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Review Article

Latest developments in the pathobiology of Ewing sarcoma

Irina Karlina [a], Brett A. Schroeder [b], Kirill Kirgizov [c], Olga Romantsova [c], Andrey L. Istranov [d], Andrey Nedorubov [e], Peter Timashev [f], Ilya Ulasov [a,*]

[a] Group of Experimental Biotherapy and Diagnostics, Institute for Regenerative Medicine, World-Class Research Centre "Digital Biodesign and Personalized Healthcare", I.M. Sechenov First Moscow State Medical University, Moscow 119991, Russia
[b] National Cancer Institute, National Institutes of Health, Bethesda, MD 20814, USA
[c] Research Institute of Pediatric Oncology and Hematology at N.N. Blokhin National Medical Research Center of Oncology, Ministry of Health of Russia Moscow, 115478, Russia
[d] Department of Oncology, radiation therapy and plastic surgery, I.M. Sechenov First Moscow State Medical University, Moscow, 119991, Russia
[e] Center for Preclinical Research, Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University, 119991 Moscow, Russia
[f] World-Class Research Centre "Digital Biodesign and Personalized Healthcare", Sechenov First Moscow State Medical University, Moscow 119991, Russia

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ABSTRACT

Ewing's sarcoma (ES) is an aggressive malignant tumor commonly affecting adolescents. The standard of care includes surgical treatment and systemic therapies, although ES patients often develop drug resistance, leading to disease progression. Tumorigenesis in Ewing's sarcoma has unique characteristics that allow for the development of targeted therapeutics. New data on the role of oncogenic drivers in ES tumorigenesis, particularly in relation to treatment-induced stress, offers new therapeutic opportunities. This review summarizes the latest information on the clinically relevant oncogenes found in Ewing's sarcoma, their biological roles, and candidate targets for improving ES patient outcomes.

1. Introduction

Ewing's sarcoma (ES) is the second most common malignancy of the skeletal system in children, and accounts for approximately 1% of all childhood cancers, with the highest incidence in adolescents and young adults. ES is a genetic translocation-driven malignancy [1,2]. Translocations are hallmarks of various cancers, including other sarcoma subtypes [3], acute myeloid leukaemia [4], chronic lymphocytic leukaemia [5], and cystic adenocarcinoma [6].

In recent years, treatment outcomes for ES patients have improved in part owing to a combined multidisciplinary approach [7]. Although cytotoxic chemotherapy remains the cornerstone of first- and second-line therapies, relapse due to refractory disease is difficult to treat. First-line therapy in North America typically includes a combination of vincristine, doxorubicin, and cyclophosphamide (VDC) alternating with ifosfamide and etoposide (IE) (See Table 1). This regimen is particularly effective, but difficult to tolerate, especially on a compressed schedule [8]. European countries often employ VIDE as first-line therapy [9], while in Scandinavia, VID is preferred [10].

Despite these treatment combinations, patient prognosis is usually poor, particularly for those with advanced disease. The current 5-year overall survival (OS) for patients with metastatic disease is less than 30%, and those with recurrent disease exhibit a dismal prognosis. Given these factors, a better understanding of the molecular mechanisms that contribute to tumor resistance could help explain the ES relapse and, consequently, the poor OS. In this review, we explore recent discoveries in ES pathobiology that could offer novel therapeutic strategies for ES.

2. Oncogenesis of sarcomas

The oncogenesis of Ewing's sarcoma is predicated upon the translocation t(11;22)(q24;q12) of the N-terminus of the *EWSR1* gene to the C-terminus of the *FLI1* gene [11–13]. The resultant EWS/FLI1 fusion protein has been shown to bind RNA helicase A and alter the activity of enhancer elements essential for tumor growth [14], invasion, and oncogenesis [15,16]. Several studies have shown that the direct interaction of this fusion protein with gene promoters represents a unique regulatory mechanism. Cells with this oncogenic chimera are usually enriched with proteins such as *MMP-2*, *MT1-MMP*, and *MMP-9*, which are critical for tumour dissemination and metastasis [2,17]. *EWS/FLI1*

* Corresponding author at: Group of Experimental Biotherapy and Diagnostics, Institute for Regenerative Medicine, World-Class Research Centre "Digital Biodesign and Personalized Healthcare", Sechenov First Moscow State Medical University, Moscow 119991, Russia.
E-mail addresses: ulasov_i_v@staff.sechenov.ru, ulasov75@yahoo.com (I. Ulasov).

