Review

UHN Microarray Centre

Gene silencing by polycomb-based histone modification is independent of promoter DNA methylation

Review of: Kondo Y, Shen L, Cheng AS, Ahmed S, Boumber Y, Charo C, Yamochi T, Urano T, Furukawa K, Kwabi-Addo B, Gold DL, SekidoY, Huang THM, Issa JPJ. Gene silencing in cancer by histone H3 lysine 27 trimethylation independent of promoter DNA methylation. Nature Genetics, 2008, 40(6):741

Two epigenetic systems involved in the repression of gene activity are Polycomb group (PcG) proteins and DNA methylation[1]. A PcG protein, namely enhancer of zeste 2 (EZH2), is a member of the polycomb repressor complex 2 (PRC2) that methylates histone H3 lysine 27[2]. Polycomb-based histone H3 lysine 27 trimethylation (H3K27triM) is one of at least two histone modifications that mediate epigenetic silencing in cancer cells[3]. H3K27triM serves as a signal for the binding of another polycomb repressor complex, PRC1, which blocks the recruitment of transcriptional activation factors and prevents the initiation of transcription[4]. The relationship between DNA hypermethylation and histone modifications, like H3K27triM, is not completely understood.

Prior to the publication of the study by Kondo and colleagues, it was thought that PcG-mediated methylation of H3K27 and *de novo* DNA methylation in cancers were linked[5-7]. Vire *et al*. suggest EZH2 controls CpG methylation through direct physical contact with DNA methyltransferases[6] and Schlesinger *et al*. used chromatin immunoprecipitation (ChIP) analysis to show that methylated genes in cancer cells are associated with nucleosomes containing H3K27triM[7].

In contrast, this study by Kondo *et al*. suggests that tumor-suppressor gene silencing in cancer by EZH2-mediated H3K27triM is mechanistically distinct from DNA methylation-associated silencing. Using ChIP coupled with CpG promoter arrays from the UHN Microarray Centre, this study compared prostate cancer cells to normal prostate and found that up to 5% of the genes on the CpG promoter array were silenced in cancer cells by H3K27triM independent of DNA methylation. The global assessment of H3K27 modifications using CpG arrays was performed to find H3K27triM gene targets and 12 genes were found. To determine whether this enrichment at H3K27triM of these genes was a cancer-specific silencing event, Kondo *et al*. studied normal (non-cancer) cells and found that these 12 genes showed no or much less enrichment for H3K27triM. This data suggests that, for many genes, H3K27triM is used by cancer cells to silence genes that should be active in normal cells. The global assessment of H3K27 modifications by promoter array was also performed. Of the 200 genes most significantly bound to H3K27triM, 16% had CpG islands and 84% did not, suggesting that H3K27triM-mediated silencing mechanism tends to target non-CpG island promoters.

This study presents several lines of evidence that support the independence of H3K27triM and DNA methylation including: H3K27triM targets show no or low DNA methylation in their promoters (with a few exceptions); the inhibition of EZH2, the main methyltransferase responsible for H3K27triM, reduces H3K27triM, suppresses clonogenicity, and reactivates hundreds of genes including genes silenced by H3K27triM, but has no effect on silencing by DNA methylation; and transfection of one of the H3K27triM targets (RARβ2) into the cells led to rapid and stable silencing, accompanied by H3K27triM but no or minimal DNA methylation[8].

This research contradicts previous reports that PcG proteins and DNA methylation systems are mechanistically linked silencing pathways[6,7]. These contradictions may be explained by tissue- and cancer-specific differences related to the activation of specific silencing pathways. Future research in gene silencing mechanisms will need to investigate why DNA methylation in cancer affects some silenced PcG targets but not others and why there is variability between different cancers[8]. This study further adds to

the complexity of epigenetic dysregulation in cancer and establishes H3K27triM-mediated silencing as a promising therapeutic target[8].

References

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