Enzyme for ubiquitin-dependent protein degradation linked to cellular senescence

May 22 2008

A new study, published by Cell Press in the May 23rd issue of the journal *Molecular Cell*, identifies a pivotal role for the CUL7 E3 ubiquitin ligase in growth control. The research makes an exciting new connection between the regulation of protein degradation and the initiation of cellular senescence.

CUL7 E3 is an E3 ubiquitin ligase that plays a critical role in mediating selective degradation of target proteins and, therefore, has a substantial impact on numerous biological processes. Recent genetic research has linked the absence of CUL7 with growth retardation. Dr. Zhen-Qiang Pan from The Mount Sinai School of Medicine and colleagues designed a series of studies to further investigate mechanisms that underlie CUL7-mediated growth regulation.

The researchers found that the CUL7 E3 ligase targeted the insulin receptor substrate 1 (IRS-1) for ubiquitin-mediated degradation and that, conversely, IRS-1 accumulated in CUL7-deficient cells. IRS-1 is a key mediator of the insulin/insulin-like growth factor 1-signaling system and plays a critical role in organismal growth and aging. Further, CUL7-mediated IRS-1 degradation required activity of mammalian target of rapamycin (mTOR), a master regulator of cell growth.

Interestingly, CUL7-deficient cells exhibited multiple biochemical and morphological characteristics associated with senescent cells, specifically with oncogene-induced senescence. Oncogene-induced senescence is an antiproliferative program that is initiated by tumor

suppressors in response to oncogenic activation of hyperproliferation.

“Our working hypothesis is that aberrant accumulation of IRS-1, resulting from inactivation of the CUL7 E3, is an oncogenic stimulus that triggers cellular senescence, presumably through sustained MAPK activation and/or increased Akt signaling, both of which were previously shown to induce senescence,” explains Dr. Pan. “These results also raise the possibility that senescence contributes to the pathogenesis of growth retardation observed in patients with disorders linked to CUL7 mutations, such as Yakuts dwarfism syndromes and the 3-M syndrome.”

Source: Cell Press