ISSN: 2157-2518
Journal of Carcinogenesis & Mutagenesis

OPEN ACCESS Freely available online

Short Communication

Transformative Preclinical Research in Rhabdomyosarcoma: Emerging Experimental Models

Eric Deutsch*

Department of Cancer, University of Helsinki, Helsinki, Finland

DESCRIPTION

Rhabdomyosarcoma (RMS) is a malignant tumor originating from skeletal muscle progenitors, predominantly affecting children and adolescents. The complexity of its pathogenesis and the challenges in treatment have driven extensive research to develop effective experimental models and preclinical strategies. Recent advancements in these areas have provided deeper insights into the biology of RMS, providing potential paths for therapeutic development [1].

Understanding the biology of rhabdomyosarcoma

RMS is categorized into two main histological subtypes: Embryonal (ERMS) and Alveolar (ARMS). ERMS is more common and typically associated with younger children, while ARMS, characterized by specific chromosomal translocations like *PAX3-FOXO1* or *PAX7-FOXO1*, is more aggressive and seen in older children and adolescents [2]. The genetic and molecular landscape of RMS is complex, involving numerous pathways related to cell growth, differentiation, and survival.

Advances in experimental models

Recent advances in experimental models for rhabdomyosarcoma research have revolutionized our understanding and treatment of this aggressive cancer. These models not only replicate the complex genetic alterations observed in human rhabdomyosarcoma but also allow for the exploration of tumor microenvironment interactions and drug responses in a controlled setting [3].

Genetically Engineered Mouse Models (GEMMs): GEMMs have been instrumental in coping the genetic alterations found in human RMS. Recent developments include conditional knockout models that allow for tissue-specific and temporally controlled expression of oncogenes and tumor suppressor genes. For instance, mice engineered to express *PAX3-FOXO1* specifically in muscle progenitors have provided potential insights into the oncogenic potential and molecular pathways activated in ARMS. These models have elucidated the role of key signaling pathways such as Hedgehog, Notch, and PI3K/AKT/mTOR in RMS pathogenesis.

Patient-Derived Xenografts (PDXs): PDX models involve implanting human RMS tissues into immunosuppressed mice, preserving the tumor's histological and genetic characteristics. These models are invaluable for studying tumor biology and drug response in a more clinically relevant context. Recent studies utilizing RMS PDXs have identified potential therapeutic targets and biomarkers for treatment response, enabling the testing of novel compounds and combination therapies in a preclinical setting [4].

Organoids and 3D culture systems: Advances in 3D culture systems and organoids have provided new platforms for studying RMS. These models better replicate the tumor microenvironment compared to traditional 2D cultures. RMS organoids derived from patient tumors have shown to maintain the genetic heterogeneity and drug response profiles of the original tumors. These models are particularly useful for high-throughput drug screening and studying tumor-stromal interactions.

Preclinical data and therapeutic insights

Preclinical data and therapeutic insights in rhabdomyosarcoma have significantly advanced our understanding of this challenging malignancy [5].

Targeted therapies: Preclinical studies have focused on targeting specific molecular abnormalities in RMS. Agents targeting the *PAX3-FOXO1* fusion protein, a driver in ARMS, have shown potential. For instance, small molecules and peptides designed to disrupt the *PAX3-FOXO1* interaction with its DNA binding partners have demonstrated antitumor activity in preclinical models. Additionally, inhibitors of downstream signaling pathways, such as the PI3K/AKT/mTOR pathway, have shown

Correspondence to: Eric Deutsch, Department of Cancer, University of Helsinki, Helsinki, Finland, E-mail: Deutsch@edu.fi

Received: 03-Jun-2024, Manuscript No. JCM-24-25962; **Editor assigned:** 05-Jun-2024, JCM-24-25962 (PQ); **Reviewed:** 19-Jun-2024, QC No. JCM-24-25962; **Revised:** 26-Jun-2024, Manuscript No. JCM-24-25962 (R); **Published:** 03-Jul-2024, DOI:10.35248/2157-2518.24.S44.005

Citation: Deutsch E (2024) Transformative Preclinical Research in Rhabdomyosarcoma: Emerging Experimental Models. J Carcinog Mutagen. S44.005.

efficacy in reducing tumor growth and enhancing the effects of conventional chemotherapy [6].

Immunotherapy: The potential of immunotherapy in RMS is being actively explored. Preclinical studies using immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, have shown limited single-agent activity but suggest potential when combined with other treatments. Adoptive cell therapies, including engineered T-cells targeting RMS-specific antigens, have demonstrated potent antitumor effects in mouse models. Additionally, oncolytic viruses engineered to selectively infect and kill RMS cells are under investigation, showing promising preclinical results [7].

