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SMALL RNAS

Bound to silence

> "…ARS2 interacts with the Microprocessor complex…"

Precise control of small RNA levels is crucial to maintain normal cellular function. Two studies in *Cell* now identify arsenate resistance protein 2 (ARS2) as a new component of the nuclear RNA cap-binding complex (CBC) that stimulates microRNA (miRNA) processing and is crucial for cell proliferation in mammals and antiviral resistance in flies. These studies provide important new insights into the link between the RNA silencing machinery and general mRNA metabolism.

Gruber *et al.* knocked down ARS2 by RNA interference in mammalian cells and observed defects in proliferation. Furthermore, knockout of *Ars2* in adult mouse haematopoietic tissues (which are highly proliferative) causes bone marrow defects, whereas the liver and kidney (which comprise mainly non-proliferating cells) are unaffected. The authors identified nuclear cap-binding protein 1 (NCBP1; also known as CBP80), which assembles on 7mG-capped RNAs, in a screen for ARS2-interacting proteins and showed that ARS2 also interacts with NCBP2 (also known as CBP20) and 7mG-capped RNAs *in vitro*.

Genetic studies in plants previously showed that SERRATE (the homologue of ARS2) is involved in miRNA biogenesis, and plants deficient in SERRATE have similar defects to those observed in CBC mutants. In agreement with these observations, Gruber *et al.* showed that knockdown of ARS2 or CBP80 in proliferating mammalian cells reduces the levels of a subset of miRNAs that have been implicated in cellular transformation (for example, let-7) and disrupts let-7 miRNA-mediated repression of a reporter transcript. Furthermore, ARS2 binds to and stimulates the activity and fidelity of Drosha, a component of the Microprocessor complex that cleaves primary miRNA transcripts (pri-miRNAs) in the nucleus to generate pre-miRNAs.

By contrast, ARS2 does not bind to Dicer, which processes pre-miRNAs to generate mature miRNAs in the cytoplasm. Notably, ARS2 is selectively expressed in proliferating cells, which suggests that processing of a subset of pri-miRNAs correlates with proliferation.

Sabin *et al.* identified ARS2 in a screen for factors that mediate viral resistance in *Drosophila melanogaster*. Insects fight viral infection by targeting and degrading viral RNAs using small interfering RNAs (siRNAs), so the authors reasoned that ARS2 might be involved in this process. Indeed, ARS2 interacts with and modulates the activity of Dicer 2, which processes siRNA precursors to mature siRNAs in the cytoplasm, and loss of ARS2 in cells and flies increases their susceptibility to RNA viruses.

Knockdown of ARS2 in *D. melanogaster* also impairs miRNA-mediated silencing and reduces the levels of pri-miRNAs. Furthermore, ARS2 interacts with the Microprocessor complex in flies, as it does in mammals. These results suggest a conserved role for ARS2 in miRNA biogenesis. Notably, the interaction between ARS2 and the CBC is conserved in *D. melanogaster*, and cells depleted of CBP80 or CBP20 have defects in the small RNA silencing pathways. Furthermore, the CBC also has an important role in restricting viral infection. Whether other factors involved in general mRNA metabolism regulate RNA silencing remains to be investigated.

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ORIGINAL RESEARCH PAPERS Gruber, J. J. *et al.* Ars2 links the nuclear cap-binding complex to RNA interference and cell proliferation. *Cell* **138**, 328–339 (2009) | Sabin, L. R. *et al.* Ars2 regulates both miRNA- and siRNA-dependent silencing and suppresses RNA virus infection in *Drosophila*. *Cell* **138**, 340–351 (2009)

FURTHER READING Kim, V. N. *et al.* Biogenesis of small RNAs in animals. *Nature Rev. Mol. Cell Biol.* **10**, 126–139 (2009)