GENETICS

ZBTB7A suppresses castration-resistant prostate cancer

Possible mechanisms underlying the development of castration-resistant prostate cancer have been identified, with a key culprit being the gene *ZBTB7A*.

ZBTB7A is a known transcription factor that has been shown to be highly expressed in non-Hodgkin lymphoma, repressing the tumour-suppressor gene *ARF*. In this context, as well as in non-small-cell lung, breast and ovarian cancers, *ZBTB7A* acts as a proto-oncogene. To explore the role of this gene in prostate cancer, Pier Paolo Pandolfi and his team of researchers generated a transgenic mouse model that overexpresses *ZBTB7A* in the prostate. To their surprise, the overexpression failed to result in neoplastic transformation.

Instead, highly penetrant adenocarcinomas were observed in mice with inactivated *ZBTB7A* and *PTEN*, loss of which is a known driver of prostate cancer. In fact, *ZBTB7A* inactivation accelerated tumorigenesis driven by *PTEN* loss. Furthermore, the *ZBTB7A* protein interacts

with Sox9 to antagonize its transcriptional activity on genes such as *MIA*, which is involved in tumour cell invasion. Thus, *ZBTB7A* is oncosuppressive in *PTEN*-null tumours of the prostate.

“...stratification of patients by *ZBTB7A* and *PTEN* status might be informative”

The researchers then went on to explore the clinical implications of these findings, and showed that castration of *PTEN*-null mice led to the induction of apoptosis and proliferation blockade and initial tumour shrinkage. However, this favourable response was bypassed in *PTEN*-null, *ZBTB7A*-null animals, leading to the development of castration resistance.

Analysis of samples from patients with prostate cancer revealed that men whose tumours had high levels of *ZBTB7A*-null cells responded poorly to androgen-deprivation therapy (ADT).

By contrast, *PTEN* loss alone could not differentiate poor responders from favourable responders, which suggests that stratification of patients by *ZBTB7A* and *PTEN* status might be informative.

Furthermore, the mechanism of *ZBTB7A* loss in triggering resistance to ADT might be mediated via the downregulation of *XAF1* and upregulation of *SRD5A1*, a pattern that was demonstrated in the mouse and human tissue studies. These biomarkers might be valuable diagnostic and prognostic tools as well as therapeutic targets—indeed, therapy targeting this mechanism in mouse models was effective *in vivo*.

Mina Razzak

Original articles Wang, G. *et al.* *Zbtb7a* suppresses prostate cancer through repression of a Sox9-dependent pathway for cellular senescence bypass and tumor invasion. *Nat. Genet.* doi:10.1038/ng.2654 | Lunardi, A. *et al.* A co-clinical approach identifies mechanism and potential therapies for androgen deprivation resistance in prostate cancer. *Nat. Genet.* doi:10.1038/ng.2650