Inhibition of Apoptosis Overcomes Stage-Related Compatibility Barriers to Chimera Formation in Mouse Embryos.

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Public Summary:
Embryonic stem cells are naïve pluripotent stem cells while epiblast-derived stem cells (EpiSCs) are primed pluripotent stem cells. Primed meaning they are primed to differentiate into specific cell linages. EpiSCs will not generate chimeras because they will undergo apoptosis once injected into the blastocysts. We have shown that if we provide anti apoptotic gene BCL2 to EpiSCs and Sox17+ endoderm progenitors it will allow integration into blastocyst and contribute to chimeric embryos. We have developed a system that will overcome cellular incompatibility issues, which have previously restricted chimera formation to embryonic stem cells.

Scientific Abstract:
Cell types more advanced in development than embryonic stem cells, such as EpiSCs, fail to contribute to chimeras when injected into pre-implantation-stage blastocysts, apparently because the injected cells undergo apoptosis. Here we show that transient promotion of cell survival through expression of the anti-apoptotic gene BCL2 enables EpiSCs and Sox17+ endoderm progenitors to integrate into blastocysts and contribute to chimeric embryos. Upon injection into blastocyst, BCL2-expressing EpiSCs contributed to all bodily tissues in chimeric animals while Sox17+ endoderm progenitors specifically contributed in a region-specific fashion to endodermal tissues. In addition, BCL2 expression enabled rat EpiSCs to contribute to mouse embryonic chimeras, thereby forming interspecies chimeras that could survive to adulthood. Our system therefore provides a method to overcome cellular compatibility issues that typically restrict chimera formation. Application of this type of approach could broaden the use of embryonic chimeras, including region-specific chimeras, for basic developmental biology research and regenerative medicine.

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