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PROTEOMICS UNVEILS BACE2 AS A LIPID GATEKEEPER IN CANCER



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Host: **Simone Scilabra, PhD**

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Abstract

Lipid metabolism is often deregulated in cancer. Indeed, enhanced lipid synthesis, storage, and uptake contribute to cancer proliferation, survival, invasion and metastasis. Rewiring of lipid metabolism has been linked to the activation of oncogenic signaling pathways as well as to the cross talk with tumor microenvironment; however, the mechanism adopted by cancer cell to become addicted to lipids is still largely unknown. Applying proteomics and lipidomics approaches we discovered that BACE2, a beta secretase often upregulated in solid tumors, is a modulator of lipid metabolism and its activity affects cancer cells growth. In particular, we observed that BACE2 expression correlates with increased lipid biosynthesis and accumulation of lipid droplets (LDs) in cancer cell lines and with a worse prognosis in melanoma, pancreatic cancer and glioma.

To gain molecular insights into this correlation, we employed mass spectrometry-based secretome and membrane proteome analysis to identify novel BACE2 targets and N-terminomics to validate the BACE2 mediated cleavages. By lipidomics techniques, we assessed the lipid metabolism rewiring induced by BACE2 activity perturbations. Mechanistically, we proved that BACE2, assisted by the tetraspanin CD63, mediates the extracellular shedding of key lipid transporters, thereby tuning fatty acid and cholesterol uptake. BACE2 inhibition increased lipid influx, triggering the activation of PPAR-alpha signaling and LDs dynamics. In lipid-rich cancer cells this leads to lipolysis and metabolic stress, indicating that BACE2 activity is crucial for preventing lipotoxicity.

Our findings uncover a novel function of BACE2 as a pivotal regulator of lipid transporter shedding, lipid uptake, and LDs homeostasis underscoring BACE2's role in maintaining a balanced lipid state critical for tumor cell survival and proliferation.

Biosketch

Prof. Bachi has extensive expertise in functional proteomics, biological mass spectrometry, and protein characterization. She received degrees in Pharmaceutical Chemistry and Pharmacy from the University of Genoa and subsequently earned a PhD in Biochemistry at the Mario Negri Institute in Milan. Following postdoctoral training at EMBL in Heidelberg, Dr. Bachi held progressively senior positions at the San Raffaele Scientific Institute, ultimately leading the Biological Mass Spectrometry Unit and the Protein Microsequencing Facility. Since 2013, Dr. Bachi has served as Principal Investigator of the Functional Proteomics Group at IFOM and Head of the Proteomics & Metabolomics Facility at Cogentech.

Her group is interested in understanding how tumors tame the microenvironment to facilitate growth and spreading. They tackle this question from a global, untargeted, -omic, point of view, as this is representative of what happens in vivo where multiple signals are simultaneously conveyed and used to establish a functional tumor-microenvironment crosstalk. Their research is aimed at uncovering mechanisms of tumor-host cells-ECM interactions that could not only represent novel drug targets but would also contribute to the development of diagnostic and prognostic clinical readouts. To achieve this task, they are developing and applying new approaches in the field of mass spectrometry-based proteomics and metabolomics.