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PROSTATE CANCER

Antagonizing AR: MYC affects transcription

New data, published in *EBioMedicine*, suggest that c-MYC (MYC) and the androgen receptor (AR) act antagonistically in prostate cancer and that MYC overexpression deregulates the AR transcriptional programme. Understanding this relationship is important for contextualizing biomarkers and therapeutic targets and selecting the optimal course of treatment for men with this disease.

MYC is commonly upregulated in prostate cancer, but its effect on AR activity is poorly understood. Thus, Barfeld and colleagues investigated the relationship between these two transcription factors in this disease. Treatment of hormone-deprived LNCaP and VCaP cells with synthetic androgen reduced MYC RNA and protein levels, suggesting an antagonistic relationship with AR. Treatment of LNCaP cells that stably express inducible MYC with doxycycline increased MYC RNA and protein expression, and induced androgen-independent growth in steroid-deprived conditions. However, MYC overexpression did not confer a growth advantage on cells growing in the presence of androgens.

ChIP-exo analysis of AR and MYC revealed overlapping binding patterns and co-occupation of approximately one-third of chromatin binding sites. This investigation also suggested that AR and MYC could share a common pioneer factor in prostate cancer cells; however, no evidence of direct interaction between the two transcription factors was observed.

Overexpression of MYC had considerable effects on the H3K27me3 and H3K4me1 histone marks and also increased DNA damage in prostate cancer cells. Overlapping histone mark sites between AR and MYC exhibited enhancer characteristics, similar to those of pure AR binding sites, indicating that these transcription factors co-occupy enhancers.

MYC overexpression repressed the expression of genes traditionally associated with AR-mediated transcriptional pathways and also had an antagonistic effect on prostate cancer biomarkers, including PSA and GNMT. Furthermore, levels of sarcosine (a metabolite of GNMT and a marker of aggressiveness and invasiveness in prostate cancer) were reduced. Moreover, an inverse relationship between MYC and PSA and GNMT staining was observed in castration-resistant prostate cancer samples.

These data suggest that an antagonistic relationship exists between MYC and AR in prostate cancer and show that MYC overexpression deregulates the AR transcriptional programme. Understanding the inverse relationship between the expression of MYC and prostate cancer biomarkers is important and could help guide treatment choice for men with this disease.

Louise Stone

> “Overexpression of MYC had considerable effects on … H3K27me3 and H3K4me1”

ORIGINAL ARTICLE Barfeld, S. J. *et al.* c-Myc antagonises the transcriptional activity of the androgen receptor in prostate cancer affecting key gene networks. *EBioMedicine* http://dx.doi.org/10.1016/j.ebiom.2017.04.006 (2017)