Epigenetic modulators: Epigenetic alterations play a significant role in RMS pathogenesis. Preclinical studies have identified several epigenetic modulators, such as Histone Deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors, which can induce differentiation and apoptosis in RMS cells. Combination therapies using epigenetic drugs with conventional chemotherapy or targeted agents are being evaluated for their synergistic effects [8].

Metabolic pathways: Altered metabolism is a symbol of cancer, and RMS is no exception. Preclinical research has identified unique metabolic dependencies in RMS cells, such as reliance on glutamine and alterations in glycolytic pathways. Targeting these metabolic pathways with specific inhibitors has shown to impair RMS cell growth and sensitize them to other treatments.

Challenges and future directions

Despite these advancements, several challenges remain in translating preclinical findings into clinical success. One major problem is the heterogeneity of RMS, both within and between tumors, which complicates the identification of universally effective treatments. Additionally, the rarity of RMS poses challenges in conducting large-scale clinical trials [9].

Future research should focus on developing more sophisticated models that better copy the human tumor microenvironment, integrating multi-omics approaches to understand tumor heterogeneity, and identifying predictive biomarkers for treatment response. Collaborative efforts between researchers, clinicians, and industry are essential to accelerate the translation of preclinical discoveries into effective therapies for RMS.

Recent advances in experimental models and preclinical research have significantly enhanced our understanding of rhabdomyosarcoma. The development of GEMMs, PDXs, organoids, and the exploration of targeted therapies, immunotherapy, epigenetic modulators, and metabolic inhibitors provide potential therapeutic ways. Continued research and collaborative efforts are potential to overcome existing challenges and improve outcomes for patients with RMS [10].

REFERENCES

1. Meister MT, Groot Koerkamp MJ, de Souza T, Breunis WB, Frazer-Mendelewska E, Brok M, et al. Mesenchymal tumor organoid models recapitulate rhabdomyosarcoma subtypes. EMBO Mol. Med. 2022;14(10):e16001.
2. Tian M, Wei JS, Shivaprasad N, Highfill SL, Gryder BE, Milewski D, et al. Preclinical development of a chimeric antigen receptor T cell therapy targeting *FGFR4* in rhabdomyosarcoma. Cell Rep Med. 2023;4(10).
3. Jardim-Perassi BV, Mu W, Huang S, Tomaszewski MR, Poleszczuk J, Abdalah MA, et al. Deep-learning and MR images to target hypoxic habitats with evofosfamide in preclinical models of sarcoma. Theranostics. 2021;11(11):5313.
4. Singh S, Abu-Zaid A, Jin H, Fang J, Wu Q, Wang T, et al. Targeting KDM4 for treating *PAX3-FOXO1*–driven alveolar rhabdomyosarcoma. Sci Transl Med. 2022;14(653):eabq2096.
5. McKay-Corkum GB, Collins VJ, Yeung C, Ito T, Issaq SH, Holland D, et al. Inhibition of NAD+-dependent metabolic processes induces cellular necrosis and tumor regression in rhabdomyosarcoma models. Clin. Cancer Res. 2023;29(21): 4479-4491.
6. Siebert J, Schneider M, Reuter-Schmitt D, Würtemberger J, Neubüser A, Driever W, et al. Rhabdomyosarcoma xenotransplants in zebrafish embryos. Pediatr Blood Cancer. 2023;70(1):e30053.
7. Rasic P, Jeremic M, Jeremic R, Dusanovic Pjevic M, Rasic M, Djuricic SM, et al. Targeting B7-H3 - A novel strategy for the design of anticancer agents for extracranial pediatric solid tumors treatment. Molecules. 2023;28(8):3356.
8. Yan C, Yang Q, Zhang S, Millar DG, Alpert EJ, Do D, et al. Single-cell imaging of T cell immunotherapy responses in vivo. J. Exp. Med. 2021;218(10):e20210314.
9. Hebron KE, Wan X, Roth JS, Liewehr DJ, Sealover NE, Frye WJ, et al. The combination of trametinib and ganitumab is effective in RAS-mutated PAX-fusion negative rhabdomyosarcoma models. Clin Cancer Res. 2023;29(2):472-487.
10. Savary C, Luciana L, Huchedé P, Tourbez A, Coquet C, Broustal M, et al. Fusion-negative rhabdomyosarcoma 3D organoids to predict effective drug combinations: A proof-of-concept on cell death inducers. Cell Rep Med. 2023 Dec 19;4(12).