Metastatic group 3 medulloblastoma is driven by PRUNE1 targeting NME1-TGF-β-OTX2-SNAIL via PTEN inhibition.


Abstract

Genetic modifications during development of paediatric groups 3 and 4 medulloblastoma are responsible for their highly metastatic properties and poor patient survival rates. PRUNE1 is highly expressed in metastatic medulloblastoma group 3, which is characterized by TGF-β signalling activation, c-MYC amplification, and OTX2 expression. We describe the process of activation of the PRUNE1 signalling pathway that includes its binding to NME1, TGF-β activation, OTX2 upregulation, SNAIL (SNAI1) upregulation, and PTEN inhibition. The newly identified small molecule pyrimido-pyrimidine derivative AA7.1 enhances PRUNE1 degradation, inhibits this activation network, and augments PTEN expression. Both AA7.1 and a competitive permeable peptide that impairs PRUNE1/NME1 complex formation, impair tumour growth and metastatic dissemination in orthotopic xenograft models with a metastatic medulloblastoma group 3 cell line (D425-Med cells). Using whole exome sequencing technology in metastatic medulloblastoma primary tumour cells, we also define 23 common 'non-synonymous homozygous' deleterious gene variants as part of the protein molecular network of relevance for metastatic processes. This PRUNE1/TGF-β/OTX2/PTEN axis, together with the medulloblastoma-driver mutations, is of relevance for future rational and targeted therapies for metastatic medulloblastoma group 3.