Highlight report: role of HNF4 α in stem-cell differentiation to hepatocytes

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Recently, Wang and colleagues from Edinburgh University performed a study, where they generated deletion and point mutants of hepatocyte nuclear factor-4 α (HNF4 α) to study their influence during differentiation to hepatocyte-like cells (Wang et al. 2019). HNF4 α is a transcription factor that plays a major role for gene expression in hepatocytes (Sladek et al. 1990). Approximately 40% of all expressed genes in hepatocytes are bound by HNF4 α (Odom et al. 2004). It contains several functional regions, the N-terminal transactivation domain (AD-1), a zinc finger DNA-binding domain, a flexible hinge region, a multifunctional ligand-binding domain with a second transactivation domain (AD-2), and a repression region (Lau et al. 2018; Dhe-Paganon et al. 2002). In the present study, Wang et al. used CRISPR-Cas 9 genome-editing techniques to understand the role of the DNA-binding domain and the transactivation domains (AD-2) during differentiation of stem cells to hepatocyte-like cells (Wang et al. 2019). Interestingly, the two modifications had a different influence on stem-cell specification. Truncation of the DNA-binding domain blocked differentiation even to hepatic progenitor cells; in contrast, modification at AD-2 still allowed differentiation of stem cells to hepatocyte progenitors, but further expression of genes characteristic for mature hepatocytes was compromised (Wang et al. 2019).

Currently, there is a need of in vitro systems with cells that closely resemble mature human cells, such as hepatocytes (Godoy et al. 2013, 2016; Ghallab et al. 2016; Hewitt et al. 2007), kidney epithelial tubular cells (Sjögren et al. 2018; Jiang et al. 2018; Leist et al. 2017), and neuronal cells (Krug et al. 2013; Waldmann et al. 2014; Rempel et al. 2015). Human hepatic differentiation protocols have been developed and optimized (Cameron et al. 2015; Rashidi et al.

2018; Sullivan et al. 2010), but the problem remains that stem-cell-derived hepatocyte-like cells still show major differences compared to primary human hepatocytes. One common problem is too low expression of hepatocyte-specific genes; a further challenge is expression of ‘unwanted genes’ that are not observed in primary human hepatocytes (Sachinidis et al. 2019; Godoy et al. 2015). The present systematic study of Wang et al. (2019) showed that HNF4 α does not only play a role in the steps of final differentiation from hepatoblasts to mature hepatocytes but also during development from endoderm to hepatoblasts.

Compliance with ethical standards

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

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