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Explicit targeting of transformed cells by VSV in ovarian epithelial tumor-bearing Wv mouse models

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ABSTRACT

Objective. Current treatment options for epithelial ovarian cancer are limited and therapeutic development for recurrent and drug-resistant ovarian cancer is an urgent agenda. We investigated the potential use of genetically engineered Vesicular Stomatitis Virus (VSV) to treat ovarian cancer patients who fail to respond to available therapies. Specifically, we examined the toxicity to hosts and specificity of targeting ovarian tumors using a Wv ovarian tumor model.

Methods. We first tested recombinant VSV for oncolytic activity in a panel of human ovarian epithelial cancer, immortalized, and primary ovarian surface epithelial cells in culture. Then, we tested VSV oncolytic therapy using the immune competent Wv mice that develop tubular adenomas, benign tumor lesions derived from ovarian surface epithelial cells.

Results. The expression of GFP encoded by the recombinant VSV genome was detected in about 5% of primary ovarian surface epithelial cells (3 lines) up to 30 days without significantly altering the growth pattern of the cells, suggesting the lack of toxicity to the normal ovarian surface epithelial cells. However, VSV-GFP was detected in the majority (around 90%) of cells that are either "immortalized" by SV40 antigen expression or cancer lines. Some variation in killing time courses was observed, but all the transformed cell lines were killed within 3 days.

We found that regardless of the inoculation route (intra bursal, IP, or IV), VSV specifically infected and replicated in the in situ ovarian tumors in the Wv mice without significant activity in any other organs and tissues, and showed no detectable toxicity. The epithelial tumor lesions were greatly reduced in VSV-targeted ovarian tumors in the Wv mice.

Conclusions. VSV oncolytic activity depends on a cell autonomous property distinguishing primary and transformed cells. The efficient oncolytic activity of VSV for the "immortalized" non-tumorigenic ovarian surface epithelial cells suggests that the selective specificity extends from pre-neoplastic to overt cancer cells. The results demonstrated the explicit targeting of ovarian epithelial tumors by VSV in immune competent, ovarian tumor-bearing mouse models, and further support the utility of VSV as an effective and safe anti-cancer agent.

Introduction

Epithelial ovarian cancer is a disease with poor prognosis, few early diagnostic markers, and limited treatment options [1–3]. Chemotherapeutic agents based on platinum derivatives have been widely used to treat a broad range of cancers including epithelial ovarian cancer with some success. Currently, a platinum- and taxane-based combination regimen remains standard frontline chemotherapy for ovarian cancer [1–4]. Unfortunately, intrinsic and acquired resistance to cisplatin/taxane has greatly limited the efficacy of the therapy [4,5]. New agents, such as Gemcitabine, Doxorubicin, and Topotecan that convey anti-cancer activities via different mechanisms, are being evaluated in clinical trials, and some have been adopted for clinical application [4,5]. Nevertheless, current treatment options are still very limited, and development of resistance to the cytotoxic chemotherapy remains a key problem to be overcome, and most women ultimately die of the disease. Development of additional chemotherapeutic regimens, biological therapeutic agents, and other unique approaches for treatment of ovarian cancer is a high priority.

An idea is to use particular types of viruses as agents to selectively kill cancer cells [6]. These viruses, referred to as oncolytic viruses, are capable of replicating in cancer but not in normal cells [6]. The

Abbreviations: GFP, green fluorescence protein; HOSE cells, human ovarian surface epithelial cells; HIO cells, Human "immortalized" ovarian surface epithelial cells; IFN, interferon; IB, intra-bursal; IP, intra-peritoneal; IV, intra-venous; pfu, plaque forming unit; PI, propidium iodide; VSV, vesicular stomatitis virus; Wv mice, white spotting variant mutant mice.

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