapidly released into the surrounding medium, shown in Figure 4A and 4B. At this concentration, Triton X-100 does not significantly affect viability, as shown in Figure 4C.

Conclusions & outlook

With this method, we observe fewer losses of encapsulated cells in Matrigel beads. Additionally, we can better control the moment of release with the surfactant. Manufacturing of large numbers of micro-tumors is now more efficient and better controlled, enabling application in larger cancer invasion studies.

In a broader sense, the developed bead generation method, with rapid release from the double emulsion, could be useful in other applications where timing of the release is required.

References


Figure 1| A) Schematic of the step-wise fabrication of the pre-invasive breast cancer model, via encapsulation (1) and embedding (2). B) Microscopic images of the fabrication process. C) Phase contrast images of the development of the microtumor, and subsequent invasion into the surrounding collagen I.

Challenge: Encapsulation and release

We originally encapsulated cells in Matrigel beads using a planar water in oil (WO) flow-focusing device. However, releasing the beads from the continuous oil phase, without damaging or aggregating them, was very challenging.

In order to circumvent this problem, we have adopted a method from Choi et al. [3] to our planar flow-focusing geometry. In this method, depicted in Figure 2, gel beads are made with an ultra-thin oil shell that can be removed by adding a water soluble surfactant to the outer phase.