Intralesional Rose Bengal in Melanoma Elicits Tumor Immunity via High Mobility Group Box 1

H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Abstract

Intralesional (IL) therapy is under investigation to treat dermal and subcutaneous metastatic cancer. Rose Bengal (RB) is a staining agent that was originally used by ophthalmologists and in Iver function studies. Previously, IL injection of RB induced regression of injected and un.injected tumors in murine models. However, the relevant mechanism is yet unknown. In this study, we used an OVA-expressing B16 melanoma murine model and found that IL RB treatment led to increased tumor-specific T cells with memory characteristics. IL RB therapy also increased antigen-specific T cell proliferation and enhanced tumor regression. In addition, IL RB facilitated dendritic cells (DCs) infiltrating lymph nodes draining from tumor. Incubation of melanoma cells with RB led to necrosis and the release of High Mobility Group Box 1 (HMGB1), which activated DCs. The blockade of HMGB1 significantly reduced the antigen-presenting ability of DCs. To determine whether this mechanism was relevant in patients treated with IL RB, we performed a pilot clinical study in melanoma patients (NCT01760499). IL RB led to tumor regression in both RB-injected and un-injected lesions, associated with an increase in circulating T cells. Increased tumor-specific response was found from those circulating T cells of 5 out of 7 treated patients after IL RB treatment. HMGB1 levels in patient sera were also elevated. Together, these results reveal a clinically relevant immunoadjuvant pathway triggered by tumor cell death secondary to ablation with RB.

Background

Rose Bengal (PV-10) was introduced in the 1980s and has been used for diagnostic and therapeutic purposes. It is a direct cytoplasmic stain for various cell types and is known to be rapidly excreted via the bile. Intralesional (IL) therapy is under investigation to treat dermal and subcutaneous metastatic cancer. Rose Bengal (RB) is a staining agent that was originally used by ophthalmologists and in liver function studies. Previously, IL injection of RB induced regression of injected and un-injected tumors in murine models. However, the relevant mechanism is yet unknown. In this study, we used an OVA-expressing B16 melanoma murine model and found that IL RB treatment led to increased tumor-specific T cells with memory characteristics. IL RB therapy also increased antigen-specific T cell proliferation and enhanced tumor regression. In addition, IL RB facilitated dendritic cells (DCs) infiltrating lymph nodes draining from tumor. Incubation of melanoma cells with RB led to necrosis and the release of High Mobility Group Box 1 (HMGB1), which activated DCs. The blockade of HMGB1 significantly reduced the antigen-presenting ability of DCs. To determine whether this mechanism was relevant in patients treated with IL RB, we performed a pilot clinical study in melanoma patients (NCT01760499). IL RB led to tumor regression in both RB-injected and un-injected lesions, associated with an increase in circulating T cells. Increased tumor-specific response was found from those circulating T cells of 5 out of 7 treated patients after IL RB treatment. HMGB1 levels in patient sera were also elevated. Together, these results reveal a clinically relevant immunoadjuvant pathway triggered by tumor cell death secondary to ablation with RB.

IL PV-10 elicits a tumor-specific immunity

IL PV-10 leads to DC inflation and maturation

Increased serum HMGB1 levels in patients after IL PV-10 therapy

IL PV-10 facilitates the proliferation of tumor-specific CD8+ T cells

IL PV-10 leads to the release of HMGB1 from necrotic melanoma cells

Conclusion

IL PV-10 led to the necrosis of melanoma cells and release of HMGB1 to activate DCs and elicit a systemic anti-tumor immune response.

Hypothetic Model:

Acknowledgement: This study was supported by the Cancer Center Support Grant P30 CA076292 from the National Cancer Institute and NCI 5K23CA178083-02 (AAS). PV-10 was provided by Provectus Biopharmaceuticals Inc.