Targeting HO-1 by SnPP Induces Necrosis in KSHV-Infected Cells and Suppresses Tumorigenesis in vivo

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INTRODUCTION

Kaposi sarcoma-associated herpesvirus (KSHV), also known as Human Herpesvirus-8 (HHV-8), causes several types of cancers in immunocompromised patients, including Kaposi sarcoma (KS). KS affects endothelial cells lining the blood and lymphatic vessels resulting in purple, red, or brown clusters of skin lesions. There are four subtypes of KS: European (classic) KS, African (endemic) KS, AIDS-related (epidemic) KS, and transplant-related (iatrogenic) KS. The introduction of antiretroviral therapy has dramatically decreased the incidence of KS overall, but AIDS-KS still represents the most common AIDS-associated malignancy.

An inducible enzyme, heme oxygenase-1 (HO-1), is highly expressed in AIDS-KS lesions and its enzymatic activity is upregulated within KSHV-infected cells. HO-1 metabolizes heme to generate free iron, carbon monoxide, and biliverdin which in turn facilitates the recruitment of chemokines and growth factors, particularly vascular endothelial growth factor (VEGF). The accumulation of VEGF-A increases angiogenesis, a crucial process required for KSHV-associated tumorigenesis. Tin protoporphyrin IX (SnPP), a potent HO-1 competitive inhibitor, is effective in downregulating HO-1 activity and suppressing VEGF-A expression in some cancer cells.

OBJECTIVES

- In this study, we sought to determine whether targeting HO-1 by SnPP induces KSHV-infected cell death and through which underlying mechanisms.
- We are also investigating whether targeting HO-1 can be developed as a novel therapeutic strategy to improve KS treatment.

METHODS

- Immunoblot and immunofluorescence were used to detect gene expression in some cancer cells.
- Flow cytometry was used to quantify programmed cell death.
- ELISA was used to detect VEGF concentration in cultured cell supernatant.
- Flow cytometry was used to quantify programmed cell death.

CONCLUSION

- HO-1 is highly expressed in KSHV-infected cells and AIDS-KS tumor tissues.
- SnPP induced KSHV-infected cell death occurs through DNA damage and necrosis.
- Targeting HO-1 by RNAi or SnPP reduces VEGF production from KSHV-infected cells.
- SnPP treatment successfully suppresses KSHV-infected cell growth and tumorigenesis in a KS-like nude mouse model.

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