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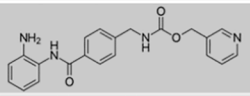
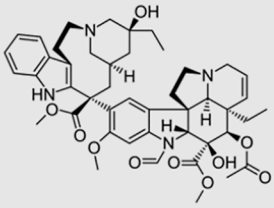
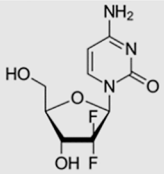
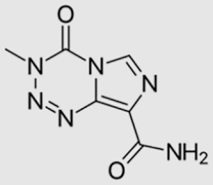
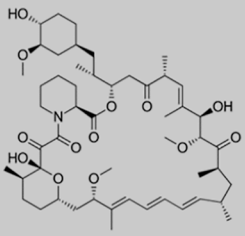
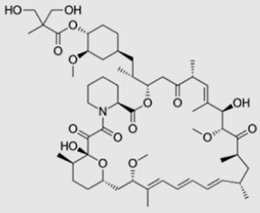
induces growth arrest or apoptosis in differentiated primary cells [18], but it is stably maintained by mesenchymal stem cells (hMSC) [19] and even induces a gene expression profile strikingly similar to that of ES. Multiple efforts have identified targets of the EWS/FLI1 fusion that are involved in ES tumorigenesis, including *TRIM8* [20], *H3K27ac*, and *RNA polymerase II* genes [21]. Another approach to combating ESW-FLI1 oncoprotein expression involves targeting L1RAP and phosphoglycerate dehydrogenase (PHGDH), which augment cysteine [22] and serine [23] uptake, or inhibiting BTG [24], which induces cell proliferation.

There is some evidence that gene fusions and elevated levels of tumor

Table 1
Pharmacological agents used during clinical trials in the treatment of ES patients.

Name	Chemical structure	Pharmacology	Medical uses	Clinical trials
Entinostat		Histone deacetylase inhibitor	Various cancers	Phase I trial
Vincristine		Works partly by binding to the tubulin protein, stopping the tubulin dimers from polymerizing to form microtubules, causing the cell to be unable to separate its chromosomes during the metaphase. The cell then undergoes apoptosis	Acute lymphocytic leukemia, sarcomas and osteosarcomas, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer	Phase III
Gemcitabine		Gemcitabine is metabolized inside the cell under the action of nucleoside kinases to form active diphosphate and triphosphate nucleosides. Diphosphate nucleosides inhibit ribonucleotide reductase, which catalyzes DNA synthesis reactions	Testicular cancer, breast cancer, ovarian cancer, non-small cell lung cancer, sarcomas and osteosarcomas, pancreatic cancer, and bladder cancer	Phase II
Temozolomide		Alkylate/methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues	Glioblastoma and anaplastic astrocytoma	Phase II
Rapamycine		Mechanistic target of rapamycin kinase (mTOR) inhibitor that inhibits activation of T cells and B cells by reducing their sensitivity to interleukin-2	Coronary stents, prevent organ transplant rejection, treat a rare lung disease called lymphangioleiomyomatosis, and treat perivascular epithelioid cell tumor (PEComa)	Phase II
Temsirolimus		Specific inhibitor of mTOR and interferes with the synthesis of proteins that regulate proliferation, growth, and survival of tumor cells	Renal cell carcinoma	Phase III

suppressors in the genome of ES cells represent cell vulnerability and may serve as drivers of neoplastic transformation. In an ES mouse model, the loss of *p53* alone or in combination with *pRb* is instrumental in the oncogenic transformation of ES cells [25,26]. De Alava *et al.*, discovered a defined *EWS/FLI1* fusion as well as *TP53* mutations in ES cells [27], indicating that *EWS/FLI-I* is still a key player in the ES phenotype and progression (Fig. 1). Other studies [28] have found that cohesion complex subunit *(STAG2), CDKN2A,* and *TP53* mutations are present in ES cells at rates of 21.5%, 13.8%, and 6.2%, respectively [29]. The inactivation of *TP53* and *CDKN2A* genes causes dysregulation of key processes, including cell proliferation, invasion, metabolic reprogramming, and stemness.

