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Anthelmintic drug ivermectin inhibits angiogenesis, growth and survival of glioblastoma through inducing mitochondrial dysfunction and oxidative stress

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Highlights

- Ivermectin is effective in glioblastoma cells *invitro* and *invivo.*
- Ivermectin inhibits angiogenesis.

- Ivermectin induces mitochondrial dysfunction and oxidative stress.
- Ivermectin deactivates Akt/mTOR signaling pathway.

Abstract

Glioblastoma is one of the most vascular brain tumour and highly resistant to current therapy. Targeting both glioblastoma cells and angiogenesis may present an effective therapeutic strategy for glioblastoma. In our work, we show that an anthelmintic drug, ivermectin, is active against glioblastoma cells *invitro* and *invivo*, and also targets angiogenesis. Ivermectin significantly inhibits growth and anchorage-independent colony formation in U87 and T98G glioblastoma cells. It induces apoptosis in these cells through a caspase-dependent manner. Ivermectin significantly suppresses the growth of two independent glioblastoma xenograft mouse models. In addition, ivermectin effectively targets angiogenesis through inhibiting capillary network formation, proliferation and survival in human brain microvascular endothelial cell (HBMEC). Mechanistically, ivermectin decreases mitochondrial respiration, membrane potential, ATP levels and increases mitochondrial superoxide in U87, T98G and HBMEC cells exposed to ivermectin. The inhibitory effects of ivermectin are significantly reversed in mitochondria-deficient cells or cells treated with antioxidants, further confirming that ivermectin acts through mitochondrial respiration inhibition and induction of oxidative stress. Importantly, we show that ivermectin suppresses phosphorylation of Akt, mTOR and ribosomal S6 in glioblastoma and HBMEC cells, suggesting its inhibitory role in deactivating Akt/mTOR pathway. Altogether, our work demonstrates that ivermectin is a useful addition to the treatment armamentarium for glioblastoma. Our work also highlights the therapeutic value of targeting mitochondrial metabolism in glioblastoma.

Introduction

Glioblastoma is the common primary malignant brain tumour in adults with very poor prognosis [1]. Glioblastoma is characterized by extensive vascularization, molecular heterogeneity and prominent invasiveness and resistance to combination of radiation and chemotherapy. Essential signaling pathways involved in the progression of glioblastoma and its resistance to current therapies are phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) [2], p53 or Wnt pathway [3], [4]. Transcript profiling and genomic aberrations have shown that glioblastoma is extensively intra- and inter-tumour

heterogeneous [5], [6]. Targeting common between different molecular subclasses of glioblastoma represents an alternative therapeutic strategy for glioblastoma.

Metabolic activities in cells rely primarily on mitochondrial respiration to generate ATP for energy [7]. Recent studies have revealed that compared to normal cells, tumour cells have increased mitochondrial biogenesis and are more dependent on mitochondrial functions to meet energy demands, promote growth and maintain survival [8], [9], [10]. In lines with these findings, targeting mitochondrial respiration by pharmacological or genetic approaches has been shown to selectively display cytotoxic effects in cancer cells while sparing normal cells [9], [11].

Ivermectin is a FDA-approved anti-parasitic drug used for the treatment of intestinal worm infections. The mechanism of the action of ivermectin in parasites is not clear. It is also a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity [12]. However, recent studies have shown that ivermectin is a novel type of anti-cancer drug. It inhibits growth and induces death of ovarian and breast cancer cells [13], [14], [15]. The mechanisms of anti-cancer activities of ivermectin vary in different tumour types, including deactivation of the oncogenic kinase PAK1 and modulate P2X4 receptors [14], [15].

In this study, we investigated the effect of ivermectin in glioblastoma cells and angiogenesis. We demonstrate that ivermectin effectively targets glioblastoma cells *invitro* and *invivo*. Ivermectin also inhibits angiogenesis through suppressing capillary network formation, proliferation and induces apoptosis of human brain microvascular endothelial cells (HBMEC). We further show that ivermectin acts on glioblastoma and HBMEC cells through inducing mitochondrial dysfunction and oxidative stress and deactivating Akt/mTOR pathway.

Section snippets

Cell culture, generation of ρ0 cell line and drugs

Human glioblastoma cell lines A172 and U138-MG were purchased from American Type Culture Collection and were grown in Dulbecco's Modified Eagle Medium (DMEM) (life technologies, US) supplemented with 10% fetal bovine serum (FBS, Hyclone, UK), penicillin/streptomycin and L-glutamine (Life Technologies, US). Primary Human Brain Microvascular Endothelial Cells (HBMEC) (Cell Systems Inc. US) were grown in Complete Human Endothelial Cell Medium (ECM, Cell System, US). Mitochondria DNA-deficient A172 …

Ivermectin is effective against glioblastoma cells *invitro* and *invivo*

We investigated the effects of ivermectin on the proliferation and apoptosis in human glioblastoma cell lines U87 and T98G. These two cell lines have been extensively employed as relevant glioblastoma cell models [18]. We found that ivermectin significantly inhibited proliferation of U87 and T98G cells in a dose-dependent manner, with ED_{50} of ~5μM (Fig. 1A). Ivermectin also induced apoptosis in these cells as assessed by quantitative measurement of Annexin V (Fig. 1B). In addition, a …

Discussion

Glioblastoma is one of the most vascular tumors due to the expression of a variety of proangiogenic factors [21]. Besides extensive vascularization, glioblastoma is highly molecular heterogeneous with distinctive genetic aberrations [6]. There is a need to identify compounds that are effectively against angiogenesis and common tractable target in glioblastoma. In this work, we evaluated ivermectin as a potential agent for glioblastoma treatment. We are the first to demonstrate that ivermectin …

Conflict of interest

All authors declare no conflict of interest. …

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