LUNG CANCER

A surprising competitor

Lara Crow/NPG

> the *Hmga2* RNA can contribute to lung cancer progression by functioning as a molecular sink to 'mop up' available let-7 miRNAs

The majority of patients with non-small-cell lung cancer (NSCLC) are diagnosed when the disease is at an advanced stage (metastatic). One protein-coding gene known to be involved in the progression of this disease is high mobility group AT-hook protein 2 (*HMGA2*). Julian Downward and colleagues have found that the *Hmga2* RNA also contributes to lung cancer development and progression in mice through its function as a competing endogenous RNA (ceRNA).

The *Hmga2* RNA contains let-7 microRNA (miRNA) binding sites in its 3′ untranslated region, indicating that *Hmga2* is regulated by this miRNA family. miRNAs often have several RNA targets, and the increased expression of one of these targets can alter the expression levels of the other targets by functioning as a 'molecular sink' (or ceRNA) for the miRNAs. Downward and colleagues investigated whether *Hmga2* can function as a ceRNA for the let-7 family. In order to differentiate between the protein and the RNA effects of HMGA2, the authors made a series of *Hmga2* mutants: a mutant in which all seven let-7 binding sites are mutated (m7), and so this mutant cannot bind to let-7 miRNAs but produces a functional protein; a mutant in which the ATG start codon is defective (ATG WT) and therefore produces no protein; and a double mutant (ATG m7), which produces no protein and an RNA that is unable to bind let-7 family members. Expression of these constructs in mouse lung adenocarcinoma cell lines showed that wild-type HMGA2 and ATG WT increased colony formation in soft agar, whereas the m7 mutant had less of an effect, despite high levels of protein expression, and the ATG m7 mutant had no effect, indicating that HMGA2 protein and RNA promote colony formation. Expression of wild-type HMGA2 and ATG WT also restored lung cancer development and metastasis in mice injected with lung adenocarcinoma cells expressing *Hmga2*-targeted short hairpin RNAs (shRNAs); the m7 mutant had less of an effect in promoting lung cancer growth. Expression of wild-type HMGA2 and the *Hmga2* mutants had no effect on the expression levels of let-7 miRNAs. Thus, these findings indicate that the *Hmga2* RNA can contribute to lung cancer progression by functioning as a molecular sink to 'mop up' available let-7 miRNAs.

Further investigation indicated that several RNAs are affected by *Hmga2* RNA expression and that these also contain let-7 binding sites. In particular, the authors found that the protein, and to a lesser extent, the RNA levels of transforming growth factor-β (TGFβ) receptor 3 (*Tgfbr3*) are regulated by *Hmga2* RNA. Expression of wild-type HMGA2 or ATG WT also increases TGFβ signalling in lung adenocarcinoma cells, and the increased expression of TGFBR3 probably contributes to this effect Indeed, depletion of *Tgfbr3* in cells expressing wild-type HMGA2 reduces both TGFβ signalling and colony formation in soft agar.

The authors also examined human NSCLC samples and found a correlation between the expression levels of *HMGA2* RNA and *TGFBR3* RNA.

Overall, these data indicate that, in addition to its protein functions, *Hmga2* ceRNA can compete with other RNAs that bind let-7 miRNA molecules, leading to an increase in the expression of some let-7 miRNA target RNAs. Whether *Hmga2* functions as a ceRNA in the other tumour types in which it is also abundantly expressed has yet to be determined. These findings also raise the possibility that other oncogenic proteins might promote tumour development through a ceRNA function.

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ORIGINAL RESEARCH PAPER Kumar, M. S. *et al.* HMGA2 functions as a competing endogenous RNA to promote lung cancer progression. *Nature* **505**, 212–217 (2014)