Endogenous Wnt signalling in human embryonic stem cells generates an equilibrium of distinct lineage-specified progenitors.

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Public Summary:
Human embryonic stem cells depend on extracellular signals for their correct differentiation into specialized cells. We fond that signaling by the Wnt factors is important for human embryonic stem cells to generate endodermal cells (which will form the gut and pancreas) and to form cardiac cells. The latter will generate heart cells. We were able to manipulate the levels of Wnt factor signaling, which results in a more efficient method to allow human embryonic stem cells to differentiate.

Scientific Abstract:
The pluripotent nature of human embryonic stem cells (hESCs) makes them convenient for deriving therapeutically relevant cells. Here we show using Wnt reporter hESC lines that the cells are heterogeneous with respect to endogenous Wnt signalling activity. Moreover, the level of Wnt signalling activity in individual cells correlates with differences in clonogenic potential and lineage-specific differentiation propensity. The addition of Wnt protein or, conversely, a small-molecule Wnt inhibitor (IWP2) reduces heterogeneity, allowing stable expansion of Wnt(high) or Wnt(low) hESC populations, respectively. On differentiation, the Wnt(high) hESCs predominantly form endodermal and cardiac cells, whereas the Wnt(low) hESCs generate primarily neuroectodermal cells. Thus, heterogeneity with respect to endogenous Wnt signalling underlies much of the inefficiency in directing hESCs towards specific cell types. The relatively uniform differentiation potential of the Wnt(high) and Wnt(low) hESCs leads to faster and more efficient derivation of targeted cell types from these populations.