Human Embryonic Stem Cells Express Elevated Levels of Multiple Pro-Apoptotic BCL-2 Family Members.

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Public Summary:
The therapeutic potential of human embryonic stem cells is extraordinary. Without a doubt, regenerative medicines will save thousands of lives in the years to come. Before that day arrives, much needs to be learned from the cells themselves. The reasons that these cells hold so much promise are two-fold: (1) embryonic stem cells can renew themselves indefinitely (divide and divide and...) and (2) embryonic stem cells can be trained to become any cell type of the body (neurons, heart muscle, skin, liver, kidney...). However, it should be emphasized that these two points are only valid if the growth conditions are properly established. While we have made great strides in developing culture conditions that can support self-renewal of embryonic stem cells, we are a long way from mastering the conditions necessary for differentiating embryonic stem cells into every cell type of the body (of which there are about 200). Ultimately, if therapies based on stem cells are to be realized, these cells will have to be grown in massive quantities, with an unprecedented level of quality control to ensure that only one cell type can be found in the lot. Furthermore, the fate of stem cells is crucial to their use in new therapies - in other words, these cells must be kept alive and functional to have benefit to human patients. However, one of the major challenges facing the growth of embryonic stem cells is the abundance of cell death that occurs. Cells typically die when their needs are not met (either lack of proper nutrients or growth factors) or when they face harsh conditions. If we could somehow block the cell death that occurs in these cultures or if we could change the conditions to remove the components that trigger cell death, we could achieve growth of hESCs of a greater scale. It turns out that when cells die, they do not do so passively. Instead, once given a “go” signal, cells utilize their own energy and cellular machinery to dismantle themselves, a process known as programmed cell death. The published work identifies some of the key molecules inside hESCs that are responsible for driving cell death in standard growth conditions. With these players now known, we are positioned to make some predictions as to how better to grow the cells in the laboratory.

Scientific Abstract:
Two of the greatest challenges in regenerative medicine today remain (1) the ability to culture human embryonic stem cells (hESCs) at a scale sufficient to satisfy clinical demand and (2) the ability to eliminate teratoma-forming cells from preparations of cells with clinically desirable phenotypes. Understanding the pathways governing apoptosis in hESCs may provide a means to address these issues. Limiting apoptosis could aid scaling efforts, whereas triggering selective apoptosis in hESCs could eliminate unwanted teratoma-forming cells. We focus here on the BCL-2 family of proteins, which regulate mitochondrial-dependent apoptosis. We used quantitative PCR to compare the steady-state expression profile of all human BCL-2 family members in hESCs with that of human primary cells from various origins and two cancer lines. Our findings indicate that hESCs express elevated levels of the pro-apoptotic BH3-only BCL-2 family members NOXA, BIK, BIM, BMF and PUMA when compared with differentiated cells and cancer cells. However, compensatory expression of pro-survival BCL-2 family members in hESCs was not observed, suggesting a possible explanation for the elevated rates of apoptosis observed in proliferating hESC cultures, as well as a mechanism that could be exploited to limit hESC-derived neoplasms.