An effective approach to prevent immune rejection of human ESC-derived allografts.

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Public Summary:

Scientific Abstract:
Human embryonic stem cells (hESCs) hold great promise for cell therapy as a source of diverse differentiated cell types. One key bottleneck to realizing such potential is allogenic immune rejection of hESC-derived cells by recipients. Here, we optimized humanized mice (Hu-mice) reconstituted with a functional human immune system that mounts a vigorous rejection of hESCs and their derivatives. We established knockin hESCs that constitutively express CTLA4-Ig and PD-L1 before and after differentiation, denoted CP hESCs. We then demonstrated that allogenic CP hESC-derived teratomas, fibroblasts, and cardiomyocytes are immune protected in Hu-mice, while cells derived from parental hESCs are effectively rejected. Expression of both CTLA4-Ig, which disrupts T cell costimulatory pathways, and PD-L1, which activates T cell inhibitory pathway, is required to confer immune protection, as neither was sufficient on their own. These findings are instrumental for developing a strategy to protect hESC-derived cells from allogenic immune responses without requiring systemic immune suppression.