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 in human cells as well as in NCI-60 cancer cell lines.

Method and Result

We designed a unique strategy that allowed for the observation of common transcriptome changes aneuploidy by averaging out karyotype-specific dosage effects using aneuploid yeast cell populations with random and diverse chromosome stoichiometry. This analysis uncovered a common aneuploidy gene-expression (CAGE) signature suggestive of hypo-osmotic stress. Consistently, aneuploid cells exhibited increased plasma membrane (PM) stress leading to impaired endocytosis, and this defect was also observed in aneuploid human cells. Thermodynamic modeling showed that hypo-osmotic stress is a general outcome of proteome imbalance caused by aneuploidy and predicted a ploidy-cell size relationship validated in yeast and aneuploid cancer cells. A genome-wide screen further uncovered a general dependency of aneuploid cells on a pathway of ubiquitin-mediated endocytic recycling of nutrient transporters. Loss of this pathway coupled with the aneuploidy-inherent endocytic defect leads to marked alteration of intracellular nutrient homeostasis.

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. In the future, to apply our work to translational medicine, we aim to dissect how the inherent membrane stress in aneuploidy changes metabolic pathways and metastatic ability in prostate cancer.

Conflict of Interest

The authors claim no conflict of interest.

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