TUMORIGENESIS

Taking an alternative route

DOI:
10.1038/nrm2307

The polycomb group (PcG) gene *BMI1*, which is required for proliferation of both differentiated cells and adult stem cells, is overexpressed in various cancers and acts as an oncogene. Its oncogenic function has been attributed primarily to repression of the *CDKN2A* locus, which encodes the tumour suppressors INK4a and ARF. However, some defects in *Bmi1*-knockout mice seem to be independent of INK4a and ARF, so Maarten van Lohuizen and colleagues set out to determine whether the same was true for BMI1-dependent tumorigenesis.

Because BMI1 has INK4a- and ARF-independent functions in the brain and is involved in neural stem cell (NSC) proliferation and self-renewal, the authors examined the role of BMI1 in a mouse model of glioma. Either NSCs or astrocytes are used as the cell of origin for the disease, and tumours are induced by *Cdkn2a* deficiency in combination with retroviral expression of a constitutively active epidermal growth factor receptor (*EGFR). $Cdkn2a^{-/-}$, but not $Bmi1^{-/-}$;$Cdkn2a^{-/-}$, primary astrocytes cultured *in vitro* undergo transformation when *EGFR is expressed. Furthermore, treatment with EGF or silencing of BMI1 using short hairpin RNA in $Cdkn2a^{-/-}$ cells has the same effect as *EGFR expression or *Bmi1* knockout, respectively.

Most human gliomas express BMI1, but does BMI1 have a role in gliomagenesis *in vivo*? The authors observed an increase in the time to tumour development and prolonged survival of mice that were orthotopically transplanted with $Bmi1^{-/-}$;$Cdkn2a^{-/-}$ primary astrocytes expressing *EGFR compared with $Cdkn2a^{-/-}$ astrocytes expressing *EGFR. The same result was observed when primary NSCs were injected rather than astrocytes. These data indicate that BMI1 is required for the development of gliomas and has functions that are independent of INK4a and ARF. However, there was a difference in the types of tumours that formed from *Bmi1*-null astrocytes and NSCs. Although grade IV tumours (glioblastoma multiforme (GBM)) arose from both $Bmi1^{-/-}$ and $Bmi1^{+/+}$ astrocytes, $Bmi1^{-/-}$ NSCs never formed GBM, and the authors propose that this is because BMI1 has additional functions in NSCs that are required for the cells to become fully malignant.

The authors also examined markers of stem cells and differentiated cells in the tumours. Control tumours expressing BMI1 derived from both astrocytes and NSCs expressed the stem-cell marker nestin and the neuronal marker TuJ1. By contrast, only approximately half of the tumours derived from *Bmi1*-null cells of either lineage expressed nestin, and most lacked TuJ1, indicating that loss of BMI1 might impair self-renewal and differentiation of these cells.

Gene-expression profiling of $Cdkn2a^{-/-}$ and $Bmi1^{-/-}$;$Cdkn2a^{-/-}$ astrocyte-derived tumours indicated that *Bmi1*-null cells undergo significantly more transcriptional changes during tumorigenesis, and the cluster of genes differentially expressed by $Bmi1^{-/-}$;$Cdkn2a^{-/-}$ cells are involved in cellular movement, proliferation and differentiation. So, it is these pathways that are probably affected independently of INK4a and ARF.

The data presented by van Lohuizen and colleagues have interesting implications for understanding how BMI1 and possibly other PcG genes regulate both stem cells and cancers driven by a stem-cell population.

Sarah Seton-Rogers, Associate Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Bruggeman, S. W. *et al.* Bmi1 controls tumor development in an Ink4a/Arf-independent manner in a mouse model for glioma. *Cancer Cell* **12**, 328–341 (2007)
FURTHER READING Sparmann, A. & van Lohuizen, M. Polycomb silencers control cell fate, development and cancer. *Nature Rev. Cancer* **6**, 846–856 (2006)