Disulfiram targets glioblastoma-stem-like cells in vitro and in vivo

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BACKGROUND
Glioblastoma multiform (GBM) is the most aggressive adult primary brain tumour with median survival time less than 12 months. GBM are extensively hypoxygenated tumours. Intra-tumoural hypoxia induces GBM-stem-like-cells (GSCs) are highly locally invasive and resistant to all currently available chemotherapeutic agents. The GSCs are responsible for the GBM local invasion and relapse. Hypoxia triggers hypoxia inducible factors (HIFs), NF-κB and stem cell markers, but the relationships among hypoxia, stemness and chemoresistance still remain obscure. Therefore, understanding the molecular mechanisms behind hypoxia-induced GSCs and developing GSC-targeting drug is of clinical significance and urgency. Disulfiram (DS), a clinically used anti-alcoholism drug in combination with copper (Cu) can effectively reverse chemoresistance and block metastasis in multiple cancers. The clinical application of DS is limited by its short half-life in the bloodstream. We recently developed and characterized a poly lactic-co-glycolic acid (PLGA)-encapsulated DS nanoparticles, protecting DS from degradation and thereby extending its half-life in the bloodstream. We evaluated the in vivo efficacy of the DS-PLGA nanoparticles in orthotopic xenograft GBM mouse model.
METHODS
Hypoxic culture, stable transfection, MTT, CSC markers, Nano-encapsulation, orthotopic GBM mouse model.
RESULTS
Hypoxic GBM cells displayed stem markers along with increased invasiveness and resistance to temozolomide (TMZ). NFκB and HIFs transfected GBM cells exhibited GSC features and resistance to TMZ indicating their pivotal role in hypoxia induced resistance. DS/Cu effectively reversed resistance and invasion of hypoxic GBM cells at low nanomolar levels. In combination with copper, DS-PLGA significantly inhibited GBM tumour in orthotopic xenograft mouse models at a very low dose (<1/10 of antialcoholism dose).
CONCLUSIONS
The new formulation of DS/Cu effectively suppressed GBM with no toxicity to normal tissues. Both DS and PLGA are FDA approved products and can freely pass through the BBB. Our study may lead to a breakthrough in GBM treatment.