

Proopiomelanocortin

Pro-opiomelanocortin (POMC) is a [protein precursor](#) with 241 [aminoacid](#) residues. POMC is synthesized in the [pituitary](#) from the 285-amino-acid-long polypeptide precursor pre-pro-opiomelanocortin (pre-POMC), by the removal of a 44-amino-acid-long signal peptide sequence during translation.

Reincke et al. performed [exome sequencing](#) of 10 [corticotroph adenomas](#). They found [somatic mutations](#) in the [USP8 deubiquitinase](#) gene in 4 of 10 adenomas. The mutations clustered in the [14-3-3 protein](#) binding [motif](#) and enhanced the [proteolysis cleavage](#) and [catalytic activity](#) of USP8. Cleavage of USP8 led to increased deubiquitination of the [Epidermal growth factor receptor](#), impairing its downregulation and sustaining [EGFR signaling pathway](#). USP8 mutants enhanced promoter activity of the gene encoding [proopiomelanocortin](#) ¹⁾.

Results demonstrated that [triptolide](#) inhibited cell viability and colony number of [AtT20](#) cells in a dose- and time-dependent pattern. Triptolide also suppressed [proopiomelanocortin](#) (Pomc) mRNA expression and extracellular [adrenocorticotrophic hormone](#) (ACTH) secretion in AtT20 cells. Flow cytometry prompted that triptolide leaded to G2/M phase arrest, apoptosis program and mitochondrial membrane depolarization in AtT20 cells. Moreover, dose-dependent activation of caspase-3 and decreased Bcl2/Bax proportion were observed after triptolide treatment. By western blot analysis we found that triptolide impeded phosphorylation of [NF-κB p65](#) subunit and [extracellular signal regulated kinase](#) (ERK), along with reduction of [cyclin D1](#), without any impact on other NF-κB related protein expression like total p65, p50, IκB-α, p-IκB-α. Furthermore, the mouse [xenograft](#) model revealed the inhibition of [tumor growth](#) and hormone secretion after triptolide administration. Altogether this compound might be a potential pharmaceutical choice in managing [Cushing's disease](#) ²⁾.

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Reincke M, Sbiera S, Hayakawa A, Theodoropoulou M, Osswald A, Beuschlein F, Meitinger T, Mizuno-Yamasaki E, Kawaguchi K, Saeki Y, Tanaka K, Wieland T, Graf E, Saeger W, Ronchi CL, Allolio B, Buchfelder M, Strom TM, Fassnacht M, Komada M. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. Nat Genet. 2015 Jan;47(1):31-8. doi: 10.1038/ng.3166. Epub 2014 Dec 8. PMID: 25485838.

²⁾

Li R, Zhang Z, Wang J, Huang Y, Sun W, Xie R, Hu F, Lei T. Triptolide suppresses growth and hormone secretion in murine pituitary corticotroph tumor cells via NF-kappaB signaling pathway. Biomed Pharmacother. 2017 Sep 8;95:771-779. doi: 10.1016/j.biopha.2017.08.127. [Epub ahead of print] PubMed PMID: 28892788.

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