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Delivering cytokine gene therapy to prostate tumors using adipose-derived mesenchymal stem cells

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It is critical to develop new therapeutic approaches for prostate cancer, since there is no effective treatment for patients in the advanced stages of this disease. And although many gene therapy approaches have been evaluated to date, clinical responses unfortunately remain poor. We have examined the potential of developing more effective cell-based gene therapies for preventing prostate cancer progression, using adipose-derived mesenchymal stem cells (ASC) as vehicles. ASC have gained interest as promising tools for delivering cancer therapy. Adipose tissue can be obtained readily in amounts sufficient for ASC isolation, which can be expanded rapidly, allowing its use at low passage numbers, and can be transduced by viral and nonviral means. And since current techniques allow isolation of ASC from an individual's own adipose tissue, this could help prevent immune reaction, suggesting that ASC could be far more efficient as a gene delivery vehicle than viral vectors currently in clinical trials. The present study reports our observations using this novel gene therapy modality. In this study we have examined the potential of new antiangiogenesis and proapoptotic therapies delivered by ASC and evaluated their ability to reduce prostate tumor growth rate in vitro and in vivo. We expressed in ASC several antitumor cytokine therapies, and all were found to be highly effective in preventing tumor progression in vivo using prostate and breast cancer xenograft models. Overall, ASC-delivered PEDF prevented HUVEC tube formation in vitro and induced strong apoptosis of cocultured cancer cells, suggesting a potential bystander effect that might be useful for therapeutic applications. Similar antitumor findings were observed when Mda7 or IFNb were delivered by ASC, with induction of strong cell cycle arrest, and viability reduction by an increase in the apoptosis of cocultured tumor cells as assessed by Caspase 3/7 detection. The transgene expression was overall non-toxic and did not appear to interfere with the normal differentiation potential of ASC (osteogenesis or adipogenesis). We also observed that ASC retained their innate ability to migrate towards tumor cells in co-culture and this ability could be blocked by inhibition of CXCR4 signaling. ASC were found to be non-tumorigenic *in vitro* using a soft agar assay, as well as *in vivo*, utilizing two prostate cancer xenograft models. PEDF was the most promising therapeutic cytokine delivered, and completely prevented prostate tumor establishment *in vivo* of both the TC2Ras and PC3 highly aggressive prostate cancer models. In conclusion, ASC expressing antitumor cytokines could effectively reduce prostate tumor growth *in vivo*, suggesting ASC-cytokine therapies might have translational applications. Future studies will aim to target cytokines to tumor tissues by virtue of peptide targeting moieties to enhance cytokine therapy effects

Biography

Dr. Figueiredo has completed her Ph.D from the University of Wisconsin-Madison in 2002 and postdoctoral studies from the University of California at Los Angeles. She is an Assistant Professor at the University of Texas Medical Branch in Galveston, Texas in the Department of Pharmacology & Toxicology. She serves as Editorial Board member for Biological Procedures Online, Frontiers of Bioscience, and Journal of Cancer Research and Therapy

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