Imaging-Based Screen Identifies Laminin 411 as a Physiologically Relevant Niche Factor with Importance for i-Hep Applications.

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Public Summary:
Human iPSCs represent a potentially unlimited source of cells in regenerative medicine. However, we need to develop methods to differentiate iPSCs into mature and functional cell types. For example, if we could make mature liver cells from iPSCs, these could be used to treat patients with liver failure, who are currently on very long donor waitlists. Here, we developed new technologies to screen for conditions that promoted liver cell generation from iPSCs. We identified an extracellular matrix protein, Laminin411, as an important factor promoting iPSC-derived liver production.

Scientific Abstract:
Use of hepatocytes derived from induced pluripotent stem cells (i-Heps) is limited by their functional differences in comparison with primary cells. Extracellular niche factors likely play a critical role in bridging this gap. Using image-based characterization (high content analysis; HCA) of freshly isolated hepatocytes from 17 human donors, we devised and validated an algorithm (Hepatocyte Likeness Index; HLI) for comparing the hepatic properties of cells against a physiological gold standard. The HLI was then applied in a targeted screen of extracellular niche factors to identify substrates driving i-Heps closer to the standard. Laminin 411, the top hit, was validated in two additional induced pluripotent stem cell (iPSC) lines, primary tissue, and an in vitro model of alpha1-antitrypsin deficiency. Cumulatively, these data provide a reference method to control and screen for i-Hep differentiation, identify Laminin 411 as a key niche protein, and underscore the importance of combining substrates, soluble factors, and HCA when developing iPSC applications.