Despite numerous genetic alterations in ES cells, few signaling pathways have emerged as prominent role-players in the cellular dysregulation. Like in other cancers, angiogenesis is a hallmark of ES oncogenesis and is dependent on growth factors including *VEGF*, *FGF*, as well as the secretion of *MMP*. It has been demonstrated that ES patients frequently have high levels of *VEGF* expression [30] as well as CD31 and CD99 [31] and that tumors with high VEGF immunoreactivity correlate with poor patient outcomes [32]. *TGF-* and *VEGF*, as well as *IGF1* [33] and YAP [34,35], have previously been linked to ES oncogenic pathways in other studies.

While EWS-FLI1 is pivotal to gene regulation in ES tumor cells, numerous studies have implicated miRNAs as key modulators of tumor cell signalling. For instance, alterations in miR-22, miR-30a-5p, miR-145, and -7a [36] expression levels lead to the activation of embryonic stem genes such as *OCT4*, *SOX2*, and *NANOG* [19], suggesting high plasticity for ES cells. Since *EWS-FLI1* and miR-145 have been shown to act on a common *SOX2* target, *EWS-FLI1* may contribute to stemness [37].

3. Inherited and acquired therapeutic resistance modulate the oncogenic phenotype of ES cells

Multiple studies have investigated the primary structure and oncogenic impact of genetic fusions in ES tumors. Although investigators detected *EWS/ERG*, *EWS/ETV1*, and *EWS/E1AF* fusion variants, the biological significance of these variants for ES tumor progression was initially unknown [38]. Subsequent experiments demonstrated that these fusions give rise to abnormal cellular proteins [39,40] and contribute to oncogenic processes, including cell apoptosis [41], proliferation, and migration [42]. These rearrangements were also found in several highly aggressive ES tumors, suggesting a role in this phenotype [43].

Of the many genetic alterations that occur in ES cells cancer cells, leading to cell division and cancer development, *ESR1/FLI1* fusion is the most important. Recent work has started to characterize many downstream genetic events regulated by this gene fusion. On of such study used a ES highly expressed PPP1R1A in regulating of ES-mediated tumor growth and progression. Study by Luo *et al.*, demonstrated that PPP1R1A depends on its phosphorylation and activation by PKA [44] to mediate ES tumorigenesis and metastasis (Fig. 2). Moreover, inhibition of PP1 by PPP1R1A resulted in phosporylation of various kinases such as AKT, PKA, etc suggesting PPP1R1A pshohorylation is an important player in promoting prometastatic changes that occur during ES progression. These observations also suggest that, under certain conditions, dephosphorylation of PP1R1A may act as a tumor suppressor. Given that constant activation of ESR1/FLI1 lays the groundwork for activation of

