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PROSTATE CANCER

WNT SIGNALLING INDUCES RESISTANCE

The development of resistance to androgen-receptor (AR) targeting therapies is a major challenge to the effective treatment of patients with metastatic prostate cancer. Now, research published in *Science* shows that activation of noncanonical Wnt signalling in single circulating tumour cells (CTCs) from patients with prostate cancer correlates with reduced effectiveness of antiandrogen treatment.

On the reasons for studying CTCs, first author David Miyamoto explains: "Drug resistance mechanisms in metastatic prostate cancer are difficult to study owing to the predominance of bone metastases, which are challenging to biopsy;" thus, "CTCs in the blood represent a readily accessible source of tumour cells."

In this study, single-cell RNA sequencing profiles of a total of 77 intact CTCs, from 13 different patients with metastatic, castration-resistant prostate cancer were established. A total of 711 genes were found to be highly expressed in CTCs compared with primary tumour material.

60 CTCs were found to express the AR and a considerable degree of intratumour heterogeneity was observed in terms of the splice variants expressed. Interestingly, significant enrichment of noncanonical Wnt signalling was observed in CTCs from patients whose prostate cancer progressed in the presence of enzalutamide, particularly among CTCs with reduced glucocorticoid receptor expression.

The effects of Wnt signalling were then tested *in vitro*. Ectopic expression of a range of Wnt proteins in androgen-sensitive prostate cancer cells was found to enhance cell survival in the presence of enzalutamide, with Wnt5a found to be particularly effective in this regard.

In conclusion, considerable heterogeneity in RNA expression exists between individual CTCs, even among those from the same patient. Miyamoto adds "We also found significant enrichment of the noncanonical Wnt signalling pathway in CTCs from patients with resistance to the potent antiandrogen enzalutamide."

When asked about the potential of this research, Miyamoto concludes: "If our findings are confirmed, the noncanonical Wnt signalling pathway might serve as a potential new target in prostate cancers that are resistant to antiandrogen therapy."

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Original article Miyamoto, D. T. *et al.* RNA-Seq of single prostate CTCs implicates noncanonical Wnt signaling in antiandrogen resistance. *Science* **349**, 1351–1356 (2015)