Linking transgene expression of engineered mesenchymal stem cells and angiopoietin-1-induced differentiation to target cancer angiogenesis.

Abstract:

To specifically target tumor angiogenesis by linking transgene expression of engineered mesenchymal stem cells to angiopoietin-1-induced differentiation. Mesenchymal stem cells (MSCs) have been used to deliver therapeutic genes into solid tumors. These strategies rely on their homing mechanisms only to deliver the therapeutic agent. We engineered murine MSC to express reporter genes or therapeutic genes under the selective control of the Tie2 promoter/enhancer. This approach uses the differentiative potential of MSCs induced by the tumor microenvironment to drive therapeutic gene expression only in the context of angiogenesis. When injected into the peripheral circulation of mice with either, orthotopic pancreatic or spontaneous breast cancer, the engineered MSCs were actively recruited to growing tumor vasculature and induced the selective expression of either reporter red fluorescent protein or suicide genes [herpes simplex virus-thymidine kinase (TK) gene] when the adoptively transferred MSC developed endothelial-like characteristics. The TK gene product in combination with the prodrug ganciclovir (GCV) produces a potent toxin, which affects replicative cells. The homing of engineered MSC with selective induction of TK in concert...
with GCV resulted in a toxic tumor-specific environment. The efficacy of this approach was
demonstrated by significant reduction in primary tumor growth and prolongation of life in both tumor
models. This “Trojan Horse” combined stem cell/gene therapy represents a novel treatment strategy
for tailored therapy of solid tumors.

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