Multiomics analyses of HNF4α protein domain function during human pluripotent stem cell differentiation.

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Details

Abstract

During mammalian development, liver differentiation is driven by signals that converge on multiple transcription factor networks. The hepatocyte nuclear factor signaling network is known to be essential for hepatocyte specification and maintenance. In this study, we have generated deletion and point mutants of hepatocyte nuclear factor-4alpha (HNF4α) to precisely evaluate the function of protein domains during hepatocyte specification from human pluripotent stem cells. We demonstrate that nuclear HNF4α is essential for hepatic progenitor specification, and the introduction of point mutations in HNF4α's Small Ubiquitin-like Modifier (SUMO) consensus motif leads to disrupted hepatocyte differentiation. Taking a multiomics approach, we identified key deficiencies in cell biology, which included dysfunctional metabolism, substrate adhesion,

tricarboxylic acid cycle flux, microRNA transport, and mRNA processing. In summary, the combination of genome editing and multiomics analyses has provided valuable insight into the diverse functions of HNF4α during pluripotent stem cell entry into the hepatic lineage and during hepatocellular differentiation.

Beteiligte Forschungseinheiten

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