CF-1.9 CCL5 and Tie2 mediated tissue-specific suicide-gene expression of mesenchymal stem cells in tumor microenvironments inhibits growth of hepatocellular carcinoma

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Background: Engineered mesenchymal stem cells (MSCs) have been demonstrated to be potent therapeutic vehicles for the treatment of experimental pancreatic and breast cancer. The role of MSCs in the context of hepatocellular carcinoma (HCC) has been controversial. The general approach uses engineered MSCs to target different aspects of tumor biology, including angiogenesis or the fibroblast-like stromal compartment, through the use of tissue specific expression of therapeutic transgenes. The aim of the present study was to 1) evaluate the effect of exogenously added MSCs on the growth of hepatocellular carcinoma (HCC), and 2) the establishment of an MSC based suicide gene therapy for experimental HCC.

Methods: MSCs were isolated from bone marrow of C57/Bl6 p53⁻/⁻ mice and were injected into mice with HCC xenografts that had formed after intrahepatic injections of Huh7 hepatocellular carcinoma cells. The influence of MSCs on tumor proliferation and angiogenesis was evaluated. The cells were then stably transfected with Red Fluorescent Protein (RFP) or Herpes simplex virus thymidine kinase (HSV-Tk) gene under control of the Tie2 promoter/enhancer or the CCL5 promoter. MSCs were injected intravenously into mice with orthotopically growing xenografts of hepatocellular carcinoma and treated with Ganciclovir (GCV). All animal experiments were conducted after approval by the animal rights commission of the State of Bavaria.

Results: Tumor specific recruitment, enhanced tumor growth, and increased microvessel density after non-therapeutic MSC injections was revealed after scarification of the animals. Following homing to the hepatic xenografts engineered MSCs demonstrated activation of the Tie2 or CCL5 promoter as shown by RFP expression. Application of the suicide gene carrying HSV-TK transfected MSCs in combination with GCV significantly reduced tumor growth by 41% as compared to the control group and by 63.3% as compared to non-therapeutic MSC injections.

Conclusion: Intravenously applied MSCs are recruited to growing HCC xenografts with concomitant activation of the CCL5 or Tie2 promoters within the MSCs. Stem cell mediated delivery of suicide genes into the tumor followed by prodrug administration was effective for treatment of experimental HCC and thus may help fill the existing gap in bridging therapies for patients suffering from advanced HCCs before receiving a liver transplant.