Combination therapies with epigenetic inhibitors for the treatment of soft tissue sarcomas

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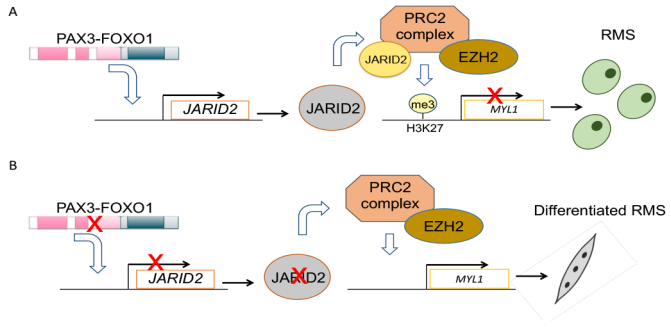
Differentiation therapy is an approach that has had notable success in a limited number of cancer types including acute promyelocytic leukaemia and neuroblastoma but remains underexplored for most tumour types. Therapeutic drugs have been shown to promote differentiation in preclinical models including soft tissue sarcomas (STS) that often resemble undifferentiated mesenchymal tissues. Rhabdomyosarcomas (RMS) are the most common paediatric STS and appear as developing skeletal muscle that are unable to terminally differentiate through aberrant recapitulation of developmental programs. Histone modifications are known to govern these developmental programs by controlling activities such as DNA transcription and cell differentiation. Enhancer of Zeste Homolog 2 (EZH2) confers histone methyltransferase activity to the Polycomb Repressive Complex 2 (PRC2), and is known to control stem cell renewal and differentiation.

We have shown that EZH2 and other members of the Polycomb Repressive Complex 2 (PRC2) play a role in the differentiation program of RMS and are required to maintain the undifferentiated phenotype of these tumours. Single agent modulation of EZH2 using a tool compound or clinical drug candidate results in modest differentiation of RMS cell lines, a phenotype that we show is augmented by combination with differentiating agents in vitro. Furthermore, we show that this combination can also be used to effectively reduce proliferation in synovial sarcoma lines in vitro. Thus combining inhibition of histone modifying enzymes with differentiating agents or other frontline therapies already in clinical use represent a novel potential avenue for therapeutic intervention for use in the treatment of STS.



The Polycomb Repressive Complex 2 (PRC2) complex maintains the undifferentiated state of rhabdomyosarcoma (RMS) cells. (A) We have shown that the PAX3-FOXO1 fusion protein present in high-risk Alveolar RMS tumours directly regulates the expression of JARID2, a member of the PRC2 complex, which in turn methylates H3K27 on the promoter of myogenic genes to maintain the proliferative, undifferentiated state of RMS cells. (B) Silencing of JARID2, and other members of the PRC2 complex, results in removal of these methyl marks and ultimately to differentiation of RMS cells to a more benign state.

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