

Before continuing with the analysis, we wanted to validate that the differentiations for the samples we used for RNAseq and ATACseq were successful and contained primarily our target cell types. The very low expression of *NANOG*, a marker for pluripotency, across all differentiations indicates that the samples contain very few iPSCs (Agoglia et al., 2021). For cardiomyocytes (CM), *NKX2-5*, *MYBPC3*, and *TNNT2* definitively distinguish CM from other heart cell types and their high expression indicates successful differentiations (Burrige et al., 2014). For motor neurons, the high expression of *ELAVL2*, a pan-neuronal marker, indicates the presence of many neurons in the sample (Mickelsen et al., 2019). The expression of *ISL1* and *OLIG2* further demonstrates that these are motor neurons and not other types of neurons (Maury et al., 2015). For retinal pigment epithelium (RPE), the combined expression of *MITF*, *PAX6*, and *TYRP1* provides strong evidence that the differentiations were successful in producing RPE cells (Sharma et al., 2019). For skeletal muscle, the very high expression of *MYL1*, *MYLPP*, and *MYOG* indicates that these samples contain a high proportion of skeletal muscle cells (Chal et al., 2016). In general, all these populations of cells contain some proportion of progenitors as there is detectable expression of *MKI67* in all samples.

The low expression of *ALB* (a marker for mature hepatocytes) and the high expression of *TTR* and *GPC3* (markers for hepatocyte progenitors) combined with the high expression of *HNF1B* indicate that the bulk of the cells in the HP samples are indeed hepatocyte progenitors and not hepatocytes or endoderm cells, although there are likely some endoderm cells and immature hepatocytes in the sample (Hay et al., 2008; Mallanna & Duncan, 2013). Similarly, the combined expression of *PDX1* and *NKX6-1* and the low expression of *NEUROG3* (a marker of endocrine progenitors which differentiate from pancreatic progenitors) in the PP samples indicates that the PP samples primarily contain pancreatic progenitors but likely contain some endocrine progenitors and endoderm cells (Cogger et al., 2017; Korytnikov & Nostro, 2016).

Notably, HP and PP are closely related cell types that are derived from the same lineage. Indeed, heterogeneous multipotent progenitors can contribute to both the adult liver and adult pancreas in mice (Willnow et al., 2021). Progenitors that express *PDX1* (often used as a marker for the pancreatic lineage) can differentiate into hepatocytes (Willnow et al., 2021). As a result, some overlap in the transcriptomic signature of both cell types is expected and we cannot rule out that the HP samples contain cells that could differentiate into pancreatic cells or that the PP samples contain cells that could differentiate into hepatocytes. However, the expression of *NKX6-1* and *GP2*, markers for pancreatic progenitors, in the PP samples but not the HP samples indicates that these two populations of cells are to some extent distinct. Overall, the similarity of PP and HP likely explains the lower number of cell type-specific genes and genes showing cell type-specific ASE for these cell types. This similarity does not alter the conclusions presented in the main text.

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