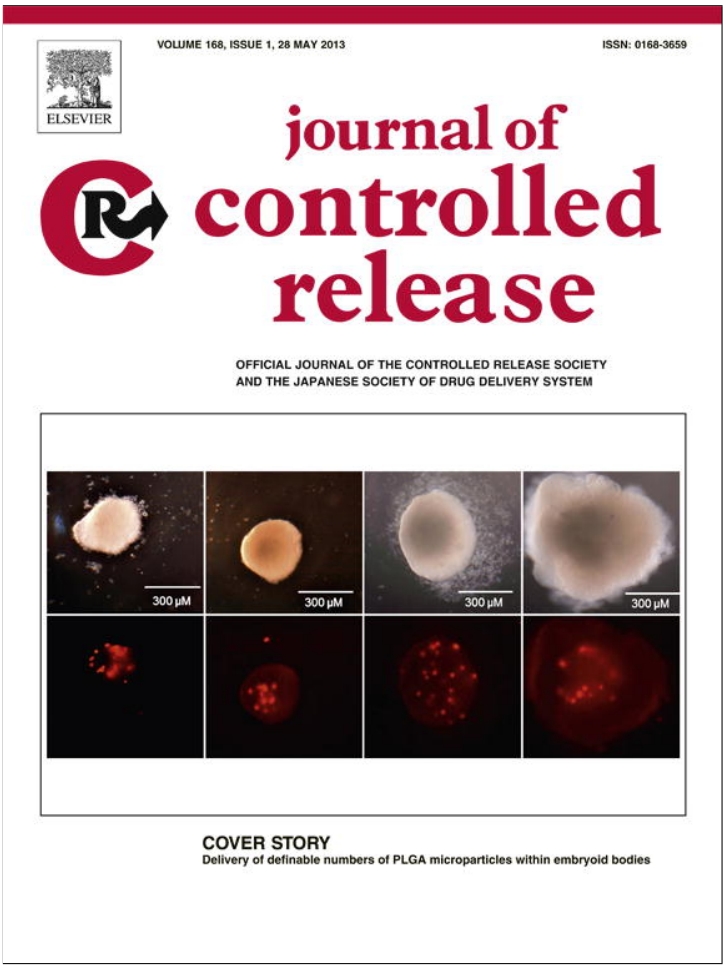

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Cover story

Delivery of definable numbers of PLGA microparticles within embryoid bodies

The formation of human tissues requires defined three dimensional (3D) tissue structures and organization which are co-ordinated by the release of specific biochemical factors and the establishment of signaling gradients. Reproducing these signaling gradients and controlling formation of 3D tissues for stem cell and regenerative medicine therapies or in vitro 3D cell culture models, and studying disease processes or test drugs, are a significant challenge.

Embryoid bodies (EBs), which are multicellular aggregates often formed during differentiation of embryonic stem cells (ESC), have been used extensively as in vitro 3D cell models. The proclivity for most ESC lines to form EBs makes them a relatively easy 3D cell culture model to use, but achieving a homogeneous differentiation of EBs has proved to be more challenging. The conventional approach is to form EBs (or indeed aggregates of other cell types) and then soak them in a culture medium containing growth factors or drug molecules, but this does not ensure their effective delivery throughout the 3D environment and fails to mimic the spatial confinement and control of signaling [1]. An obvious approach to overcoming this limitation is to include microparticles (MPs), capable of releasing chemical factors, into the process of forming EBs and thereby to enable the delivery of factors directly within the 3D environment and this has been demonstrated with some success [2,3]. However, in many of these studies, there is limited control over the process of incorporating MPs within EBs and can result in variability in a number of MPs per EB, affecting both amounts of chemical factor delivered and subsequent cell responses.

In this issue, Dr. Lee Buttery and his colleagues at the University of Nottingham describe an approach to reproducibly incorporate definable numbers of poly(lactic acid-co-glycolic acid) (PLGA) MPs into human EBs and thereby to have greater control over the delivery of biochemical signals and tuning of cell responses. By loading the MPs with different drug molecules or cytokines Dr. Buttery also shows a controlled release of these factors and a localized, directed differentiation within the EBs. The team also shows an osteogenic differentiation and an endothelial differentiation using MPs loaded with simvastatin or BMP2 and VEGF, respectively. With the cell:MP ratio ranging from 50:1 to 3000:1 and brief centrifugation in 96 well V-bottom plates the Buttery team could reliably and reproducibly control the number of MPs incorporated into the EBs, down to 1 MP per EB. The MPs had an average diameter of 13 μm, making them sufficiently large to avoid intracellular uptake, but not so large as to significantly disrupt the physical architecture of the EBs. Prior coating of the MPs with human ESCs lysate was also significant to their retention within the EB and enabled a long-term culture up to 21 days. Without lysate coating, MPs were expelled from EBs within 1–2 days, suggesting that lysate improves their compatibility within the EB. A time-lapse video imaging reveals the EB environment to be a dynamic one, with notable mobility of cells and MPs. It is not known if such movement of MPs induces any biophysical signals, but it does appear to favor a wider delivery of factors loaded within MPs.

This simple and effective method of controllable delivery of chemical factors within 3D cell environments has wide ranging applications to stem cell biology, tissue engineering and regenerative medicine. Obvious challenges remain, such as scalability and application to cell types with less natural tendency to form 3D cultures. The work by the Buttery team, however, will open a new avenue towards a more effective investigation of multiple gradients from different molecules of interest within complex 3D environments. Such a strategy may lead to a better understanding of the processes involved in tissue formation and repair as well as to the development of tissue engineered products for clinical applications.

References

[1] T. Cao, B.C. Heng, C.P. Ye, H. Liu, W.S. Toh, P. Robson, P. Li, Y.H. Hong, L.W. Stanton, Osteogenic differentiation within intact human embryoid bodies result in a marked increase in osteocalcin secretion after 12 days of in vitro culture, and formation of morphologically distinct nodule-like structures, Tissue Cell 37 (2005) 325–334.

[2] R.L. Carpenedo, A.M. Bratt-Leal, R.A. Marklein, S.A. Seaman, N.J. Bowen, J.F. McDonald, T.C. McDevitt, Homogeneous and organized differentiation within embryoid bodies induced by microsphere-mediated delivery of small molecules, Biomaterials 30 (2009) 2507–2515.

[3] L. Ferreira, T. Squier, H. Park, H. Choe, D.S. Kohane, R. Langer, Human embryoid bodies containing nano- and microparticulate delivery vehicles, Adv. Mater. 20 (2008) 2285-+.

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