PROSTATE CANCER TRANSDIFFERENTIATE TO PREVAIL

New *in vitro* and *in silico* data published in *Cancer Research* demonstrate that long-term androgen deprivation causes human prostate cancer cells to transdifferentiate into nonmalignant neuroendocrine-like (NEL) cells that sustain the growth of castration-resistant tumour cells.

Neuroendocrine differentiation is known to assist in the development of prostate adenocarcinomas and has been correlated to poor prognosis, but the exact mechanism of this process has not been fully elucidated. “We designed our study to investigate a possibly more human-like model of androgen resistance than permitted by classical protocols of neuroendocrine differentiation,” explains corresponding author Alessia Ligresti, Institute of Biomolecular Chemistry, Pozzuoli, Italy. “We adopted a multilevel approach based on different ‘omic’ sciences and mathematical modelling to overcome the limitations of previous experiments.”

The team cultured LNCaP cells in media with low androgen levels for up to 14 days, when cells had acquired neurite-like protrusions and expressed neuroendocrine markers. Incubation of LNCaP cells with growth media from these NEL cells resulted in attenuated LNCaP proliferation. Metabolic and genomic profiles established using NMR and mRNA transcript analyses demonstrated that androgen deprivation resulted in an NEL phenotype that was less malignant than the parental LNCaP cells.

Based on these data, the team developed a mathematical model to project the further development of their model system. The prediction revealed that up to 150 days LNCaP cells were almost eliminated while the number of NEL cells remained constant. Subsequently, the numbers of NEL cells and then of LNCaP cells increased, reaching equilibrium by 300 days. It seemed that androgen deprivation resulted in LNCaP cells transdifferentiating into the NEL phenotype to enable production of sufficient androgen-like factors to support the growth of androgen-independent tumour cells.

“We hypothesize that hormonal therapy can generate nonmalignant NEL cells that sustain tumour relapse over time,” says Ligresti. “Validation of our results could be the start to developing parameterized predictive models for new biomarkers of occurrence of androgen independence, which might lead to more successful therapies.”

Clemens Thoma

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