



New exciting possibilities for the development of precision medicine therapies to restore the expression of the *INK4/ARF* locus

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Provenance: This is an invited Letter to the Editor commissioned by Editor-in-Chief Xi-Hua Liu, MD (Chinese Research Hospital Association, Beijing, China).

Response to: Fang M. The mechanisms of INK4-ARF inactivation. *Ann Res Hosp* 2017;1:21.

Received: 27 July 2017; Accepted: 31 July 2017; Published: 08 August 2017.

doi: 10.21037/arh.2017.08.04

View this article at: <http://dx.doi.org/10.21037/arh.2017.08.04>

Loss of expression of the genes encoded in the *INK4/ARF* locus (*p14^{ARF}*, *p15^{INK4B}* and *p16^{INK4A}*) is a common event in human cancers (1). Recent publications shed light on the mechanisms involved in the *INK4/ARF* locus silencing, which opens an exciting window for the design of new therapeutic strategies for cancer patients.

As recently reviewed by Minggang Fang in *Annals of Research Hospitals*, several mechanisms account for silencing of the *INK4/ARF* locus in the context of cancer cells. Besides somatic deletions of the genes encoded in this locus, the entire locus is frequently subdued by epigenetic repression. Loss of the expression of the *INK4/ARF* locus results from aberrant DNA hypermethylation. This has been demonstrated for some patients with KRAS-driven colorectal cancer, where upregulation of the transcriptional repressor ZNF304 recruits co-repressor proteins to the promoter of the *INK4/ARF* encoded genes, leading to promoter hypermethylation and transcriptional silencing (2). Importantly, Serra and co-authors demonstrated that in colorectal cancer KRAS increases ZNF304 protein levels, triggering promoter hypermethylation and thereby initiating oncogenesis.

Another KRAS-driven cancer that frequently presents with loss of *INK4/ARF* gene expression is Non-Small Cell Lung Cancer (NSCLC) (3). Since inactivation of the *INK4/*

ARF locus in NSCLC patients is frequently due to promoter hypermethylation, it will be pertinent to explore if these patients present high levels of ZNF304, as demonstrated in colorectal cancer patients. In this context, we recently published an alternative mechanism for the silencing of the *INK4/ARF* locus in NSCLC patients, independent of promoter hypermethylation. This mechanism involves the E3 ligase and transcription co-factor E6AP (E6-Associated Protein, encoded by the *UBE3A* gene) (4). We demonstrated that in normal cells, E6AP restricts the abundance of CDC6, a key negative regulator of the *INK4/ARF* locus, resulting in high expression of the tumour suppressor genes encoded in the *INK4/ARF* locus. Loss of E6AP expression results in high levels of CDC6 and repression of the *INK4/ARF* locus, which is tumorigenic in lung. Importantly, we were able to identify a subset of KRAS-positive NSCLC patients with a E6AP-low/CDC6-high/*p16^{INK4a}*-low expression profile that showed low frequency of *p16^{INK4a}* promoter hypermethylation. The clinical relevance of this novel regulatory pathway is supported by the observation that this cohort of patients presented with the worst overall survival, indicating the potential prognostic value for the E6AP-low/CDC6-high/*p16^{INK4a}*-low expression profile.

These newly identified pathways not only have prognostic value but also provide attractive opportunities to explore new therapeutic options. Generic epigenetic-based

therapies (i.e., DNA demethylating agents and histone deacetylase inhibitors) have shown promising results in pre-clinical models as well as in some cancers (5). However, the use of non-selective drugs is frequently associated with a broad spectrum of adverse effects. The inhibition of specific components of pathways, such as the ones described by Serra *et al.* and by us, is likely to provide more selective therapeutic options.

For those NSCLC patients with E6AP-low/CDC6-high/p16^{INK4a}-low expression profile, one exciting therapeutic possibility is to restore p16^{INK4a} expression and tumour suppression by reducing CDC6 abundance. Recently published data demonstrated that CDC6 induction and the consequent repression of the *INK4/ARF* locus, is stimulated by the histone acetyl-transferase, MOZ (6). This opens the opportunity to design novel therapies to restore the expression of the tumour suppressor genes encoded in the *INK4/ARF* locus by targeting MOZ activity. Small molecule inhibitors of MOZ have now been developed (7) and their therapeutic potential in the treatment of cancer is currently being assessed.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

doi: 10.21037/arh.2017.08.04

Cite this article as: Gamell C, Haupt S, Haupt Y. New exciting possibilities for the development of precision medicine therapies to restore the expression of the *INK4/ARF* locus. *Ann Res Hosp* 2017;1:32.

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References

1. Kim WY, Sharpless NE. The regulation of INK4/ARF in cancer and aging. *Cell* 2006;127:265-75.
2. Serra RW, Fang M, Park SM, et al. A KRAS-directed transcriptional silencing pathway that mediates the CpG island methylator phenotype. *Elife* 2014;3:e02313.
3. Sterlacci W, Tzankov A, Veits L, et al. A comprehensive analysis of p16 expression, gene status, and promoter hypermethylation in surgically resected non-small cell lung carcinomas. *J Thorac Oncol* 2011;6:1649-57.
4. Gamell C, Gulati T, Levav-Cohen Y, et al. Reduced abundance of the E3 ubiquitin ligase E6AP contributes to decreased expression of the INK4/ARF locus in non-small cell lung cancer. *Sci Signal* 2017;10.
5. Kelly TK, De Carvalho DD, Jones PA. Epigenetic modifications as therapeutic targets. *Nat Biotechnol* 2010;28:1069-78.
6. Sheikh BN, Phipson B, El-Saafin F, et al. MOZ (MYST3, KAT6A) inhibits senescence via the ^{INK4A}-ARF pathway. *Oncogene* 2015;34:5807-20.
7. Falk H, Connor T, Yang H, et al. An efficient high-throughput screening method for MYST family acetyltransferases, a new class of epigenetic drug targets. *J Biomol Screen* 2011;16:1196-205.