Protective effect of human amniotic fluid stem cells in an immunodeficient mouse model of acute tubular necrosis.

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Public Summary:
BACKGROUND: Some human cancers demonstrate cellular hierarchies in which tumor-initiating cancer stem cells generate progeny cells with reduced tumorigenic potential. This cancer stem cell population is proposed to be a source of therapy-resistant and recurrent disease. Ewing sarcoma family tumors (ESFT) are highly aggressive cancers in which drug-resistant, relapsed disease remains a significant clinical problem. Recently, the cell surface protein CD133 was identified as a putative marker of tumor-initiating cells in ESFT. We evaluated ESFT tumors and cell lines to determine if high levels of CD133 are associated with drug resistance. METHODS: Expression of the CD133-encoding PROM1 gene was determined by RT-PCR in ESFT tumors and cell lines. CD133 protein expression was assessed by western blot, FACS and/or immunostaining. Cell lines were FACS-sorted into CD133+ and CD133- fractions and proliferation, colony formation in soft agar, and in vivo tumorigenicity compared. Chemosensitivity was measured using MTS (3-(4,5-dimethylthiazol-2-y1)-5-(3-carboxy-methoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium) assays. RESULTS: PROM1 expression was either absent or extremely low in most tumors. However, PROM1 was highly over-expressed in 4 of 48 cases. Two of the 4 patients with PROM1 over-expressing tumors rapidly succumbed to primary drug-resistant disease and two are long-term, event-free survivors. The expression of PROM1 in ESFT cell lines was similarly heterogeneous. The frequency of CD133+ cells ranged from 2-99% and, with one exception, no differences in the chemoresistance or tumorigenicity of CD133+ and CD133- cell fractions were detected. Importantly, however, the STA-ET-8.2 cell line was found to retain a cellular hierarchy in which relatively chemo-resistant, tumorigenic CD133+ cells gave rise to relatively chemo-sensitive, less tumorigenic, CD133- progeny. CONCLUSIONS: Up to 10% of ESFT express high levels of PROM1. In some tumors and cell lines the CD133+ fraction is relatively more drug-resistant, while in others there is no apparent difference between CD133+ and CD133- cells. These studies reveal heterogeneity in PROM1/CD133 expression in ESFT tumors and cell lines and confirm that high levels of PROM1 expression are, in at least some cases, associated with chemo-resistant disease. Further studies are required to elucidate the contribution of PROM1/CD133 expressing cells to therapeutic resistance in a large, prospective cohort of primary ESFT.

Scientific Abstract:
Acute Tubular Necrosis (ATN) causes severe damage to the kidney epithelial tubular cells and is often associated with severe renal dysfunction. Stem-cell based therapies may provide alternative approaches to treating of ATN. We have previously shown that clonal c-kit(pos) stem cells, derived from human amniotic fluid (hAFSC) can be induced to a renal fate in an ex-vivo system. Herein, we show for the first time the successful therapeutic application of hAFSC in a mouse model with glycerol-induced rhabdomyolysis and ATN. When injected into the damaged kidney, luciferase-labeled hAFSC can be tracked using bioluminescence. Moreover, we show that hAFSC provide a protective effect, ameliorating ATN in the acute injury phase as reflected by decreased creatinine and BUN blood levels and by a decrease in the number of damaged tubules and apoptosis therein, as well as by promoting proliferation of tubular epithelial cells. We show significant immunomodulatory effects of hAFSC, over the course of ATN. We therefore speculate that AFSC could represent a novel source of stem cells that may function to modulate the kidney immune milieu in renal failure caused by ATN.