THE EPHRIN RECEPTOR KINASE INHIBITOR GLPG1790 REVERTS ONCOPHENOTYPE, INDUCES MYOGENIC DIFFERENTIATION AND RADIOSENSITIZES EMBRYONAL RHABDOMYOSARCOMA CELL LINES IN VITRO AND IN VIVO.

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Malignant tumors of skeletal muscle rhabdomyosarcomas (RMS) are the most common soft-tissue sarcoma in childhood. RMS is thought to derive from cells along the skeletal muscle cell axis and distinct in several histological variants with the embryonal (ERMS) subtype representing the most common variant. RMS treatment is based on surgery combined to radiation- (RT) and chemo-therapy treatment. However, often treatments fail providing only a transient tumor control with a consequent infaust prognosis. Eph receptors are the largest receptor tyrosine kinase family of transmembrane proteins with an extracellular domain capable of recognizing signals from the cells' environment and influencing cell-cell interaction and cell migration. Eph overexpression can result in tumorigenesis as related to tumor growth and survival and is associated with angiogenesis and metastasis in many types of human cancer. We previously showed a global up-regulation of Eph B-type receptors in RMS tumours. This report describes the effects of GLPG1790, a new potent pan-EPH inhibitor, in human RD and TE671 human ERMS cell lines, in in vitro and in vivo experiments. GLPG1790 induced G1-growth arrest as demonstrated by RB, Cyclin A and Cyclin B1 decrease, as well as by p21 and p27 increment. GLPG1790 reduced migratory capacity and clonogenic potential of ERMS cells, prevented rhabdosphere formation and down-regulated CD133, CXCR4 and Nanog stem cell markers. Drug treatment committed ERMS cells towards skeletal muscle terminal differentiation by inducing a myogenic-like phenotype and increasing MYOD1, Myogenin and MyHC levels. Furthermore, GLPG1790 significantly affected growth and radiosensitized in vivo ERMS cells by affecting the DNA double-strand break repair pathway and so increasing radiation-therapy-induced DNA damages. Finally, our study showed, for the first time, a significant up-regulation of EPH-A2 receptor and Ephrin-A1 ligand in 16 ERMS tumour samples in comparison to normal skeletal muscle. Taken together, our data suggest that altered EPH signalling plays a key role in ERMS development and its pharmacological inhibition might represents a potential therapeutic strategy to impair steaminess, radioresistance and to rescue myogenic program of this tumour cells.