METASTASIS

# Twisting BMI1

Epithelial to mesenchymal transition (EMT) is an essential and highly regulated process that occurs during embryogenesis and wound healing, and is also induced during tumour metastasis. Previous studies identified TWIST1 as a crucial transcription factor that is required for EMT, and linked tumour cells that had undergone EMT to stem cell-like attributes. A recent paper in *Nature Cell Biology* shows that the polycomb group protein BMI1, which is expressed in stem cells, is a TWIST1 target gene.

The expression of BMI1 in stem cells leads to the repression of the tumour suppressor locus *CDKN2A*, which encodes INK4A and ARF, through the polycomb repressor complexes PRC1 and PRC2. PRC1, of which BMI1 is a component, binds to the chromatin mark histone 3 trimethylated on lysine 27 (H3K27me3) that is induced by PRC2 and maintains gene repression. The link between EMT, TWIST1 and stem cell-like phenotypes prompted Muh-Hwa Yang, Dennis Shin-Shian Hsu and colleagues to look for a molecular explanation. They screened three head and neck squamous cell carcinoma (HNSCC) cell lines overexpressing *TWIST1*, *SNAI1* and *SNAI2* for the expression of genes associated with stem cell-like properties and found that BMI1 was consistently expressed in all three lines overexpressing *TWIST1*. Expression of BMI1 was associated with reduced expression levels of *INK4A* and *CDH1*, which encodes E-cadherin. Expression levels of TWIST1 are increased under hypoxic conditions, and BMI1 was also expressed in hypoxic cells and in cells expressing a constitutively active form of hypoxia inducible factor 1α (HIF1α). *BMI1* contains a TWIST1 binding site (E-box) in intron 1 and, through mobility shift assays, chromatin immunoprecipitation and transient transfection, the authors confirmed that *BMI1* is a direct target of TWIST1.

Further analyses showed that the expression of HIF1α, TWIST1 or BMI1 induced HNSCC lines to express markers that are associated with stem cells, and increased spheroid-forming capacity and the ability to produce tumours in nude mice. So, do HIF1, TWIST1 and BMI1 work in concert? Knock down of *BMI1* expression prevented EMT-induced changes by TWIST1 and constitutively active HIF1α, and BMI1 was unable to induce EMT and stem cell-like characteristics in cells in the absence of TWIST1, indicating that both BMI1 and TWIST are required. Moreover, the authors found that both TWIST1 and BMI1 bind the promoters of *CDH1* and *INK4A* to repress their expression. Examination of 132 HNSCC samples showed increased expression of both TWIST1 and BMI1 in patients with the poorest prognosis.


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The requirement for both TWIST1 and BMI1 in inducing EMT and stem cell-like properties in HNSCC indicates that chromatin remodelling is essential for tumour progression.

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**ORIGINAL RESEARCH PAPER** Yang, M.-H. *et al.* BMI1 is essential in TWIST1-induced epithelial–mesenchymal transition. *Nature Cell Biol.* 5 Sep 2010 (doi:10.1038/ncb2099)