Laminin Confers the Long-Term Proliferative Capability on Mouse Dlk$^+$ Hepatoblasts

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Hepatoblasts are liver stem cells which differentiate to hepatocytes and cholangiocytes. We isolated hepatoblasts from mouse fetal liver as Dlk$^+$ cells using a specific monoclonal antibody and a cell sorter. Dlk$^+$ hepatoblasts proliferate well *in vitro*, but it was difficult to keep them growing for long time.

By testing several extracellular matrices to coat culture-dishes, we found that Dlk$^+$ hepatoblasts continuously grew on plates coated with laminin. The cells grown on laminin could proliferate even after one-month of culture. We named these cells HPPL, hepatic progenitor cells proliferating on laminin. HPPL are induced to express hepatic differentiation markers, such as tyrosine aminotransferase (TAT) and carbamoylsynthetase (CPS), by overlay of EHS-gel and to form tubule-like structures which were stained with antibody against cytokeratin 19 (CK19), a marker of cholangiocytes, in collagen gel. Moreover, HPPL that committed to the hepatic lineage accumulated polysaccharide in their cytosol and detoxified ammonia in culture medium. Micro-array analysis showed that long-term culture on laminin upregulated transforming growth factor α (TGFα), a possible autocrine growth factor, and downregulated p57, a negative regulator of cell cycle progression, which probably elicits the long-term proliferative capability of HPPL. Taken together, by keeping hepatoblasts on laminin we can established hepatic progenitor cells with bidirectional differentiation potential.

References

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