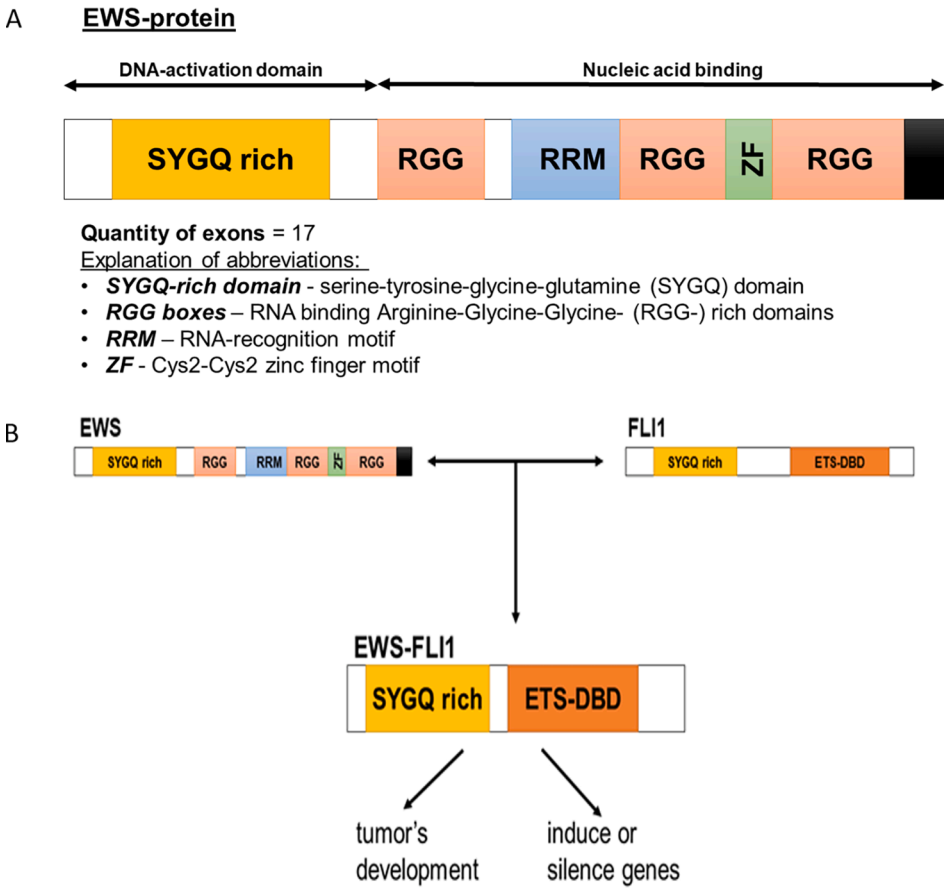


Fig. 1. The genetic structure and the functional role of the EWS-FLI1 fusion in the Ewing's Sarcoma oncogenesis. SYCQ – serine-Tyrosine-Glycine-Glutamine-rich domain (synonym – activation domain); RGG boxes – RNA binding Arginine-Glycine-Glycine-rich domain; RRM – RNA-recognition motif; ZN – Zinc finger motif; ETS-DBD – E26 transformation-specific gen' DNA binding domain.

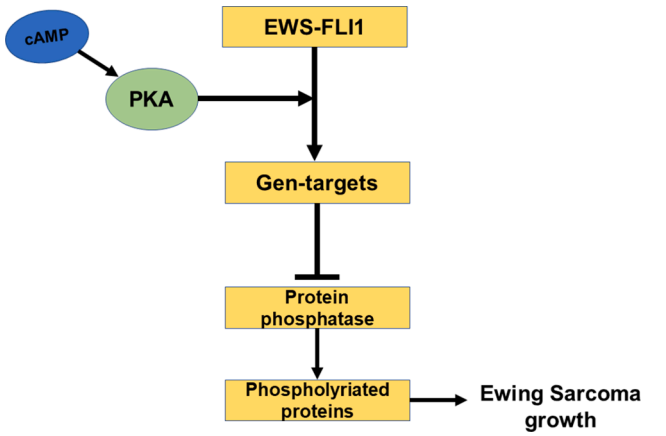


Fig. 2. Schematic representation of Ewing sarcoma growth via PKA/PP1/PPP1RA1 signalling The suggested method through which the PKA/PPP1R1A/PP1 pathway promotes ES pathogenesis is depicted in this diagram. EWS/FLI upregulates PPP1R1A, which is subsequently phosphorylated and activated by PKA, which inhibits PP1 and causes a rise in the phosphorylation level of numerous kinase/phosphatase substrates, finally leading to ES pathology (Adapted from Luo *et al.*[44]).

PKA/PPP1R1A/PP1, targeting this signaling may be an appealing strategy for combating ES metastasis.

IGF1R is a critical component of ES signalling and biomarker research. For instance, nuclear localization of IGF1R is associated with better overall survival (OS) and progression-free survival (PFS) of ES patients treated with IGF-1R Ab therapy [45]. However, IGF1R suppression is not sufficient to prevent refractory disease [46]. A better therapeutic effect may be achieved by combining IGF1R and mTOR inhibitors [47] and thereby targeting ES metabolism in combination with the removal of malfunctioning proteins and organelles via autophagy [48].

The role of autophagy in ES cells has been a matter of debate since its discovery [49]. It has been shown that radiation and chemotherapy activate autophagy regulatory proteins, including Beclin-1 [50,51]. Interestingly, preclinical studies reveal a dual function of Beclin-1 in ES cells. In the early stages of ES carcinogenesis, autophagy plays an inhibitory role in tumor development that is mediated by the autophagy regulator Beclin-1 [52], but during later disease stages, Beclin-1 promotes tumor growth by providing protection from stress conditions, such as hypoxia [53].

To date, little data exists regarding autophagy in ES oncogenesis. While the *EWS/FLI1* fusion plays a critical role in oncogenesis, its role in the stress response is less understood. Lu *et al.* noticed that the *EWS/FLI1* chimera protein is integral to the regulation of autophagy, and increases the expression of the regulatory protein ATG4B, which inhibits apoptotic cell death [54]. Given that in some cancers, ATG4B expression is associated with drug resistance [55–57], profiling of recurrent ES patients based on ATG4B expression levels might elucidate the role of autophagy in treatment responders versus non-responders, as well as identify key modulators with respect to autophagy-protein status and disease course.

