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Hedgehog signaling negatively co-regulates BH3-only protein Noxa and TAp73 in TP53-mutated cells

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Abstract

In the present study, we show that pharmacological repression by the Hedgehog (Hh) pathway inhibitor (HPI) GANT61 induces expression of the proapoptotic protein Noxa in TP53-mutated rhabdomyosarcoma (RMS) and medulloblastoma (MB) cells. Similarly, genetic silencing of Gli1 by siRNA causes increased Noxa mRNA and protein levels, while overexpression of Gli1 results in decreased Noxa expression. Furthermore, TAp73 mRNA and protein levels are increased upon Gli1 knockdown, while Gli1 overexpression reduces TAp73 mRNA and protein levels. However, knockdown of TAp73 fails to block Noxa induction in GANT61-treated cells, suggesting that Noxa is not primarily regulated by TAp73. Interestingly, mRNA levels of the transcription factor EGR1 correlate with those of Noxa and TAp73. Silencing of EGR1 results in decreased Noxa and TAp73 mRNA levels, indicating that EGR1 is involved in regulating transcriptional activity of Noxa and TAp73. These findings suggest that Gli1 represses Noxa and TAp73, possibly via EGR1. These findings could be exploited for the treatment of Hh-driven tumors, e.g. for their sensitization to chemotherapeutic agents.