Strategies to Identify and Target Aneuploidy-Associated Vulnerabilities in Lung Cancer

Novel research tool and therapeutic approach to address the effects of aneuploidy on cancer progression and survival.

Technology

NYU inventors have developed an innovative tool for studying the effects of aneuploidy on cancer progression and therapeutic response, called KaryoScramble. This system, based on previously patented technology from NYU (KaryoCreate), induces large numbers of chromosome mis-segregation events in cultured mouse cell lines. KaryoScramble induces chromosome mis-segregation using a CRISPR gRNA that targets a specific DNA sequence within the mouse centromere, which is tethered to dCas9 and the centromere protein Aurora B. Since the targeted centromeric DNA sequence (mini-satellite 5) is present in all mouse centromeres, this system has the potential to generate multiple chromosome mis-segregations in one cell division, thereby mimicking the highly aneuploid state often observed in tumors. The inventors validated this tool in a mouse lung adenocarcinoma (LUAD) cell line (KRAS-TP53, KP) and injected the resulting aneuploid cells into mice to study effects of aneuploidy on tumor progression. These studies revealed that aneuploidy is a driver of tumor growth, as tumors from the high-aneuploid cells grew larger than low-aneuploid ones. Subsequent RNA-seq analysis showed increased expression levels of CCL2 (ligand for C-C chemokine receptor CCR2) and C3 (activator of compliment signaling) in the high-aneuploid tumors. Treatment with antibodies against CCL2 or inhibitors of C3 significantly prolonged the survival of mice with high-aneuploid tumors, thus validating both proteins as novel targets for treatment of LUAD or other cancers with high aneuploidy.

Background

Aneuploidy is defined as the presence of chromosome losses or gains and is a hallmark of cancer. Over 90% of solid tumors exhibit these chromosomal aberrations, with lung adenocarcinoma (LUAD) being particularly associated with high levels of aneuploidy[1]. Given that lung cancer is the leading cause of cancer-related deaths in the U.S., there is a pressing need for new therapeutic approaches. Targeting CCL2 or C3 presents a promising and necessary new strategy for treating this devastating disease.

All eukaryotic chromosomes contain a centromere, a long, repetitive DNA region where cells regulate chromosome segregation during mitosis. This process involves chromosome interaction with a microtubule filament that pulls, or "segregates" it to one of the two newly forming daughter cells. The KaryoScremble system employs a gRNA targeting centromeric DNA to direct the regulatory protein Aurora B to the centromere, where it disrupts the interaction between chromosomes and microtubules, preventing proper segregation and resulting in aneuploid daughter cells (Figure).

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Category

Life Sciences/Therapeutics/Oncology

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(1) Knouse, K.A., Davoli, T., Elledge, S.J., and Amon, A. Annual Review of Cancer Biology. 2017 Mar;1:335-354

Development Stage

Currently, this technology is being validated in pre-clinical, *in vivo* work at NYU. These studies include an expanded set of aneuploidy-specific targets in addition to CCL2 and C3.

Applications

- **Broadly applicable research tool:** KaryoScramble can be used to study aneuploidy in any type of mouse cancer model.
- **Accurately recapitulates tumor aneuploid states:** Can generate high and low-aneuploid lines that accurately recapitulate aneuploid states of tumor cells.
- **Novel therapeutic targets:** CCL2 and C3 are novel therapeutic targets for LUAD, a high-mortality cancer with unmet need for new therapeutic interventions.
- **Broadly applicable treatment strategy:** CCL2 and C3-targeted therapies may have anti-cancer activity in other types of cancer with high-aneuploidy.

Advantages

- **Therapeutic treatment:** Existing CCL2 and C3-targeted therapies can be used for treatment of LUAD or other high-aneuploidy cancers.
- **Drug development:** New small molecules or biologics targeting CCL2 or C3.
- **Research tool:** KaryoScramble is a powerful tool for characterizing the role of aneuploidy on cancer progression and therapeutic efficacy.

Intellectual property

NYU has a pending PCT patent application related to methods of generating aneuploidy in mice and treating cancer with aneuploid-specific therapeutic strategies.

Related Technology

KaryoCreate: generating chromosome-specific aneuploidies in human cells (NYU ref. DAV06-02)

References

1. Kristin A. Knouse, Teresa Davoli, Stephen J. Elledge, and Angelika Amon , https://www.annualreviews.org/content/journals/10.1146/annurev-cancerbio-042616-072231