4. Immunotherapy arises as a vital anticancer option against ES tumor cells

Ewing's sarcoma is characterized by the lowest frequency of DNA mutations [58]. Unlike other tumors such as melanoma, where the presence of genetic mutations in JAK1- JAK2 signaling pathway disrupts the production of interferon gamma by T cells and is resistant to the checkpoint inhibitor such as Keytruda [59], ES cells exhibit one of the lowest mutation rates among all cancers (0.15 mutations/Mb). Although ES tumors yield a paucity of pharmacologically actionable mutations, several studies got attention. One of them was conducted by Brohl *et al.*, [29] where the authors detected STAG2 mutations in the genome of ES cells. Considering the clinical significance of that mutation for the pathobiology of ES cells, targeting such tumor cells with immunotherapy approaches has become personalized.

Over the last decade, immunotherapy has been a rapidly evolving field, particularly for cellular therapy. Engineering T cells and other strategies of arming and mobilizing T cells have begun to revolutionize ES therapy. A growing cancer targeting technology employing CAR-modified T cells allows specific recognition of the ES tumor-associated antigen by a recombinant Chimeric Antigen Receptor (CAR) that is genetically-engineered into T cells isolated from ES patients. T cell recognition of ES by CAR triggers activation of an ES tumor cell killing response [60]. T cells have been frequently engineered to express anti-CD19 CAR for various malignancies [61,62]. More recently, researchers have targeted EphA2 [63] and disialoganglioside GD2, proteins with limited expression in neuronal and mesenchymal stroma cells [64] but abundant on the surface of ES cells. Despite the effect demonstrated *in vitro* by ES-targeted CAR-T cells, no clinical benefit has yet been shown. For this reason, investigators sought to improve GD2 targeting with CAR T cells by combining it with the HGF-targeted neutralizing AMG102 antibody [65].

Uncovering new potential targets is a major focus for CAR T cell therapy. One advancement was the identification of CD276 (B7-H3), an immunoregulatory protein that plays either a costimulatory or coinhibitory role in T cell activation [66]. Recent studies using human and mouse tumor models showed that CD276 elicits activation of CD4 T and CD8 T cells along with the production of effector cytokines, including IFN-γ. Using a mouse orthotopic EW8 model, Majzner *et al.*, demonstrated improved survival for mice treated with CD276 targeting CAR-T cells [67]. Multiple ES clinical trials have since been initiated (NCT02982941, NCT04483778, and NCT04433221). However, some concerns have been raised regarding the tumor-selectivity of the CD276 marker [67,68]. During inflammation [69], normal cells upregulate CD276, which may compromise the specificity of CAR-T cell therapy [70]. Yet, suppressing the coinhibitory activity of CD276 (B7-H3), which is exploited by tumors in their immune evasion, may be a new experimental approach.

Modulation of the antitumor potential of the immune system is a powerful and highly promising therapeutic approach to combat cancer. Among immune cells, effector cells "educated" to exhibit specificity for ES-tumor antigens [71], natural killer cells (NK) have gained attention as they play a fundamental role during ES development and aid in tumor clearance. Despite some encouraging *in vitro* data, a significant clinical breakthrough using NK-based therapy for ES has not been achieved [72,73], likely related to the immune suppressive nature of the tumor microenvironment. Treatment with HDAC-based entinostat was found effective in activating receptors on NK cells [74], such as NKG2D E (74), and offers a new approach to augment NK cell response and increase NK cytotoxicity [75]. Additionally, entinostat induces the expression of stress-induced molecules that function as ligands for NKG2D on the surface of ES cells. Whether this effect is beneficial for immune therapy against ES remains to be determined.

In order to overcome tumor mediated immune suppression, a new technology, commonly referred to as a "T cell engager", was developed that allows direct interaction of T cells with target tumor cells. Tumor endothelial marker 1 (TEM1) is a glycoprotein commonly expressed in the vasculature and stroma of sarcomas. Fierle *et al.*, [76] investigated the possibility of lysing ES cells with anti-TEM1 single-chain variable fragments (scFv) reagents. The authors found these fragments capable of conferring cytolytic activity when expressed as chimeric antigen receptors (CARs), and prevented the establishment of ES tumors in a xenograft model, offering a promising new approach for the treatment of ES.

