ABSTRACT

Intratumoral gene delivery is a novel immunotherapy showing promise in cutaneous cancers such as melanoma. However, the broad application of this technology is limited by delivery efficiency and tumor accessibility. Efficient gene delivery requires intimate association of DNA and cells and a coincident electric field. Due to the low diffusion of plasmid DNA combined with standard injection provided by a standard syringe, conventional electroporation transfer yields a small volume of transfected tissue. Our novel use of a helical delivery needle provides the dual benefit of increased DNA-tissue interface and anchoring of the device necessary for endoscopic use. This device has yielded efficient and repeatable delivery of cytokine expressing plasmid DNA and reporter genes in several tumor models. Anchoring associated with the action of helical needle attachment ensures co-localization of the electric field with the injected tissue volume. The small form factor of this device makes it compatible with standard medical devices, including trocars, endoscopes and other catheter based devices, enabling intratumoral gene immunotherapy of previously inaccessible cancers, including breast cancer, lung cancer, and hepatocellular carcinoma.

INTRODUCTION

Immunotherapeutic intratumoral gene delivery of cytokines is an effective anti-tumor therapy for cancer, including melanoma, Merkel cell carcinoma, and head and neck squamous cell carcinoma. Plasmid containing human IL-12 delivered to cutaneous tumors promotes immune recognition and attack of both treated tumor and distant metastases. This technology requires direct access to tumors, limiting treatment to cutaneous disease. To access visceral tumors, alternative intratumoral gene delivery approaches are required. Conventional devices have been used for electroporation mediated gene delivery to internal organs, however these devices require surgical procedures, resulting in longer recovery times and an increased risk of complications. Alternately, endoscopic electroporation techniques have been developed, but not in the context of gene delivery.

ADVANTAGES

HELICAL NEEDLE BENEFITS:

- Circuitous injection channel increases injection retention and DNA/tissue interaction within the treatment area, improving gene delivery efficiency.

INTEGRATED DEVICE BENEFITS:

- Integrated injection and electrodes increase procedure reliability and reduce user error.

Small form factor allows deep tissue access via trocar or other medical devices.

METHODS

SYRINGE INJECTION

- Intratumoral injection provides the dual benefit of increased DNA-tissue interface and anchoring of the device necessary for endoscopic use. This device has yielded efficient and repeatable delivery of cytokine expressing plasmid DNA and reporter genes in several tumor models. Anchoring associated with the action of helical needle attachment ensures co-localization of the electric field with the injected tissue volume. The small form factor of this device makes it compatible with standard medical devices, including trocars, endoscopes and other catheter based devices, enabling intratumoral gene immunotherapy of previously inaccessible cancers, including breast cancer, lung cancer, and hepatocellular carcinoma.

RESULTS

The helical integrated applicator is a novel device which allows the immunotherapeutic gene delivery of tumors up to 10cm in tissue through minimally invasive means, such as a trocar or endoscope. The helical injection needle provides the dual benefits of increased DNA distribution for more effective gene delivery and tumor anchoring for reliable treatment of compliant tumors. These characteristics yield enhanced efficacy of IL-12 plasmid electroporation in an aggressive B16F10 melanoma model, with improved tumor growth control and survival with a single treatment. This device will allow the application of intratumoral IL-12 gene immunotherapy to a broad range of deep tissue cancers.

CONCLUSIONS

The helical integrated applicator is a novel device which allows the immunotherapeutic gene delivery of tumors up to 10cm in tissue through minimally invasive means, such as a trocar or endoscope. The helical injection needle provides the dual benefits of increased DNA distribution for more effective gene delivery and tumor anchoring for reliable treatment of compliant tumors. These characteristics yield enhanced efficacy of IL-12 plasmid electroporation in an aggressive B16F10 melanoma model, with improved tumor growth control and survival with a single treatment. This device will allow the application of intratumoral IL-12 gene immunotherapy to a broad range of deep tissue cancers.