OMICS Group Conferences
Accelerating Scientific Discovery
3rd World Congress on Virology
November 20-22, 2013 DoubleTree by Hilton Baltimore-BWI Airport, USA

Mesenchymal stem cells as carriers and amplifiers in CRAd delivery to tumors

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Abstract

BACKGROUND:

Mesenchymal stem cells (MSCs) have been considered to be the attractive vehicles for delivering therapeutic agents toward various tumor diseases. This study was to explore the distribution pattern, kinetic delivery of adenovirus, and therapeutic efficacy of the MSC loading of E1A mutant conditionally replicative adenovirus Adv-Stat3(-) which selectively replicated and expressed high levels of anti-sense Stat3 complementary DNA in breast cancer and melanoma cells.

METHODS:

We assessed the release ability of conditionally replicative adenovirus (CRAd) from MSC using crystal violet staining, TCID(50) assay, and quantitative PCR. In vitro killing competence of MSCs carrying Adv-Stat3(-) toward breast cancer and melanoma was performed using co-culture system of transwell plates. We examined tumor tropism of MSC by Prussian blue staining and immunofluorescence. In vivo killing competence of MSCs carrying Adv-Stat3(-) toward breast tumor was analyzed by comparison of tumor volumes and survival periods.

RESULTS:

Adv-Stat3(-) amplified in MSCs and were released 4 days after infection. MSCs carrying Adv-Stat3(-) caused viral amplification, depletion of Stat3 and its downstream proteins, and led to significant apoptosis in breast cancer and melanoma cell lines. In vivo experiments confirmed the preferential localization of MSCs in the tumor periphery 24 hours after tail vein injection, and this localization was mainly detected in the tumor parenchyma after 72 hours. Intravenous injection of MSCs carrying Adv-Stat3(-) suppressed the Stat3 pathway, down-regulated Ki67 expression, and recruited CD11b-positive cells in the local tumor, inhibiting tumor growth and increasing the survival of tumor-bearing mice.

CONCLUSIONS:

These results indicate that MSCs migrate to the tumor site in a time-dependent manner and could be an effective platform for the targeted delivery of CRAd and the amplification of tumor killing effects.