5. Do gene rearrangements and mutations offer a new therapeutic option?

Chromosomal rearrangements can produce gene fusions encoding chimera kinase-based proteins with transcription factor properties. Selvanathan *et al.*,[77] reported a new interaction with the BAF chromatin complex. Since the BAF complex plays a tumor suppressor and oncogene role, the development of small molecular inhibitors represents a major challenge for ES therapy.

Transcriptome analysis of ES cells has provided new insights into the transcriptional regulation of tumor progression and cellular signaling integral to tumor growth. Mutations in the FEV transcription factors may lead to alterations in cellular functions. Although ES tumors with the FEV gene rearrangements are relatively rare (~3.5% of all ES tumors), in a recent cohort study of patients with the WSWR1/FUS-FEV fusion, 80% of patients had distant sites of metastasis, suggesting a role for this fusion in disease dissemination [78]. Interestingly, it was previously demonstrated [79] that tumor cells harboring FEV mutations are sensitive to PNU-74654 (FDR = 0.004), Merck60 (FDR = 0.005) and zebularine (FDR = 0.005).

The other transcript ES tumor cells are enriched in is that of the ephrin receptor (EPHB1), which belongs to the receptor-tyrosine kinase (RTK) family. Binding of the cognate ligand to this receptor mediates the cellular processes of angiogenesis [80], cell adhesion through MAPK-ERK signalling [81], actin dynamics, and tumor cell survival via the protein kinase B (AKT) pathway [82]. Sarcomas, besides the production of normal (wild type) transcriptomes, often generate transcripts with genetic alterations. According to the COSMIC (Catalogue of Somatic Mutations in Cancer) depository (https://www.cancer.sanger.ac.uk), 0.34–14.2% of all sarcoma types bear mutations in the EPHB1 gene, particularly in the Ephrin type A-transmembrane domain. Bioinformatic evidence [79] suggests that tumor cells with EPHB1 mutations become sensitive to SN-38, LY-2183240, and N9-isopropylolomoucine (CTD2 Dashboard), while some other tumor cells, such as those of lung cancer, show resistance. Although a direct link between the accumulation of EPHB1 mutations and tumor cell resistance has yet to be established, targeting sarcoma stem cells as a source of such resistance via AKT signaling enhancement may provide a “magic bullet” for slowing ES progression and hastening the patient’s recovery. To date, various therapeutic options demonstrate only modest clinical success in ES therapy [83], suggesting that combinational therapy approaches may become more effective. Since the effect of one of the chemotherapeutic drugs such as vincristine requires activation of AKT, the potentiation of tumor cell death via a combination of the commonly used chemotherapies (vincristine [84], gemcitabine [85], etc.) with autophagy modulators, such as temozolomide [86], hydroxychloroquine, rapamycin [87], or temsirolimus [87], may be a great option for future ES therapeutic intervention (Tabl. 1). Furthermore, such an approach could allow for lower doses of chemotherapy drugs, thereby minimizing drug toxicities and the associated adverse side effects.

6. Conclusion

Individual cells of soft tissue tumors, including Ewing’s sarcoma, often acquire resistance to chemotherapy treatments, which commonly leads to therapy failure. Recent preclinical developments have pioneered new approaches that utilize unique genetic and phenotypic properties to target therapy-resistant ES cells. Immunotherapy methods employing CAR-T cell technology or utilizing NK cell activation may become promising clinical options for patients with ES. A better understanding of the molecular mechanisms that lead to treatment resistance and/or immune escape will offer new treatment options, some of which may have already been demonstrated *in vitro* efficacy. Further, the genetic heterogeneity of ES tumors will require advancements in bioinformatics, including the expansion of genetic and proteomic databases, and tumor tissue depositories, to aid in the development of novel drug discoveries and more accurate predictions of efficacy, with the ultimate goal of combinatorial therapies ready for patients in the clinical setting.

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CRediT authorship contribution statement

Irina Karlina: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Brett A. Schroeder:** Writing – review & editing, Writing – original draft. **Kirill Kirgizov:** Writing – review & editing. **Olga Romantsova:** Writing – review & editing. **Andrey L. Istranov:** Writing – original draft, Writing – review & editing. **Andrey Nedorubov:** Writing – original draft, Writing – review & editing. **Peter Timashev:** . **Ilya Ulasov:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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