

Seminar

“Forward genetic screens give new insights into protein homeostasis and aging”

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The protein homeostasis network is a complex regulatory system that controls protein synthesis, folding, posttranslational modifications, and degradation. Failure of protein quality control is an early event in aging, and many animal models of longevity display improved protein folding and turnover capacity.

In a number of independent screening approaches, we found that the metabolic hexosamine pathway is a novel regulator of protein homeostasis. In fact, we identified two independent regulators of the hexosamine pathway (HP) that are highly conserved: mutagenesis screens in *Caenorhabditis elegans* revealed gain-of-function (gof) mutations in glutamine-fructose-6-phosphate aminotransferase (*gfat-1*), the key enzyme of the HP. These result in elevated levels of the HP product UDP-N-acetylglucosamine (UDP-GlcNAc). *C. elegans* mutants carrying *gfat-1* gof alleles display increased ER-associated degradation and autophagy, resulting in significant protection from various toxic misfolding-prone proteins and lifespan extension. Furthermore, in genetic screens using mouse haploid embryonic stem cells, we identified AMDHD2 as a new HP enzyme that regulates metabolite flux in the pathway. Finally, to test if HP activation improves mammalian protein quality control, we expressed poly-glutamine Huntingtin in Neuro2a cells. Supplementation with the HP precursor GlcNAc resulted in decreased Huntingtin aggregation. This suggests that the HP might be a viable pharmacological target to prevent age-associated diseases such as neurodegeneration. Given the high conservation of the HP, we expect that its activation will likewise promote healthspan in humans. Furthermore, we know that cellular UDP-GlcNAc concentrations decrease with age in the nematode. It will be of particular interest to examine whether this metabolite might serve as a biomarker for cellular fitness in aging.

- **Date: 2:00PM/Aug. 14(Tue.)/2018**
- **Place: Life Science Bldg. #104**
- **Inquiry: Prof. Seung-Jae Lee (279-2351)**

***This seminar will be given in English.**

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