## BMI-1 promotes ewing sarcoma tumorigenicity independent of CDKN2A repression.

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**Public Summary:**

**Scientific Abstract:**
Deregulation of the polycomb group gene BMI-1 is implicated in the pathogenesis of many human cancers. In this study, we have investigated if the Ewing sarcoma family of tumors (ESFT) expresses BMI-1 and whether it functions as an oncogene in this highly aggressive group of bone and soft tissue tumors. Our data show that BMI-1 is highly expressed by ESFT cells and that, although it does not significantly affect proliferation or survival, BMI-1 actively promotes anchorage-independent growth in vitro and tumorigenicity in vivo. Moreover, we find that BMI-1 promotes the tumorigenicity of both p16 wild-type and p16-null cell lines, demonstrating that the mechanism of BMI-1 oncogenic function in ESFT is, at least in part, independent of CDKN2A repression. Expression profiling studies of ESFT cells following BMI-1 knockdown reveal that BMI-1 regulates the expression of hundreds of downstream target genes including, in particular, genes involved in both differentiation and development as well as cell-cell and cell-matrix adhesion. Gain and loss of function assays confirm that BMI-1 represses the expression of the adhesion-associated basement membrane protein nidogen 1. In addition, although BMI-1 promotes ESFT adhesion, nidogen 1 inhibits cellular adhesion in vitro. Together, these data support a pivotal role for BMI-1 ESFT pathogenesis and suggest that its oncogenic function in these tumors is in part mediated through modulation of adhesion pathways.