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Thyroid hormone suppresses medulloblastoma progression through promoting terminal differentiation of tumor cells

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Abstract

Hypothyroidism is commonly detected in patients with medulloblastoma (MB). However, whether thyroid hormone (TH) contributes to MB pathogenicity remains undetermined. Here, we find that TH plays a critical role in promoting tumor cell differentiation. Reduction in TH levels frees the TH receptor, TRα1, to bind to EZH2 and repress expression of NeuroD1, a transcription factor that drives tumor cell differentiation. Increased TH reverses EZH2-mediated repression of NeuroD1 by abrogating the binding of EZH2 and TRα1, thereby stimulating tumor cell differentiation and reducing MB growth. Importantly, TH-induced differentiation of tumor cells is not restricted by the molecular subgroup of MB, suggesting that TH can be used to broadly treat MB subgroups. These findings establish an unprecedented association between TH signaling and MB pathogenicity, providing solid evidence for TH as a promising modality for MB treatment.

Keywords: EZH2; NeuroD1; TRα1; differentiation therapy; epigenetic regulation; hypothyroidism; medulloblastoma; terminal differentiation; thyroid hormone.