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Short Commentary

Exploring Stem Cell Differentiation from a Mechanobiological Perspective: Insights from Neural Precursor Cells and Beyond

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The surface of mammalian cells consists of the plasma membrane lined by an underneath cortical actomyosin cytoskeleton. This pair of structures forms the Membrane-Cytoskeleton Complex (MCC), a known regulator of cellular processes, ranging from shape control and cell migration to molecule presentation and signaling [1-3]. The MCC exerts and reacts against forces due to its elastic properties [1-3]. It has been shown that these elastic properties vary greatly between cell types [4,5] and can influence the morphology and differentiation of cells not only in healthy [6] but also in disease contexts, such as cancer, where changes in MCC stiffness for example is a relevant parameter for the progression of the disease [6,7].

Over the years, different micromanipulation tools such as atomic force microscopy, Optical Tweezers (OT), traction force microscopy and magnetic twisting cytometry, among others, have been used to exert forces on MCCs to characterize their elastic responses [4]. OT uses a precisely focused laser beam, attached to an optical microscope, to trap and move microscopically translucent objects, which can then be used to probe forces within a sample. The trapped object behaves as if attached to a string, meaning that a displacement from the trap equilibrium position creates a proportional pulling force [8,9]. The spring constant equivalent, known as trap stiffness, can be verified through previous calibration and finally tuned adjusting the laser power output [8,9]. Thus, it is possible to determine forces exerted onto trapped objects by measuring their displacements in the trap via conventional microscope video imaging.

Using such tool, membrane tether pulling assays have been applied to extract tethers from cells [10,11], vesicles and model membranes [12]. Briefly, an optically-trapped bead is pressed against the membrane for about 5 seconds to allow attachment. The probe is then withdrawn from the membrane surface and a thin membrane tube, also known as membrane tether, is formed. Why do they form? When a point force is applied to a thin membrane using, for example, a bead trapped in an OT and moving this probe away from the membrane surface, one should expect to observe the formation of a catenoid structure connecting the membrane and the bead [13,14]. This catenoid does appear, but is then replaced by a thin membrane tube, which is formed because membranes are always under tension – in other words, they are prone to minimize their surface area. Hypothetically, the minimum area would be reached when nearly the entire membrane is retracted to its original configuration, leaving just an infinitesimally thin tube. However, for such slim tube to occur, the membrane curvature would drastically increase above prohibitive values, due to their bending rigidity or bending modulus, understood as the resistance of such membrane to bend. So, during tether formation, the balance between membrane tension and bending rigidity generates a tube with a given radius that is maintained by a certain point force.

Consequently, during tether pulling assays in cells, if one measures the tether radius and the force necessary to maintain this tether, it is possible to determine both the Cell Membrane Tension (CMT) and the Cell Membrane Bending Modulus (CMBM) [15]. Tether force can be simultaneously measured during OT-tether extraction experiments. However, measuring the tether radius is a challenge, as its size is typically below the resolving limit of conventional optical microscopes. Therefore, a correlative microscopy-based method was established [5,11,16]. In this method, a tether is extracted via OT and the force required to perform tether extraction is obtained during the experiment, while the tether radius is later measured by Scanning Electron Microscopy (SEM).

In a recently published article from our research group [16], it was shown that the membrane elastic properties of Neural Precursor Cells (NPCs) strongly vary during their transformation into neurons, astrocytes and oligodendrocytes, correlating with shape and phenotype changes that occur throughout each of these differentiation events. Using fluorescence microscopy to track changes in actin cytoskeleton, together with a correlative OT-SEM-based method previously described to precisely measure CMT and CMBM, their variations were mapped over time (from 2 to 240h after induction of differentiation) and compared to NPCs kept in culture as undifferentiated cells (neurospheres or dissociated cells).

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On undifferentiated NPCs and NPCs induced to differentiate into neurons, changes in membrane elastic properties were detected only over the first hours of culture, with a drop in CMT correlated with changes in cell morphology during spreading, but once these cells reached their typical morphologies in culture, after a few hours, both cell types showed stabilization of CMT over the remaining days, although CMBM remained unchanged during the entire experiment. This scenario was, however, quite different for the other cells.

When NPCs were induced to differentiate into astrocytes, the cells also showed an initial decrease in CMT (probably related to cell spreading), but with the advancement of the differentiation process and even after spreading is complete, a peak in CMT and CMBM occurred after 72h, correlated with a notable actin reorganization process, followed by an increase in glial fibrillary acidic protein (GFAP) expression.

In oligodendrocytes, the cell morphology was altered more dynamically over the culture period, adopting different cell shapes. At later differentiation stages, the formation of vesicles around the cell surface was observed. All the morphological changes were correlated with alterations in CMT, which decreased over the hours in culture, while CMBM remained almost constant. The observed vesicles, when probed, showed similar membrane tension but higher bending modulus when compared to those found for the membrane of oligodendrocytes.

Overall, the results of our study [16] displayed an entire spectrum of how NPC membrane elastic properties are varying along their distinct differentiation fates and also established correlations between these changes and striking morphological phenotype variations that occur with the cells [16]. It is then possible to further investigate whether these modifications could conversely play an important role in NPC differentiation processes or even affect the regulatory pathways controlling cell fate decisions. Indeed, this view has only recently started to be explored. In studies yet to be published [17,18], two distinct groups described that a decrease in CMT occurred when mouse embryonic stem cells changed from their round and naïve state to a spread and primed state, and that the observed decrease in CMT is correlated with a decrease in membrane-to-cytoskeleton attachment [17,18] via GSK3β-driven β-catenin degradation [18], which in turn appears to control CMT and allow exit from naïve pluripotency. However, whether this described pathway is active in human embryos, other pluripotent precursors that are no longer in this naïve state or beyond 2D cell cultures remains to be studied. Therefore, the interplay between cell morphology, surface mechanics and differentiation is still a stimulating and versatile field to be explored from a mechanobiological perspective.

This versatility has allowed similar experiments conducted with NPCs that investigated the membrane elastic properties as an indicator and predictor of developmental neurotoxicity after exposure to toxic compounds [19]. Moreover, other approaches exploring cell mechanics and differentiation have been conducted on different cell types, other than neural, such as human bone marrow-derived progenitor cells [20] and mesenchymal stem cells [21] on their osteogenic differentiation process, and also human embryonic stem cells induced to differentiate into cardiac cells [22]. Taken together, the results from these experiments all show that membrane elastic properties and the underlying actin cytoskeleton play a pivotal role in the early stages of stem cell differentiation.

Furthermore, research from our team has successfully demonstrated, through similar OT and SEM experiments, the effects of cytoskeletal drugs on CMT and CMBM [23], the role of CMT on mechanical signaling for cell migration and adhesion [24], as well as phagocytosis [25], and membrane-cytoskeleton interactions during tether-pulling assays, analogous to that of filopodia formation [11]. Also, this method has been used to explore the importance of cholesterol in controlling mechanical properties of cells and its connection with lysosomal exocytosis [26] or cardiomyocyte contractility [27]. Thus, CMT and CMBM can be considered important physical parameters in cell biology for different cell types and experimental approaches, and their roles in mechanosensing and signaling should remain under investigation.

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