Retrotransposon activity predicts cancer therapy response

Stephanie Eramo*[1], Srinivas Ramachandran[1,2,3], Lynn Heasley[3,4,5], Raphael Nemenoff[3,6], and Peter Kabos[3,7]

[1]Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine – Aurora, Colorado, United States
[2]RNA Bioscience Initiative, University of Colorado School of Medicine – Aurora, Colorado, United States
[3]University of Colorado Cancer Center – Aurora, Colorado, United States
[4]Department of Craniofacial Biology, University of Colorado Anschutz Medical Campus – Aurora, Colorado, United States
[5]Eastern Colorado VA Healthcare System, Rocky Mountain Regional VA Medical Center – Aurora, Colorado, United States
[6]Department of Medicine, University of Colorado Anschutz Medical Campus – Aurora, Colorado, United States
[7]Division of Medical Oncology, University of Colorado Cancer Center – Aurora, Colorado, United States

Abstract

Cancer therapy has progressed significantly in the past two decades, yielding revolutionary cancer treatments, including targeted therapies and immunotherapy. However, the reasons some patients respond to these treatments and others do not remain a mystery in the field. Recent studies have shown that the immune system may play a role in response to targeted therapies against EGFR- and ALK-driven tumors. The marked importance of the immune system for treatment response to targeted therapies indicates a need to monitor tumor immunogenicity to better predict response. Here, we find that retrotransposon activity could predict response to therapy. In syngeneic, orthotopic murine models of ALK-driven lung cancer, we find a treatment responsive tumor (EA2) to have increased retrotransposon expression compared to tumors that have residual disease post-treatment (EA1 and EA3). The increased retrotransposon expression is observed along with an increased expression of interferon genes in EA2 but not EA1/3, combined with the known immune infiltration in EA2, point to the possibility that retrotransposon expression is driving immune states that favor response to the targeted therapy alectinib. We are developing plasma cfDNA-based biomarkers to capture these altered retrotransposon states to better predict response to targeted therapy. In summary, this study aims to develop more informative biomarkers, leveraging often neglected genomic sequences, to enhance our understanding of the biological underpinnings of treatment outcomes, ultimately contributing to the development of personalized and more effective cancer therapies.

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*Speaker

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