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EDITORIAL

Highlight report: spheroids from stem cell-derived hepatocyte-like cells

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In the August issue of the Archives of Toxicology Hassan Rashidi from the University of Edinburgh and colleagues published a study about 3D liver tissue-like spheroids generated from pluripotent stem cells (Rashidi et al. 2018). The authors used hPSC cell lines including the stem cell lines H9 and Man12, and the hiPSC lines FSPS13B and P106 (Cameron et al. 2015). Stem cells were differentiated via definitive endoderm to form hepatoblasts and were further differentiated to hepatocyte-like cells under the influence of HGF and OSM using culture conditions where the cells can form spheroids (Rashidi et al. 2018). Under these conditions, the spheroids could be maintained in culture for up to 1 year. The spheroids showed a high expression of HNF4A and albumin (Rashidi et al. 2018). Expression of hepatocyte markers, such as CYP3A4, SULT1 or MRP1, was seen in the periphery of the spheroids but not in the center. Importantly, similar results were obtained with hESC and hiPSC using the same protocol (Rashidi et al. 2018). Moreover, it was possible to transplant the spheroids intraperitoneally or subcutaneously into mice after partial hepatectomy as extrahepatic support system.

Currently, much research work is performed to establish hepatocyte in vitro systems for toxicity testing (Godoy et al. 2016; Hewitt et al. 2007; Leist et al. 2017; Deharde et al. 2016; Ghallab 2017; Stöber 2016; Hammad 2013). Besides their well-established use as metabolizing systems and for studies of enzyme induction, they are increasingly used for omics-based studies of test compounds (Parmentier et al. 2017; Vatakuti et al. 2017; Rodrigues et al. 2018; Grinberg et al. 2014; Arbo et al. 2016; Shinde et al. 2015). Often interpretation of in vivo studies of hepatotoxicity is supported by in vitro experiments and in silico methods (Schenk et al. 2017; Ghallab et al. 2016; Jansen et al. 2017; Vartak et al. 2016; Stöber 2016; Sezgin et al. 2018). One of the perspectives of this branch of stem cell research is that it may lead to an unlimited supply of human hepatocytes (Hammad et al. 2014; Godoy et al. 2013, 2016; Gomez-Lechon and Tolosa 2016; Brulport et al. 2007). A further prospect is that iPS cells from humans with genetic, e.g., metabolic diseases may be used to generate adult cells of organs or tumor cells (Lee et al. 2018; Stewart et al. 2012). However, a limitation of current differentiation protocols is that the generated 'hepatocyte-like cells' (HLC) still show major differences compared to naturally developed or 'primary' human hepatocytes (Godoy et al. 2016, 2018). On the one side, numerous genes responsible for hepatocyte functions are expressed at much too low levels compared to primary hepatocytes. On the other side, HLC express genes representing, e.g., colon features that are not seen in real hepatocytes. Rashidi et al. are to be congratulated that their technique opens new perspectives for in vivo applications. A limitation is that the differentiation status of their HLCs has not been characterized by an unbiased method, e.g. genome-wide expression analysis, compared to primary human hepatocytes. Future, studies will have to show whether the supportive effect of HLC-spheroids in mouse models of partial hepatectomy have a clinical perspective.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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