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 and transcriptome 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 trafficking pathways, to identify potential druggable targets against aneuploid populations. In addition, a karyotypically heterogeneous aneuploid population with thousands of aneuploid strains was generated to perform both whole genome sequencing and transcriptome analysis. In our general statistic model, when the population size of aneuploid strains with diverse karyotypes is large enough, the karyotypically mirrored changes of gene expression could be minimized as the appearance of each aneuploid chromosome in the population is near equal, and aneuploidy-associated transcriptional signatures could be revealed. We found that the aneuploidy-associated transcriptional response only resembles few genomic responses to specific stresses and correlates to the essentiality of trafficking pathways in our independent genetic screen. Thus, while aneuploidy can potentiate stress adaptation, common genetic and transcriptional signatures occur across the population in response to the drastic genomic alternation when cell becomes aneuploid regardless of karyotypes.

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.

Conflict of Interest

The authors claim no conflict of interest.

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