Cellular Plasticity and Reprogramming in Lethal Neuroendocrine Prostate Cancer

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Abstract

The major clinical challenge for prostate cancer treatment is targeting the highly aggressive and incurable disease that emergences under the pressure of contemporary AR pathway inhibitors (ARPIs) such as enzalutamide (ENZ): neuroendocrine prostate cancer (NEPC). The aim of our study is to understand what regulates the cellular plasticity that allows prostate cancer cells to shed their dependence on the AR and re-emerge as "AR-indifferent" NEPC.

Our data suggest that NEPC transdifferentiation is aligned with dynamic cellular reprogramming which occurs as a response to AR pathway inhibitors. Our data reveals novel AR binding proteins that orchestrate the self-renewal and neuroendocrine transdifferentiation programs leading to aggressive disease form of prostate cancer. These reprogramming factors, including BCOR, FOXM1, BRN2 and EZH2, are also very attractive therapeutic targets. In addition, we have developed novel live-cell cellular plasticity imaging methods that allow us to capture the cellular reprogramming and neuroendocrine transdifferentiation live in in vitro prostate cancer models. By utilizing our models and imaging methods, we have identified novel players of cellular plasticity whose overexpression by ARPIs lead to a cellular morphology change and development of NEPC. The expression of the novel cellular modulators identified were validated in patients with incurable NEPC, and the morphology changes in vitro were validated using super-resolution confocal and scanning electron microscope imaging in both prostate cancer and neurodegenerative disease models.

Taking together, by identifying and inhibiting the cellular plasticity and reprogramming processes in neuroendocrine prostate cancer, we hope to develop a better care for men with this fatal disease.

Keywords—*Neuroendocrine Prostate cancer, Cellular Plasticity, Reprogramming*

Professional Biography

Dr. Kirsi Ketola has completed her PhD at the age of 29 years from University of Turku and postdoctoral studies from University of British Columbia School of Medicine. She is the director of the Cellular Plasticity and Neuroendocrine Transdifferentiation program at the University of Eastern Finland School of Medicine. He has published more than 20 papers in reputed journals and has been serving as an editorial board member of repute.



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