Targeting karyotypic heterogeneity in aneuploid populations

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Background
Therapeutic intervention for prostate cancer has been challenging because prostate tumors are relatively small in size and intermixed with normal stromal cells. In addition to the complex tumor environment, the inner genetic heterogeneity of prostate cancers, mostly aneuploidy, not only contributes to the aggressive and metastatic phenotypes but also drug resistances in hormonal and chemotherapies. Unfortunately, common molecular features in aneuploidy is poorly known, and the lack of understanding on aneuploidy-driven cancer evolution becomes the major impediment of developing effective therapies for prostate cancers. Here, we investigate the impact of aneuploidy on cellular physiology in a model organism budding yeast and further to exploit its molecular features for designing effective intervention strategies for prostate cancer.

Method and Results
To unbiasedly target a heterogeneous aneuploid population, we have successfully developed a high-throughput genetic screen to initiate a comprehensive genome-wide characterization of cellular pathways affecting the fitness of aneuploid cells. We have successfully defined the gene essentiality for the population growth in aneuploid populations with the diverse karyotypes. Currently we are dissecting the potential molecular mechanisms, specifically on intracellular trafficking pathways, to identify potential drugable targets against aneuploid populations. In addition, an “evolutionary trap” is designed to develop combinatorial drug treatments for prostate cancer. The design principle is based on stress-driven rapid karyotypic evolution in heterogeneous aneuploid populations. We have performed a proof-of-principle experiment in yeast that we are able to use this combinatorial strategy to eliminate drug-resistant populations. Currently, we further exploit pharmacogenomics analysis to predict selective drugs that force aneuploid cells to adopt particular karyotypes for survival, and thus heterogeneous tumor populations can be channeled into desired traits with homogeneous features for more effective targeting.

Conclusion
Aneuploidy can potentiate the adaptability in a heterogeneous population and eventually leads to drug resistances during prostate cancer therapy. Here, we are targeting the aneuploidy-driven heterogeneity by improving our knowledge of common genetic pathways in genetically heterogeneous aneuploid populations. Furthermore, to apply our work to translational medicine, we aim to identify new combinatorial treatment strategies to fight against prostate cancer. Most importantly, our strategy, which is focused on the available FDA-approval drugs, aims to be proven for clinical use in a relative short period of trial time.

Conflict of Interest
The authors claim no conflict of interest.

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