Nature Reviews Cancer | AOP, published online 12 August 2010; doi:10.1038/nrc2919

LEUKAEMIA

Comfortably MSI2–NUMB

Little is known about the mechanisms governing the progression of chronic myelogenous leukaemia (CML) from the slow-growing chronic phase to the aggressive blast crisis. Blast crisis is the stage at which CML is most refractory to treatment, so a greater understanding of its molecular hallmarks is crucial for the development of more effective therapies.

A team led by Tannishtha Reya focused on a signature trait of blast crisis — a block in cellular differentiation leading to an accumulation of immature cells. Reya and colleagues reasoned that, in these cells, the transition to blast crisis might rely on the attenuation of normal differentiation cues. To test this theory, her group modelled the chronic and blast crisis phases of CML by transplanting irradiated recipient animals with haematopoietic stem cells that were transduced with *BCR–ABL* alone (chronic phase) or *BCR–ABL* together with *NUP98–HOXA9* (blast crisis). Armed with these tools, they showed that the RNA binding protein Musashi 2 (MSI2) was dramatically upregulated during blast crisis compared with chronic phase disease. This was a compelling result given the known role of MSI2 as a regulator of asymmetric division in stem and progenitor cells, but was it actually required for progression to blast crisis? Reya and colleagues turned to mice harbouring a targeted disruption in *Msi2* and noted impaired leukaemic growth *in vivo*. Next, short hairpin RNA against *Msi2* was introduced into established blast crisis cells, resulting in decreased disease propagation in recipient mice. These results suggest a fundamental requirement for MSI2 in the establishment and maintenance of blast crisis.

During development, MSI2 represses NUMB, a key regulator of cell commitment and differentiation, so the authors asked whether this was also the case in CML. Accordingly, NUMB levels were significantly downregulated at blast crisis compared with chronic phase, and increased when *Msi2* expression was inhibited. Crucially, forced expression of NUMB in *BCR–ABL*; *NUP98–HOXA9*-transduced cells attenuated disease progression *in vivo*, and leukaemias that did develop were of a more differentiated phenotype. So, perturbations of the MSI2–NUMB axis in CML disrupts the equilibrium between the differentiated and undifferentiated states, and this propels the disease towards blast crisis.

What about human CML? Reya's team analysed 120 samples of CML and found that high levels of MSI2, together with reduced NUMB expression, correlated with advanced, aggressive disease. Further analysis of patients with blast crisis showed that high MSI2 strongly associated with the risk of relapse and risk of death, underscoring the potential of MSI2 as a prognostic tool for CML. Whether MSI2 proves to be relevant in other cancer types remains to be seen, but this study certainly introduces MSI2 as a new heavyweight in myeloid leukaemia and suggests that the modulation of MSI2 activity might be an effective therapeutic strategy.

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ORIGINAL RESEARCH PAPER Ito, T. *et al.* Regulation of myeloid leukaemia by the cell-fate determinant Musashi. *Nature*, 18 Jul 2010 (doi:10.1038/nature09171)

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