Editorial

The mechanisms of *INK4-ARF* inactivation

Minggang Fang[1,2]

[1]Howard Hughes Medical Institute, [2]Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School, Worcester, MA 01605, USA

Correspondence to: Minggang Fang. Howard Hughes Medical Institute, University of Massachusetts Medical School, Worcester, MA 01605, USA. Email: minggang.fang@umassmed.edu.

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Inactivation of the *INK4-ARF* locus is one of the most frequent events in cancers. The mechanistic basis of epigenetic silencing was not well understood. Recently Gamell *et al.* found a novel mechanism, in which loss of an E3 ubiquitin ligase E6AP results in the silencing of *INK4-ARF* locus through E2F-CDC6 pathway.

Cancer is the disease caused by mutations to genes which results in gain of function of oncogene and loss of function of tumor suppressor gene, allowing cells to multiply in an out of control manner. Three well-known tumor suppressors: $p14^{ARF}$, $p16^{INK4A}$ (also known as *CDKN2A*), and $p15^{INK4B}$ (also known as *CDKN2B*) are located in close proximity to one another (within a 35 kb region) at the *INK4-ARF* locus, yet each is transcribed from a distinct promoter. Interestingly, $p14^{ARF}$ and $p16^{INK4A}$ share exons two and three, but each is translated in a different reading frame, yielding unrelated polypeptides. Inactivation of the *INK4-ARF* locus is one of the most frequent events in cancers (1). It is well established that in many cancers specific genes affecting cellular growth control are hypermethylated and transcriptionally silenced (2,3). Besides of the somatic mutation, the loss of expression of *INK4-ARF* due to epigenetic alteration often contributes to the initiation and progression of cancers. However, the mechanistic basis of epigenetic silencing was not understood. Through an RNA interference (RNAi) screen, Serra, Fang *et al.* have identified an oncogene directed transcriptional repression pathway for the silencing of *INK4-ARF* locus in colorectal cancer (4). The pathway is initiated on DNA by binding of the transcriptional repressor, ZNF304, which recruits a corepressor complex that includes SETDB1, KAP1 and DNMT1, leading to promoter hypermethylation and transcriptional silencing. Activated KRAS regulates the pathway by maintaining high levels of ZNF304, which drives DNA binding.

In a newly published study, an alternative mechanism has been found for the silencing of the *INK4-ARF* locus involving the E3 ubiquitin ligase and transcriptional cofactor E6AP (also known as UBE3A) (5). In a healthy lung tissue, E6AP induced the expression of the *INK4-ARF* locus at the transcriptional level by inhibiting *CDC6* transcription, a gene encoding a key repressor of the locus in non-small cell lung cancer (NSCLC). In cancer cells, low or lost expression of *E6AP* results in high abundance of CDC6, which represses the *INK4-ARF* locus and therefore results in low amounts of *p16INK4a*, which is tumorigenic in the lung. Loss of *p16INK4a* or increased *CDC6* expression in NSCLC patients is linked to poor prognosis of NSCLC patients. Gamell *et al.* indicate novel opportunities to therapeutically restore tumor suppression by p16INK4a in NSCLC with the E6AP-low/CDC6-high/p16INK4a-low expression profile.

In summary, the inactivation of *INK4-ARF* locus is explained in three mechanisms (*Figure 1*): genetic deletion due to its localization in a common chromosome fragile site FRA9G (6), promoter hypermethylation and transcription silencing by KRAS-ZNF304-DNMT1 pathway (4), transcriptional silencing through low E6AP-high CDC6 axis in a methylation free manner (5).

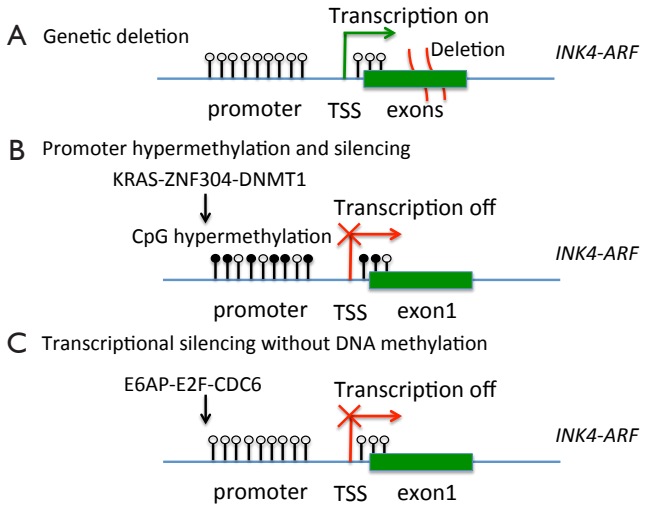

Figure 1 Three mechanisms for the inactivation of INK4-ARF locus. (A) The frequent genetic deletion of *INK4-ARF* genes; (B) activated oncogene KRAS stabilizes ZNF304, which drives binding of DNMT1 and its corepressor for the hypermethylation of promoter and silencing of *INK4-ARF*; (C) loss of E6AP leads to accumulation of repressor CDC6, which inhibits the transcription of *INK4-ARF* without promoter methylation.

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Footnote

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