Nature Reviews Urology | Published online 25 Oct 2016; doi:10.1038/nrurol.2016.220

sergunt/iStock/Getty

Androgen receptor splice variant 7 (AR-V7) can be isolated from exosomal RNA in the bloodstream, with the potential to be used as a new prognostic test, according to a recent study published in *European Urology*.

The constitutively active AR-V7 lacks a ligand-binding domain (LBD) and is associated with resistance to hormonal prostate cancer therapies, in particular enzalutamide (which binds to the LBD on the wild-type receptor) and abiraterone. A validated marker for determining resistance to these second-line therapies would be extremely useful for treatment planning and prognostication, as the currently available biomarkers, such as PSA, are poor. "The AR-V7 analysis developed on RNA extracted from plasma-derived exosomes could represent a sensitive, easy-to-perform, and fast laboratory approach to screen patients," corresponding author Marzia Del Re told *Nature Reviews Urology*.

Del Re and colleagues developed a new approach to isolating AR-V7 from circulating exosomal RNA in order to confirm its role as a marker of therapeutic resistance.

VCaP cells, which are known carriers of AR-V7, were used to develop the AR-V7 RNA isolation digital droplet PCR (ddPCR) method. Once the ddPCR method was finalized and the sensitivity assessed, 36 patients with metastatic castration-resistant prostate cancer (mCRPC) were enrolled, who donated 3 ml blood before enzalutamide or abiraterone therapy was commenced. A further sample was taken at disease progression. Exosomes were isolated from the blood samples and the RNA was then extracted.

The AR-V7 transcript was detectable, even at low levels (2 copies/ml) using the ddPCR platform. 14 of the 36 patients were AR-V7$^+$ at baseline, before hormonal therapy was started. Of these, seven had a sample also taken at disease progression, which showed a nonsignificant increase in AR-V7 levels. Progression-free survival, measured by either clinical or radiographic progression, was longer in AR-V7$^-$ patients than AR-V7$^+$ patients (20 months versus 3 months; $P<0.001$), in whom overall survival was significantly shorter (8 months versus not reached; $P<0.001$), suggesting that exosomal AR-V7 is a valuable resistance marker. AR-V7$^+$ patients were more likely to be younger, have a tumour Gleason Score >8, visceral metastases, increased PSA, and have received prior docetaxel, than those who were AR-V7$^-$. "The findings suggest that plasma-derived exosomal RNA is a reliable source of AR-V7 and that ddPCR can sensitively detect it," commented Del Re. "Moreover, our data confirmed that resistance to hormonal therapy can be predicted by AR-V7, making it a clinically relevant biomarker."

The AR-V7 test is already available in Del Re's laboratory for patients who have progressed under hormonal therapy, with a very short turnaround time. They now plan to analyse additional mechanisms of resistance — that is, other common androgen receptor splice variants — to better understand tumour heterogeneity and progression towards refractoriness to hormonal manipulation.

Annette Fenner

ORIGINAL ARTICLE Del Re, M. *et al.* The detection of androgen receptor splice variant 7 in plasma-derived exosomal RNA strongly predicts resistance to hormonal therapy in metastatic prostate cancer patients. *Eur. Urol.* http://dx.doi.org/10.1016/j.eururo.2016.08.012 (2016)