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Kruthi Suvarna

Introduction

The 26S proteasome is the main mediator of protein degradation in eukaryotic cells, essential for multiple cellular processes including protein quality control, regulation of transcription, and cell division. Structurally, the proteasome is composed of the 19S regulatory particle (RP) and the 20S core particle (CP). The RP recognizes polyubiquitinated substrates and inserts them into the CP, which contains the proteolytic active sites. Rpn11 is an active site in the RP subunit that removes the polyUb chain from substrates. Rpn11 is a potential alternative target to inhibit the proteasome in cancer treatment.

Capzimin is a potent and specific inhibitor of proteasome isopeptidase Rpn11

Jing Li, Tanya Yakushi, Seth M Cohen & Raymond J Deshaies. *Nature Chemical Biology, Vol 13, May 2017.*

Abstract

The proteasome is a vital cellular machine that maintains protein homeostasis, which is of particular importance in multiple myeloma and possibly other cancers. Targeting of proteasome 20S peptidase activity with bortezomib and carfilzomib has been widely used to treat myeloma. However, not all patients respond to these compounds, and those who do eventually suffer relapse. Therefore, there is an urgent and unmet need to develop new drugs that target proteostasis through different mechanisms. We identified quinoline-8-thiol (8TQ) as a first-in-class inhibitor of the proteasome 19S subunit Rpn11. A derivative of 8TQ, capzimin, shows >5-fold selectivity for Rpn11 over the related JAMM proteases and >2 logs selectivity over several other metalloenzymes. Capzimin stabilized proteasome substrates, induced an unfolded protein response, and blocked proliferation of cancer cells, including those resistant to bortezomib. Proteomic analysis revealed that capzimin stabilized a subset of polyubiquitinated substrates. Identification of capzimin offers an alternative path to develop proteasome inhibitors for cancer therapy.