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Genomic comparison of prostate cancer cells eradicated by and resistant to treatment

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An international team led by researchers from Tampere University and the University of Eastern Finland has discovered how comparing genomic changes in cancer cells that are eradicated by and resistant to

treatment can be used to identify molecular targets for prostate cancer therapy.

The study "Subclone eradication analysis identifies targets for enhanced cancer therapy and reveals L1 retrotransposition as a dynamic source of cancer heterogeneity" was led by Academy Research Fellow Kirsi Ketola from the Institute of Biomedicine and UEF CANCER Research Community, University of Eastern Finland, and Professor Steven Bova from Tampere University. In the study, the researchers introduce Differential Subclone Eradication and Resistance Analysis (DSER), an approach developed to identify molecular targets for improved therapy in prostate cancer.

The method performs a direct comparison of genomic features of eradicated and resistant cancer cells in pre- and post-treatment samples from a patient. The study utilized a single patient with metastatic prostate cancer, "A34," to demonstrate the utility and potential of the DSER method.

Patient A34 was studied previously by Professor Bova and his team in their work in *Nature Communications* in 2020 (Woodcock et al.) and is the first demonstrated case of cancer cell eradication due to treatment in a solid tumor.

"Performing DSER in case A34 led us to discover changes in the DNA repair genes FANCI and EYA4 in his eradicated cancer cells that may have sensitized them to chemotherapy," Professor Bova describes.

"In the future, using drugs targeting genes identified using DSER could help ensure that all cancer cells in a patient remain susceptible to therapy."

One of the genes identified using DSER, EYA4, was associated with an

adjacent LINE-1 (L1) transposon insertion during the cancer evolution of A34, which raised questions surrounding the role of therapy in L1 activation. The team utilized prostate cancer cell lines to investigate whether androgen-deprivation and chemotherapy treatments could be responsible for activating L1s and thereby contributing to the eradication or resistance of cancer cells to treatment.

"We were fascinated to find that both carboplatin and enzalutamide turned on L1 transposon machinery in LNCaP and VCaP but not in PC-3 and 22Rv1 prostate cancer cell lines," says Dr. Ketola.

"The L1 activation in LNCaP and VCaP could be further inhibited by the antiretroviral drug azidothymidine, which tells us that existing drugs can be used to manipulate L1 activity in vitro."

Additionally, the researchers also found evidence of L1 activation in other tumor samples, such as in post-castration patient-derived xenograft models and in post-chemotherapy head and neck cancer cells. This suggests that L1 activation in response to treatment extends to clinical patient samples, although further studies are needed to determine to what extent this is the case.

The study demonstrates that the DSER approach provides an informative intermediate step toward effective precision cancer medicine and should be tested in future studies, especially those including dramatic but temporary metastatic tumor regression. L1 transposon activation may be a modifiable source of cancer genomic heterogeneity, suggesting the potential of leveraging newly discovered triggers and blockers of L1 activity to overcome therapy resistance.

More information: Kirsi Ketola et al, Subclone Eradication Analysis Identifies Targets for Enhanced Cancer Therapy and Reveals L1 Retrotransposition as a Dynamic Source of Cancer Heterogeneity,

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