

CREATION AND FUNCTION OF 3D MICROSCALE MODELS OF LIVER

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Some *in vitro* physiological studies of liver -- such as analysis of steps in cancer cell metastasis, regeneration, and response to chronic infection -- might best be carried out in a 3D culture system with very localized flow of fluid through tissue. We have designed and implemented a perfusion microreactor that allows us to capture some features of three dimensional liver tissue at the length scale of the capillary bed. The system can be scaled to accommodate 10^4 - 10^6 cells within a single well of a 12-well plate format, where flow through each well is governed by microfluidic, pneumatically-driven pumps. Using a prototype system that allows in situ imaging, we showed that primary rat hepatocytes maintained in this microperfused culture system exhibit greater retention of drug-metabolizing activity at basal and induced levels than do cells maintained in conventional culture, consistent with the additional finding that more global transcription factor regulators of liver-specific gene expression are also maintained at higher levels, even when the initial cell population is relatively enriched in hepatocytes (and relatively depleted in non-parenchymal cells) compared to in vivo liver. When liver-derived endothelial cell isolates are added to the 3D reactor cultures, they appear to proliferate moderately over 2 weeks and form microvessel-like networks within the tissue, and positive immunostaining for the sinusoidal endothelial cell-specific antigen SE-1 is observed. Local perfusion rates appear to govern the morphogenesis and proliferation of non-parenchymal cells within the 3D tissue structures. This approach may be useful in developing models of liver toxicology and chronic liver disease.