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Commentary

The combination of TSPO ligands and CDK1 inhibitors may be a novel approach for the treatment of malignant peripheral nerve sheath tumor

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Abstract

Malignant peripheral nerve sheath tumor (MPNST) is a highly aggressive sarcoma, often arising in patients with neurofibromatosis type I (NF1), and has a poor prognosis with a 5-year survival rate of only 8–13%. Current treatments are largely ineffective, underscoring the need for new therapeutic targets. Dysregulation of the cell cycle is a key contributor to cancer development, making cyclin-dependent kinases (CDKs) promising targets for cancer therapy. However, single-agent therapies often face rapid resistance, suggesting that combinatorial approaches may offer greater therapeutic efficacy. Notably, TSPO deficiency modulates the cell cycle in MPNSTs via CDK1, presenting a potential molecular target for both prognosis and treatment.

Commentary

MPNSTs are aggressive Schwann cell-derived sarcomas, frequently associated with NF1 mutations. Traditional treatments, including surgery and chemotherapy, are largely ineffective, highlighting the urgent need for novel therapeutic strategies. NF1 loss leads to RAS pathway activation, which in turn activates multiple signaling cascades, including RAF-MEK-ERK1/2, PI3K-AKT, and RalGDS pathways. Inhibition of these pathways has been explored, with MEK inhibitors, such as selumetinib, showing some promise in clinical trials (NCT03433183). However, combinatorial approaches targeting additional pathways, like SHP2 [1], may offer better outcomes, particularly in cases of acquired resistance to MEK inhibitors.

Immune therapy is currently a new method for treating various cancers, helping more and more patients achieve long-lasting and safe clinical responses. MPNST is filled with a large number of immune cells, such as macrophages, fibroblasts, mast cell, B cell and T cell infiltration, which provides multiple options for immunotherapy of MPNST. Immune checkpoint blockade is the signification method in immunotherapy. PD-1 is an immunosuppressive receptor that exists on immune cells such as T cells. When PD-1 binds to its ligand PD-L1, an inhibitory signal is generated, which suppresses the function of T cells and prevents the immune system from attacking the tumor. In MPNST, scholars have studied the effectiveness of CD274/PD-L1 amplification in anti-PD-1 therapy, demonstrating that anti-PD-1 therapy has a certain positive effect on MPNST [2].

Targeting tumor-associated macrophages is also an important method because macrophages are the predominant immune cells found in the tumor microenvironment across MPNST [3].

MPNSTs mainly use colony stimulating factor 1 (CSF1) to target macrophages for treatment, which is a small molecule tyrosine kinase inhibitor for receptor signaling, also known as pexidartinib [4]. When using pexidartinib to treat MPNST xenograft mice, it was found to significantly inhibit tumor growth, and it effectively reduced the TAM population by inhibiting the CSF1R, c-KIT, and PDGFRb signaling pathways [5]. Sirolimus is a PI3K/Akt pathway inhibitor for tumor growth and survival. Studies have shown that the combination of pexidartinib and sirolimus can enhance macrophage depletion and reduce tumor volume [6].

Translocator protein (TSPO) is located on the outer mitochondrial membrane and participates in various biological activities, such as metabolism, steroid formation, and inflammation/immune regulation [7]. In previous studies, TSPO was considered a marker of microglial cell activation [8]. The authors listed the expression and function with TSPO in some common cancers. But interestingly, TSPO has both procancer [9] and anticancer effects on gliomas [10]. The ligands of TSPO are divided into endogenous ligands and exogenous ligands, as well as agonists and antagonists of TSPO. In another review [11], the roles of various ligands in inflammation and immunity are elaborated, and TSPO ligands also play important roles in other biological processes.

The TSPO specific ligand vinpocetine exerts neuroprotective effects by inhibiting microglial inflammation. Vinpocetine inhibited nitrite oxides and inflammatory factors such as interleukin-1 in BV-2 microglia β (IL-1β) IL-6 and tumor necrosis factor-α (TNF-α). *In vivo* experiments, the treatment of hypoxia mice with vinpocetine also inhibited inflammatory molecules, showed that vinpocetine may be effective for the treatment of neuroinflammatory diseases [12]. In another study, midazolam inhibited the upregulation of CD80 and the release of IL-6 and NO in LPS induced THP-1 cells and PMDM, primarily inhibiting NF-κB/AP-1 in THP-1 cells and the activation of MAPK pathway [13].

TSPO ligands XBD173 and GLX35322 were used in a mouse model of glioblastoma. The result had proved TSPO deletion causes ROS and angiogenesis via NOX4 signal pathway, and the treatment was effective [14]. In hepatocellular carcinoma, TSPO ligands PK11195 combined with anti PD-1 antibodies showed that it can inhibit ferroptosis and anti-tumor immunity **(Table 1)** [15,16].

Table 1. Effects of TSPO and ligands on the microenvironment in different diseases.

