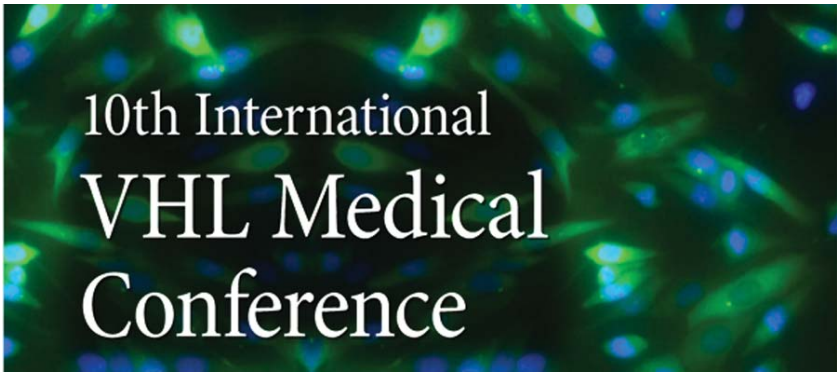

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ABSTRACT

Identification of the protein homeostasis network that controls the quality control of tumor-causing mutants in the von Hippel-Lindau tumor suppressor protein

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Identification of the protein homeostasis network that controls the quality control of tumor-causing mutants in the von Hippel-Lindau tumor suppressor protein

Protein quality control (PQC) involves a balance between protein folding, to create functional proteins, and degradation, to safeguard the cell against accumulation of misfolded proteins. PQC is determined both by intrinsic protein properties as well as by cellular chaperone machinery. Destabilizing mutations in tumor suppressor proteins such as von Hippel-Lindau (pVHL) illustrate an interplay between PQC and prevention of a cancerous phenotype. Inherited mutations in pVHL cause von Hippel-Lindau disease which involves tumor development in kidneys, central nervous system and blood. pVHL stability requires an interaction with Hsp70 and the large cytosolic heterooligomeric chaperonin TRiC to complex with cofactors elongins B and C.

The pVHL-elongin BC complex (VBC), when incorporated into the SCF E3 ubiquitin ligase complex, directs proteolytic degradation of transcription factor hypoxia inducible factor 1alpha (HIF-1alpha) under norm oxic conditions. Destabilizing pVHL mutations that prevent its association with TRiC, elongins BC or HIF-1alpha result in its proteolytic degradation, leading to increased HIF-1alpha levels and a pro-oncogenic cellular phenotype. Some tumor-causing pVHL mutants have folding potential, but fail to do so through the action of POC checkpoints that mediate their degradation. Identification of the degradation machinery that targets pVHL mutants may lead to targeted chemotherapies in which pVHL mutants are stabilized and functional. The Saccaromyces cerevisiae system was employed to identify E3 ubiquitin ligases that target pVHL.

Of a panel of 57 single ubiquitin ligase deletion mutant strains expressing GFP-pVHL, no single ubiquitin ligase was essential for pVHL degradation. Deletion of a specific ubiquitin ligase pair; however, resulted in pVHL aggregation in 70% of yeast cells while deletion of another ligase pair appeared to increase the rate of GFP-pVHL degradation. Understanding the mechanism by which pVHL is targeted for proteasomal degradation may lead to innovative therapeutic strategies to restore VHL functionality by ameliorating VHL folding and reducing its degradation.