

ABSTRACT

PU.1 downregulation within haematopoietic stem and progenitor cells (HSPCs) is the primary mechanism for the development of acute myeloid leukaemia (AML) in mice with homozygous deletion of the upstream regulatory element (URE) of *PU.1* gene. *p53* is a well known tumor suppressor that is often mutated in human haematologic malignancies including AML and adds to their aggressiveness; however its genetic deletion does not cause AML in mouse. Deletion of *p53* in the $PU.1^{ure/ure}$ mice ($PU.1^{ure/ure}p53^{-/-}$) results in more aggressive AML with shortened overall survival. $PU.1^{ure/ure}p53^{-/-}$ progenitors express significantly lower PU.1 levels. In addition to URE deletion we searched for other mechanisms that in absence of *p53* contribute to decreased PU.1 levels in $PU.1^{ure/ure}p53^{-/-}$ mice. We found involvement of Myb and miR-155 in downregulation of PU.1 in aggressive murine AML. Upon inhibition of either Myb or miR-155 *in vitro* the AML progenitors restore PU.1 levels and lose leukaemic cell growth similarly to PU.1 rescue. The MYB/miR-155/PU.1 axis is a target of *p53* and is activated early after *p53* loss as indicated by transient *p53* knockdown. Furthermore, deregulation of both MYB and miR-155 coupled with PU.1 downregulation was observed in human AML, suggesting that MYB/miR-155/PU.1 mechanism may be involved in pathogenesis of AML and its aggressiveness characterized by *p53* mutation.