TCF7L1 suppresses primitive streak gene expression to support human embryonic stem cell pluripotency.

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Public Summary:
Human embryonic stem cells (hESCs) are exquisitely sensitive to a cellular signal name WNT, a signal that triggers stem cells to lose their state of stemness so that they can develop into cell types important for fetal development. To balance a state of stemness with capabilities to properly differentiate, hESCs require robust mechanisms to keep the cells in a WNT inactive but responsive state. How they achieve this balanced state is largely unknown. We explored the role of gene regulators that mediate WNT signaling, the TCF/LEFs. TCF7L1 is the predominant family member expressed in hESCs. We discovered that this regulator binds to genes that are immediately expressed when hESCs are triggered to lose stemness and move towards differentiation - a physical process in the embryo called gastrulation. Idenfitying TCF7L1-bound sites throughout the hESC genome indicates that TCF7L1 acts largely by binding to and opposing the activation of genes that WNT signaling will turn on during gastrulation. Gain- and loss-of-function studies confirm that TCF7L1 suppresses genes that are typically activated during gastrulation. Interestingly, we find that BMP4, another cellular signal that orchestrates hESC differentiation, downregulates TCF7L1, providing a mechanism of BMP and WNT pathway intersection. That is, BMP downregulates TCF7L1 expression to eliminate its opposition to gastrulation and differentiation and to therefore enable robust WNT activation of cellular differentiation. Together, our studies indicate that TCF7L1 plays a major role in maintaining hESC pluripotency, a function that has implications for human development.

Scientific Abstract:
Human embryonic stem cells (hESCs) are exquisitely sensitive to WNT ligands, which rapidly cause differentiation. Therefore, hESC self-renewal requires robust mechanisms to keep the cells in a WNT inactive but responsive state. How they achieve this is largely unknown. We explored the role of transcriptional regulators of WNT signaling, the TCF/LEFs. As in mouse ESCs, TCF7L1 is the predominant family member expressed in hESCs. Genome-wide, it binds a gene cohort involved in primitive streak formation at gastrulation, including NODAL, BMP4 and WNT3 Comparing TCF7L1-bound sites with those bound by the WNT signaling effector beta-catenin indicates that TCF7L1 acts largely on the WNT signaling pathway. TCF7L1 overlaps less with the pluripotency regulators OCT4 and NANOG than in mouse ESCs. Gain- and loss-of-function studies indicate that TCF7L1 suppresses gene cohorts expressed in the primitive streak. Interestingly, we find that BMP4, another driver of hESC differentiation, downregulates TCF7L1, providing a mechanism of BMP and WNT pathway intersection. Together, our studies indicate that TCF7L1 plays a major role in maintaining hESC pluripotency, which has implications for human development during gastrulation.