Embryonic stem cells require Wnt proteins to prevent differentiation to epiblast stem cells.

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Public Summary:
A central question in Human Embryonic Stem Cell biology is how the state of differentiation the cells can be controlled. Solving this problem will require numerous issues to be addressed. Among these are to define conditions and factors that promote the differentiation of human ES cells into particular lineages; and to identify intermediate stages of fate commitment. We have hypothesized that the best candidate factors are those that regulate cell fate decisions in normal embryos. We also found that purified Wnt ligand, combined with LIF, is sufficient to efficiently propagate ES cells at clonal density in absence of serum or any other growth factor. Further analysis of the functions of the individual factors showed that LIF promotes survival of mouse pluripotent cells, whereas Wnt inhibits differentiation by repressing genes that would otherwise promote differentiation into ectoderm. By gene expression profiling, we established that a number of differentiation genes, including FGF5 and Otx2 are actively repressed by the Wnt signal, explaining the block in differentiation. These findings have two important consequences for the clinical application of pluripotent cells. First, they suggest that antagonism of the Wnt pathway will force all pluripotent cells to differentiate, thereby eliminating their tumorigenic potential. This may alleviate one of the main problems in using ES cells for therapeutic purposes. Second, these results suggest that Wnts would act to promote the establishment new ES cells. Indeed, we have been able to readily establish various new ES lines from several different mouse strains.

Scientific Abstract:
Pluripotent stem cells exist in naive and primed states, epitomized by mouse embryonic stem cells (ESCs) and the developmentally more advanced epiblast stem cells (EpiSCs; ref.). In the naive state of ESCs, the genome has an unusual open conformation and possesses a minimum of repressive epigenetic marks. In contrast, EpiSCs have activated the epigenetic machinery that supports differentiation towards the embryonic cell types. The transition from naive to primed pluripotency therefore represents a pivotal event in cellular differentiation. But the signals that control this fundamental differentiation step remain unclear. We show here that paracrine and autocrine Wnt signals are essential self-renewal factors for ESCs, and are required to inhibit their differentiation into EpiSCs. Moreover, we find that Wnt proteins in combination with the cytokine LIF are sufficient to support ESC self-renewal in the absence of any undefined factors, and support the derivation of new ESC lines, including ones from non-permissive mouse strains. Our results not only demonstrate that Wnt signals regulate the naive-to-primed pluripotency transition, but also identify Wnt as an essential and limiting ESC self-renewal factor.