GENETICS

A multitasking microRNA

Altered microRNA (miRNA) expression is frequently associated with cancer, but the mechanisms by which miRNAs can contribute to pathogenesis are not fully understood. The most widely appreciated role of miRNAs is post-transcriptional gene silencing by targeting the RNA-induced silencing complex (RISC) to 3′ untranslated regions (UTRs) in the target mRNAs. Eiring *et al.* now demonstrate a RISC-independent decoy activity for miR-328, which is downregulated in chronic myelogenous leukaemia blast crisis (CML-BC).

The progression of CML from chronic phase to blast crisis is characterized by the inability of myeloid progenitors to differentiate into granulocytes. Such differentiation arrest is due to translational inhibition of the transcription factor CCAAT/enhancer binding protein-α (CEBPA). The heterogeneous nuclear ribonucleoprotein E2 (hnRNPE2; also known as PCBP2), which is induced by the oncogenic fusion protein breakpoint cluster region (BCR)-ABL1, binds a C-rich element in the 5′ UTR of *CEBPA* mRNA thereby inhibiting its translation. When Perrotti and colleagues compared miRNA expression profiles in myeloid progenitor cells from patients with CML in blast crisis and chronic phase, they found several differentially expressed miRNAs. Among these, reduced expression of miR-328 in CML-BC was the most intriguing, as this miRNA harbours a C-rich element resembling that of the *CEBPA* 5′ UTR. Using a combination of RNA immunoprecipitation, ultraviolet crosslinking and RNA electrophoretic mobility shift assays on cytoplasmic extracts from BCR-ABL1$^+$ myeloid precursor cells, the authors demonstrated that endogenous, ectopic and recombinant hnRNPE2 bind miR-328 more strongly than the 5′ UTR of *CEBPA*, and this interaction is independent of RISC components. Therefore, miR-328 seems to compete with *CEBPA* mRNA for binding hnRNPE2.

The authors proposed that by competing for hnRNPE2 binding, miR-328 expression influences myeloid cell differentiation. Indeed, it was shown, both *in vitro* and *in vivo*, that miR-328 expression drives myeloid cells to differentiate into granulocytes by releasing hnRNPE2 translational repression of *CEBPA*. Together, these results suggest that miR-328 regulates *CEBPA* expression by functioning as a molecular decoy: by harbouring the C-rich RNA-binding sequence for hnRNPE2, miR-328 can sequester this regulatory RNA-binding protein (RBP). Furthermore, the authors discovered that CEBPA directly binds the *miR-328* promoter, inducing its expression in myeloid progenitors. Therefore, it seems that inhibition of CEBPA leads to downregulated miR-328 expression in CML-BC.

Does miR-328 function solely as a decoy for hnRNPE2? The authors identified a putative interaction between miR-328 and the oncogene *PIM1*, which is known to increase the survival of BCR-ABL1-transformed CML-BC progenitors. By ectopically expressing *PIM1* and miR-328 in primary CML-BC progenitors, the authors found that miR-328 silences *PIM1* by interacting with its 3′ UTR. The action of miR-328 therefore seems to be twofold: it functions as an RBP decoy to block translational inhibition of CEBPA, and silences *PIM1* through the RISC pathway.

These results show how altered expression of miR-328 might influence CML disease progression. Moreover, these findings add further complexity to the mechanisms by which miRNAs could contribute to deregulated gene expression in cancer.

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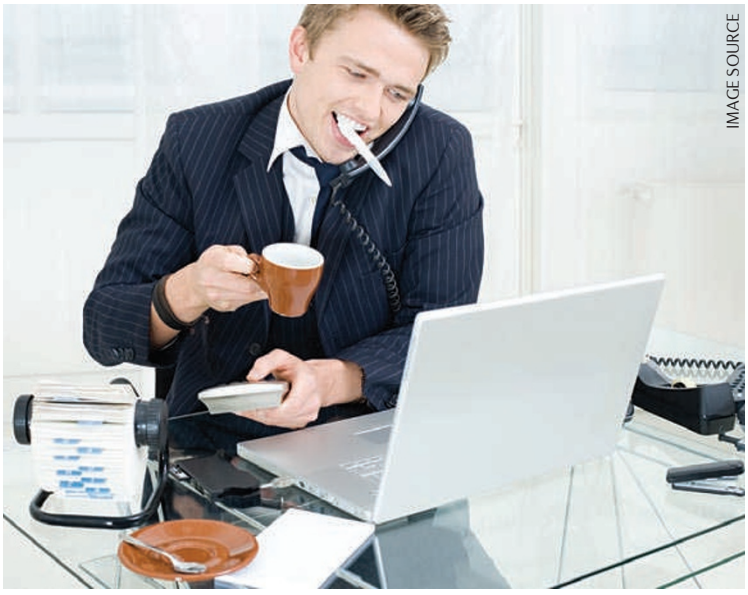
“These results show how altered expression of miR-328 might influence CML disease progression.”

ORIGINAL RESEARCH PAPER Eiring, A. M. *et al.* miR-328 functions as an RNA decoy to modulate hnRNP E2 regulation of mRNA translation in leukemic blasts. *Cell* **140**, 652–665 (2010)



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