Targeting SOX17 in human embryonic stem cells creates unique strategies for isolating and analyzing developing endoderm.

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Public Summary:
The pluripotent nature of human embryonic stem cells (hESCs) makes them a convenient in vitro model for studying aspects of early development, as well a common starting point for deriving numerous therapeutically relevant cells. Unlike in studies of embryonic mice or mouse ESCs, it remains unknown whether human ESC-derived endodermal progeny resembling liver, pancreas, or intestinal cells are produced from SOX17+ cells. To address this fundamental question, we used homologous recombination to target a reporter gene to the endogenous SOX17 locus in hESCs. By using homologous recombination in human ESCs, we inserted an enhanced green fluorescent protein (eGFP) transgene into the SOX17 locus, a postulated marker of human endoderm. Sox17 is a HMG box transcription factor required for definitive endoderm development in miceFACS purification and gene expression profiling confirmed that SOX17+-hESC progeny expressed endodermal markers and unveiled specific cell surface protein combinations that permitted FACS-based isolation of primitive gut tube endodermal cells produced from unmodified human ESCs and from induced pluripotent stem cells (iPSC). Differentiating SOX17+ endo- dermal cells expressed markers of liver, pancreas, and intestinal epithelium in vitro and gave rise to endodermal progeny in vivo.

Scientific Abstract:
Human embryonic stem cells (hESCs) can provide insights into development of inaccessible human tissues such as embryonic endoderm. Progress in this area has been hindered by a lack of methods for isolating endodermal cells and tracing fates of their differentiated progeny. By using homologous recombination in human ESCs, we inserted an enhanced green fluorescent protein (eGFP) transgene into the SOX17 locus, a postulated marker of human endoderm. FACS purification and gene expression profiling confirmed that SOX17(+)-hESC progeny expressed endodermal markers and unveiled specific cell surface protein combinations that permitted FACS-based isolation of primitive gut tube endodermal cells produced from unmodified human ESCs and from induced pluripotent stem cells (iPSC). Differentiating SOX17(+) endodermal cells expressed markers of liver, pancreas, and intestinal epithelium in vitro and gave rise to endodermal progeny in vivo. Thus, prospective isolation, lineage tracing, and developmental studies of SOX17(+) hESC progeny have revealed fundamental aspects of human endodermal biology.