

# ARF Constrains the Harm of Non-Small-Cell Lung Cancers on Health

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Non-small-cell lung carcinoma (NSCLC) is a devastating illness. Approximately 85% of lung cancers are NSCLCs, and the 5-year mortality rate ranges from 51-99% depending on the stage of diagnosis (for more information, visit the website of the [American Cancer Society](#)). Lung adenocarcinomas are common in NSCLC, and genetic analyses have revealed frequent genetic alterations at multiple loci including the oncogene *KRAS* and tumor suppressors *TP53* and *CDKN2A*. *TP53* encodes the important tumor suppressor p53, but the *CDKN2A* locus contains two genes, *INK4a* and *ARF*, each of which has been implicated in suppressing NSCLC to various degrees. However, the direct contribution of ARF to cancer cell growth control has remained enigmatic and controversial. A new study led by Dr. Kemp (Division of Human Biology) suggests that ARF plays a key role in suppressing multiple aspects of NSCLC growth and malignant progression.

The authors used a carcinogen-induced mouse model (urethane exposure) to ascertain the consequence of ARF deletion on cancer progression. *Arf*<sup>-/-</sup> mice treated with urethane had shortened life spans and increased lung tumor-associated morbidity compared to control mice (*Arf*<sup>+/+</sup> or *Arf*<sup>+/-</sup>), suggesting a critical tumor suppressive function for ARF. The lung tumors in *Arf*<sup>-/-</sup> mice were of abnormal size (4-17 mm in diameter) compared to the tumors in control animals (rarely exceeding 3 mm in diameter). The researchers also found that ARF deficiency increased the tumor burden induced by urethane exposure. The tumors in control animals exposed to urethane were mainly pulmonary adenomas, but *Arf*<sup>-/-</sup> mice had adenocarcinomas that invaded adjacent tissues and airways (see figure). Strikingly, *Arf*<sup>-/-</sup> mice also had tumors that were de-differentiated and often displayed histopathological characteristics common to pulmonary sarcomatoid carcinoma, ***an aggressive and metastatic tumor type that had not previously been seen in mice.***

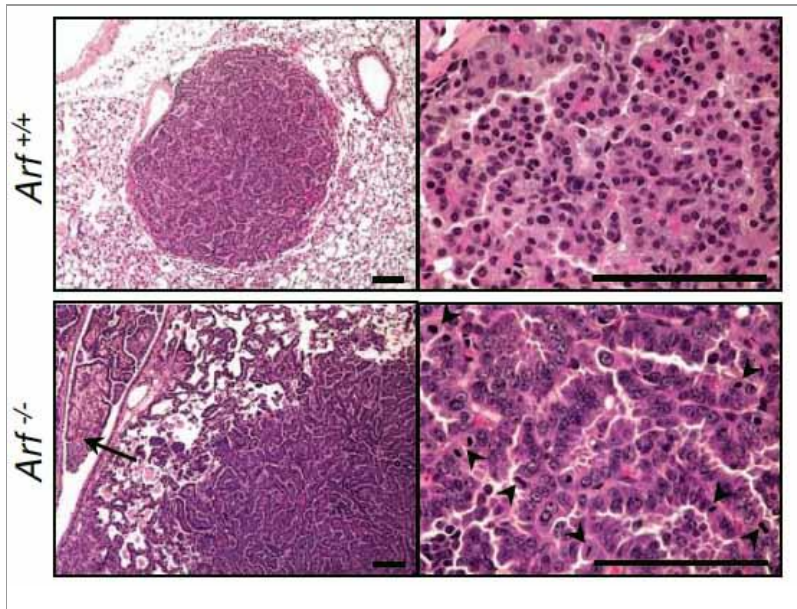
Busch *et al.* saw an increase in mitotic cells in *Arf*<sup>-/-</sup> tumors, suggesting that ARF normally inhibits cancer cell proliferation. These cells also displayed hallmarks of DNA damage. Moreover, *Arf*<sup>-/-</sup>

tumors displayed evidence of hyperactive oncogenic KRAS signaling and cyclin D1 upregulation, both of which have been shown to promote cell proliferation.

Perhaps the most controversial aspect regarding ARF's role in cancer is the question of timing, and at which point does ARF function have the greatest role in inhibiting cancer progression. Busch and colleagues found that ARF was highly expressed in early-stage adenomas but had minimal expression in malignant adenocarcinomas from *Arf*<sup>+/+</sup> urethane-treated animals. This indicated that the early cellular response to urethane treatment induced the expression of ARF to restrain cancer cell growth. The authors also explored a link between ARF and p53 tumor suppression. ARF expression coincided with that of p21, a p53 transcriptional target whose expression halts cell cycle entry. Moreover, the expression of p53 transcriptional targets was decreased in *Arf*<sup>-/-</sup> tumors, indicating that ARF functions through canonical p53 signaling pathways to inhibit cancer progression.

The new manuscript published by the Kemp group reveals that *Arf* loss facilitates the malignant progression of neoplasia originating in the lung. In human cancers, silencing of the entire *CDKN2A* locus is common, although selective silencing of *ARF* has also been documented. The sarcomatoid-like tumors found in *Arf*<sup>-/-</sup> animals suggest that ARF may suppress cancer cell de-differentiation, although its precise role in the process remains to be elucidated. Moreover, the contribution of *Arf* to p53 signaling needs to be further investigated. Clearly, the model system set up by the authors will continue to clarify the many roles that ARF plays in tumor suppression.

[Busch SE, Moser RD, Gurley KE, Kelly-Spratt KS, Liggitt HD, Kemp CJ](#). 2013. ARF inhibits the growth and malignant progression of non-small-cell lung carcinoma. *Oncogene* doi: 10.1038/onc.2013.208.



*Image obtained from the manuscript*

Arf<sup>+/+</sup> mice treated with urethane developed adenomas that had discrete borders and were uniform in appearance, rarely containing cells undergoing mitosis. In stark contrast, Arf<sup>-/-</sup> mice developed adenocarcinomas that displayed invasion (arrow) and mitotic figures (arrowheads).