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Recapitulation of the hepatic function using *in vitro* liver model from murine ES/iPS cells

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Polygonal and multipolar hepatocytes in the liver are surrounded by sinusoids, bile canaliculus, and adjacent hepatocytes. It is only in the context of hepatic tissue architecture that hepatocytes can express their specific and multiple functions. Hepatocyte polarity exerts a major influence on the physiology of the cell. Recently, we established a unique system of in vitro liver model derived from murine ES/iPS cells, *i.e.*, $IVL^{mES/iPS}$ [1, 2]. The $IVL^{mES/iPS}$, consisting of not only hepatocytes, but also endothelial networks, together with cardiac mesoderm differentiation, was induced after the embryoid body formation.

To confirm cellular polarities of the $IVL^{mES/iPS}$, first, dichlorofluorescein diacetate (CDFDA) was added into the $IVL^{mES/iPS}$. In liver, CDFDA is incorporated into hepatocytes via OATP2 which expresses at apical side, and afterward CDFDA was hydrolyzed by cytoplasmic esterase to green fluorescent CDF, and which is excreted to bile canaliculus via MRP2. CDF was observed to be accumulated at the boundary of the cells in the $IVL^{mES/iPS}$, but not in primary hepatocyte culture. Second, we tried to activate urea cycle by addition of L-ornithine in the $IVL^{mES/iPS}$ or liver perfusion system. Urea production increased and ammonia decreased in a dose-dependent manner with respect to the amount of L-ornithine both in the $IVL^{mES/iPS}$ and the liver perfusion system, but not in primary hepatocyte culture [3].

Here, we demonstrated that architectural and functional properties in the $IVL^{mES/iPS}$ were quite similar to those in the liver perfusion system, but different from those in the culture of primary hepatocytes. The $IVL^{mES/iPS}$ has great promise to be useful for drug metabolism and pharmacokinetics in liver as an alternative to animal experiments.

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