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Perspective

Exploring Novel Therapies for Kaposi Sarcoma through Preclinical Models: Immune System Interactions

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DESCRIPTION

Kaposi Sarcoma (KS) is a malignancy linked to infection with Kaposi Sarcoma-Associated Herpesvirus (KSHV), also known as Human Herpesvirus-8 (HHV-8). It is particularly prevalent among individuals with Acquired Immunodeficiency Syndrome (AIDS), where the immunodeficient state induced by Human Immunodeficiency Virus (HIV) facilitates the development of KS. Developing effective treatments for KS requires robust preclinical models to study the disease mechanisms and evaluate potential therapies.

In vitro models

KS research extensively utilizes several cell lines derived from KS lesions and KSHV-infected cells. These cell lines help study the molecular and cellular mechanisms of KS and test the efficacy of antiviral and anticancer drugs. Commonly used cell lines includes BC-3 cells and SLK cells.

BC-3 cells are derived from a Primary Effusion Lymphoma (PEL) associated with KSHV, these cells are latently infected with the virus and are used to study KSHV biology and latency where as SLK cells are derived from a KS lesion, these cells can be used to study KS-specific pathways and test therapeutic agents' effectiveness.

Primary cell cultures

Primary cultures of endothelial cells infected with KSHV provide a more physiologically relevant model. These cultures can be derived from Human Umbilical Vein Endothelial Cells (HUVECs) or other endothelial sources. Infection with KSHV induces spindle cell transformation, copying the KS phenotype observed in patients.

Three-Dimensional (3D) culture systems

3D culture systems, including spheroids and organoids, provide a more accurate representation of the tumor microenvironment compared to traditional 2D cultures. These systems allow for the study of cell-cell and cell-matrix interactions potential for KS development and progression. KSHV-infected endothelial cells in 3D cultures form structures resembling KS lesions, facilitating the testing of therapeutic agents in a more relevant context.

In vivo models

Xenograft models involve the transplantation of human KS cells or tissues into immunodeficient mice. These models are widely used to study KS pathogenesis and evaluate potential therapies in a living organism. Commonly used xenograft models includes subcutaneous xenografts and intraperitoneal xenografts. Subcutaneous xenografts in which human KS cells are injected subcutaneously into mice, where they form tumors that can be monitored for growth and response to treatment where as in intraperitoneal xenografts, human KS cells are injected into the peritoneal cavity, leading to the development of tumors on the peritoneal surfaces. This model is particularly useful for studying therapies targeting metastatic KS.

Humanized mouse models

Humanized mice are immunodeficient mice engrafted with human hematopoietic stem cells or Peripheral Blood Mononuclear Cells (PBMCs). These models provide a more accurate representation of the human immune system, making them valuable for studying the interaction between KSHV, the immune system, and potential therapies. Humanized mice infected with KSHV develop KS-like lesions, allowing for the testing of immunotherapeutic approaches and antiviral agents.

Genetically Engineered Mouse Models (GEMMs)

GEMMs have been developed to study the role of specific genes in KS development and progression. These models involve the introduction of KSHV genes or other relevant oncogenes into the mouse genome. GEMMs provide insights into the molecular

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pathways involved in KS and enable the testing of targeted therapies.

Evaluation of therapeutic strategies

Preclinical models are essential for evaluating the efficacy and safety of potential therapies for KS in patients with AIDS.

Antiviral agents: Antiviral drugs targeting KSHV replication and latency are potential for controlling KS in patients with AIDS. Preclinical models have been used to test the efficacy of agents such as ganciclovir, cidofovir, and foscarnet. These studies have shown that antiviral drugs can reduce KSHV load and inhibit KS progression.

Chemotherapy: Chemotherapeutic agents, including liposomal anthracyclines (e.g., liposomal doxorubicin) and paclitaxel, have been evaluated in preclinical models. These studies assess the drugs ability to induce tumor regression and improve survival in KS-bearing animals. Combination therapies with antivirals and chemotherapy are also being tested to enhance therapeutic outcomes.

Immunotherapy: Immunotherapeutic approaches aim to boost the immune system's ability to fight KSHV and KS. Preclinical models, particularly humanized mice, are used to evaluate the efficacy of immune checkpoint inhibitors (e.g., anti-PD-1 and anti-CTLA-4 antibodies) and adoptive cell therapies (e.g., CAR T cells targeting KSHV-infected cells).

Epigenetic modulators: Epigenetic modifications play a significant role in KSHV latency and KS development. Preclinical models are used to evaluate the efficacy of epigenetic modulators, such as Histone Deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors. These agents can reactivate latent KSHV, making the virus susceptible to antiviral therapy and inducing tumor cell death.

Preclinical models are indispensable for advancing our understanding of Kaposi sarcoma and developing effective treatments for patients with AIDS. From *in vitro* systems to sophisticated in vivo models, these tools provide critical insights into the disease's molecular mechanisms and facilitate the evaluation of novel therapeutic strategies.