Nature Reviews Urology | Published online 28 Nov 2017; doi:10.1038/nrurol.2017.202

PROSTATE CANCER

H2A.Zac activates neo-enhancers

Laurence Mouton/PhotoAlto/Getty

A new study shows that nucleosomes containing acetylated histone H2A.Z (H2A.Zac) are redistributed to new ectopic enhancers (neo-enhancers) in prostate cancer, leading to increased chromatin accessibility and activation of androgen receptor (AR)-associated enhancers.

"We previously reported that H2A.Z acetylation occurs at active promoters and is associated with oncogene activation in prostate cancer," explains senior author Susan Clark from the Garvan Insitute of Medical Research in Sydney, Australia. "However, the role of H2A.Zac in enhancer functions and during AR signalling remained unclear."

The team showed that increased levels of H2A.Zac were associated with reduced patient survival and increased tumour stage. Using normal (PrEC) and malignant (LNCaP and VCaP) prostate cell lines, the researchers found that H2A.Zac was present at more active enhancers in LNCaP and VCaP than in PrEC. Furthermore, H2A.Zac nucleosome occupancy was increased at active enhancers, indicating that H2A.Z acetylation was important in generating prostate cancer neo-enhancers. Changes in H2A.Zac nucleosome occupancy were also linked to changes in enhancer chromatin state. Investigation of gene expression showed that neo-enhancers activated by H2A.Zac redistribution in prostate cancer cells were linked to oncogenic pathways, whereas expression of tumour suppressor genes was lost. In addition, gain of H2A.Zac was associated with increased chromatin accessibility and reduced DNA methylation.

The team then tested the effect of dihydrotestosterone treatment (DHTt) on chromatin dynamics at AR sites, finding that DHTt resulted in redistributions of H2A.Zac nucleosomes from across AR binding sites to their flanks. Already low levels of DNA methylation of AR sites did not change with DHTt, but enhancers with H2A.Zac became more accessible than those without. Finally, the team showed that AR enhancers with H2A.Zac were more functionally active and that H2A.Zac facilitated AR-dependent enhancer RNA transcription.

"Our study has implications for mechanisms of oncogene deregulation and potential chromatin therapy options in prostate cancer," summarizes Clark. "We propose that during transformation H2A.Zac-occupied nucleosomes are involved in the formation of new regulatory elements. These nucleosomes favour the formation of nucleosome-depleted regions and DNA hypomethylation at enhancers and promoters, priming these new sites for gene transcription upon androgen stimulation."

Clemens Thoma

ORIGINAL ARTICLE Valdés-Mora, F. *et al.* Acetylated histone variant H2A.Z is involved in the activation of neo-enhancers in prostate cancer. *Nat. Commun.* **8**, 1346 (2017)