Identification of Amino Acid Sensor Upstream of mTORC1 via Chemoproteomics

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Abstract

Beyond their fundamental roles as protein building blocks, amino acids (AAs) act as essential mediators in signal transduction, orchestrating diverse processes from immune responses to tumorigenesis. Maintaining intracellular AA homeostasis requires a sophisticated sensing apparatus that monitors nutrient availability. Deciphering the molecular architecture of these sensing systems is vital for understanding both physiological regulation and disease progression.

The Mechanistic Target of Rapamycin Complex 1 (mTORC1) serves as a central metabolic hub, coupling cellular growth to nutrient status. While the broader signaling cascade is well-documented, the identification of specific sensors for individual amino acids remains an active area of discovery. In this study, we employed a chemical proteomic strategy utilizing a bifunctional valine (Val) probe to identify novel upstream sensors. Specifically, we developed a photoaffinity analog of valine (PA2-Val) to capture Val-specific binding proteins within the native cellular environment.2

In this study, we utilized a chemical proteomic approach involving a bifunctional valine (Val) probe to identify upstream amino acid sensors. Specifically, we developed a photoaffinity analog of valine (PA2-Val) to capture Val-specific binding proteins in living cells. Through chemoproteomic profiling and biochemical validation, we identified PA2 as a novel and exclusive sensor for Val. Our findings demonstrate that PA2 monitors Val levels via direct interaction with the GATOR supercomplex, thereby modulating downstream mTORC1 activity. This study provides new insights into the specificity of amino acid sensing mechanisms.