Disease Model	Treatment	Effect	Ligand Treatment	Outcome	Reference
Glioma U118MG in the CAM model	TSPO-KO	VEGF-α, IL-8, MMP2 ↑	-	-	[17]
Glioma U118MG *in vitro*	TSPO-KO	HIF-1α ↑	-	Hypoxia, angiogenesis, glycolysis	[10]
Mouse model of glioblastoma	Conditional deletion of TSPO	ROS ↑ NOX4 signal activation	XBD173 GLX35322	TSPO deletion induces ROS production and angiogenesis via the NOX4 signaling pathway	[14]
C20 microglial cell line	TSPO knockout	Inflammation ↓	-	-	[18]
Septic mice	TSPO knockout	Improve the survival rate Inhibit M1 cells and promote M2 cells Reduce inflammation	Koumine	Regulate M1/M2 polarization Reduce the inflammatory response	[19]
M2 microglia	- IL-4	Decrease TSPO PPAR-γ activation	PK11195 FGIN-1-27/ overexpressed TSPO	PPAR-r CD206/Arg-1/YM-1/FIZZ-1↑ PPAR-r CD206/Arg-1/YM-1/FIZZ-1↓	[20]
Th1 type immune response	TSPO ligand treatment	Inhibit the Th1 cell response	FGIN-1-27 Ro5-4846	IFN-r ↓; T-bet ↓ Inhibit nonmemory CD4+ T-cell differentiation to Th1 cells	[21]
GBM BTICs cocultured with T cells	- Silencing of TSPO	TNF-α, IFN-γ induce TSPO upregulation Sensitized BTICs against T-cell-mediated cytotoxicity Protected BTICs against TRAIL-induced apoptosis	-	-	[22]
GBM	-	-	D-DPA	Target mitochondria in TAMs to inhibit tumors	[23]
Xenograft produced by MDA-MB-231 and MCF-7 breast cancer cell lines	$^{[18\text{-}F]}$DPA-714	TSPO high expression colocalized with F4/80-positive macrophages	-	-	[24]

Breast cancer	Target TSPO for PDT	MDA-MB-231 cell apoptosis No effect on MCF-7 cells	IRT700DX-6T	Inhibit the growth of MDA-MB-231 cells	[25]
Colorectal cancer	Target TSPO for PDT	Apoptosis ICD activation	IRT700DX-6T	CD8+ T-cell ↑ Treg ↑	[26]
Pancreatic cancer	Target TSPO for PDT	Inhibit cell proliferation	IRT700DX-6T	CD8+ T-cell ↑ CD↑ Treg ↑	[27]
Hepatocellular carcinoma	TSPO overexpression	P62 accumulation Nrf2-dependent antioxidant defense system inhibits ferroptosis PD-L1 increased	PK11195 Anti PD-1 antibodies	Inhibit ferroptosis Antitumor immunity	[15, 16]

In the cell proliferation process, the cell cycle is strictly regulated by certain mechanisms [28]. Cyclin dependent protein kinases(CDKs) are a group of serine/threonine protein kinases. CDKs drive the cell cycle through chemical reactions with serine/threonine proteins and work synergistically with cyclin, making them important factors in cell cycle regulation. The binding of small inhibitor protein CDK inhibitors (CKIs) negatively regulates CDK activity [29,30]. In RNA sequencing (RNA Seq) data of the transcriptome of PNF/ANNUBP and MPNSTs, it was found that the transcription levels of FOXM1 mRNA and key transcription targets (such as AURKB, BIRC5, CENPA, CCNB1, CDK1) [31,32] were significantly increased in MPNSTs [33].

Previous studies have found that CDK4/6 inhibitor monotherapy has excellent anti-tumor effects on newly developed MPNSTs in mice, but drug resistance occurs rapidly [34]. In recent studies, the use of MEK inhibitors alone has been ineffective against MPNST. The low-dose combination of MEK inhibitor (mirdametinib) and CDK4/6 inhibitor (palbociclib) can cause significant tumor regression and improve survival rate in immunocompetent mice carrying MPNSTs [35]. The inhibition of cell cycle CDKs (CDK1, CDK2, CDK4, and CDK6) by Flavopiridol/Avocidib promotes G1 and G2 cell cycle arrest [36]. According to preliminary data, seliciclib is a relatively specific inhibitor of CDK1, CDK2, and CDK5. However, subsequent data showed that CDK7 and CDK9 were also inhibited, leading to transcriptional repression [37,38]. Dinaciclib [39], AT7519 and a flavonoid compound produced from digitalis bulbs can stimulate cell apoptosis, G0/G1 phase arrest, and the flavonoid compound produced from thistle bulbs also inhibit cancer cell angiogenesis by limiting CDK1 and CDK6 [40].

MEK inhibitors, such as trametinib, block the MAPK/ERK pathway, which is crucial for cell growth and survival in many cancers, including MPNST [41]. This pathway is often dysregulated in MPNST due to mutations in the NF1 gene. MEK inhibitors are a targeted therapy, specifically targeting the MAPK pathway, which plays a significant role in MPNST progression. Clinical trials have shown progression-free survival (PFS) benefits in certain patients with MPNST. MEK inhibitors primarily target the tumor cells and may not significantly impact the tumor microenvironment or enhance immune responses, which may be a limitation for some tumors, including MPNST [42]. Immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) like pembrolizumab and nivolumab work by blocking the PD-1/PD-L1 interaction, thereby stimulating T cells to attack tumor cells. Immune checkpoint inhibitors have demonstrated significant efficacy in cancer [43].

Overall, the author detected new resources to the MPNST field and extend our understanding of cell cycle mechanisms to targeted therapies. But inadequately, they did not provide a timely pre-clinical study to treat MPNST. According to previous literature, the author team may direct new combination strategies to optimize CDK1 inhibitor and TSPO ligands treatments for NF1-deficient MPNST patients [44].

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