Nature Reviews Cancer | AOP, published online 16 May 2013; doi:10.1038/nrc3534

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MicroRNAs (miRNAs) are known to have pleiotropic effects during tumour development. Two recently published papers have found that the disruption of miRNA maturation might also contribute to cancer-related phenotypes.

Jia Shen and colleagues examined the relationship between miRNA regulation and the epidermal growth factor receptor (EGFR). EGFR is trafficked from the cell membrane through endocytic vesicles to lysosomes for degradation and is thought to be able to participate in signalling complexes when bound in endocytic vesicles. Shen and colleagues found that EGFR in vesicles can interact with argonaute 2 (AGO2), the catalytic component of the RNA-induced silencing complex (RISC). This interaction was specifically increased under hypoxic conditions, which was consistent with previous findings that EGFR expression levels are increased in hypoxic cells owing to prolonged retention in endocytic vesicles. EGFR present in late endosomes directly interacted with AGO2 in hypoxic cells, and this interaction was promoted by the constitutive expression of hypoxia inducible factor 1α (HIF1α) and HIF2α under normoxic conditions, and was further increased under hypoxic conditions.

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As AGO2 is a component of both RISC and the RISC-loading complex that cleaves precursor miRNA (pre-miRNAs) enabling their maturation, the authors examined miRNA levels in HeLa cells with and without EGFR expression under normoxic and hypoxic conditions. They found that a specific subset of precursor miRNAs was less efficiently processed to a mature form in hypoxic cells expressing EGFR. Tyr393 in AGO2 was shown to be directly phosphorylated by EGFR, and this resulted in the disruption of the interaction of AGO2 with Dicer, a core enzyme of the RISC-loading complex. Dicer has a processing preference for miRNAs that possess a long-loop precursor structure. Further experiments indicated that the reduced interaction between phosphorylated AGO2 and Dicer suppressed the maturation of long-looped miRNAs, such as miR-31, miR-192 and miR-193a-5p, which reduced their loading onto RISC and led to an increase in the levels of their target mRNAs.

What biological effects does this have? The authors found that AGO2 phosphorylation increased cell invasiveness and reduced apoptosis *in vitro*. Moreover, areas of hypoxia in both mouse and human breast tumours showed increased EGFR expression and AGO2 phosphorylation, and Tyr393-AGO2 phosphorylation was significantly correlated with poorer overall survival in patients with breast cancer.

Changes in miRNA maturation have also been implicated in the development of Perlman syndrome, a rare fetal overgrowth syndrome. The product of *LIN28*, a known oncogene, is involved in the uridylation of let-7 pre-miRNAs (pre-let-7). Uridylated pre-let-7 miRNAs are less able to interact with Dicer and are instead degraded by an unknown RNase, which Hao-Ming Chang and colleagues have identified as DIS3L2, a 3′–5′ exonuclease. *In vitro* biochemical assays showed that DIS3L2 activity is stimulated by oligonucleotide tails that have ten or more uridines present, consistent with pre-let7 miRNAs having 14 uridines in LIN28-expressing cells. Knockdown of DIS3L2 in mouse embryonic stem cells leads to the stabilization of pre-let-7 miRNAs. Patients with Perlman syndrome have a germline mutation in *DIS3L2*, and >60% of children with Perlman syndrome who survive infancy develop Wilms' tumours. Mutation of *DIS3L2* is also evident in approximately 30% of sporadic cases of Wilms' tumour. Further work is needed to understand why this mutation causes Perlman syndrome and Wilms' tumours and whether this is related to effects on the LIN28–let-7 pathway.

Both of these papers indicate that, in addition to mutations in *DICER1* and *AGO2* that affect miRNA processing directly, proteins upstream and downstream of miRNA processing might also be involved in tumour development.

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ORIGINAL RESEARCH PAPERS Shen, J. *et al.* EGFR modulates microRNA maturation in response to hypoxia through phosphorylation of AGO2. *Nature* 1 May 2013 (doi:10.1038/nature12080) | Chang, M.-H., Triboulet, R., Thornton, J. E. & Gregory, R. I. A role for the Perlman syndrome exonuclease Dis3l2 in the Lin28–let-7 pathway. *Nature* **497**, 244–248 (2013)