オートファジー研究会セミナー

Transcription factor NRF2 regulates the expression of autophagy genes

Dr. Antonio Cuadrado
Autonomous University of Madrid

日時：9月9日（月）16：00～17：00
場所：A棟8階 カンファレンスルーム

Cells control the quality of the proteome through an integrative network of mechanisms that include protein degradation by autophagy. The regulation of this process by signaling pathways has been intensively studied but less is known about its transcriptional control. Because this degradative pathway has an essential cytoprotective role, especially under stress conditions, in this thesis we have analyzed the regulation of autophagy by the transcription factor Nuclear factor (erythroid-derived 2)-like 2 (NRF2), which is considered a master regulator of cellular homeostastis. NRF2 controls the expression of a wide battery of cytoprotective genes that have a tremendous impact on physiological responses such as inflammation, senescence or metabolism. However, its relevance in proteostasis is just starting to be unveiled. Therefore, we focused our study on the transcriptional regulation of two types of autophagy, i.e. macroautophagy and chaperone mediated autophagy (CMA). We have identified NRF2 enhancer sequences, termed antioxidant response elements (AREs), in the promoter region of 9 genes involved in different steps of macroautophagy and CMA. Consequently, we show that genetic and pharmacological manipulation of NRF2 results in the modulation of autophagy gene expression and activity. The role of NRF2 in the regulation of macroautophagy may have a significant relevance upon stressful conditions, including proteotoxic stress. To address the functional relevance of NRF2 in proteinopathy, we have generated a new mouse model of Alzheimer's disease (AD) that reproduces the amyloid and TAU pathology in the presence or absence of NRF2 expression. NRF2 deficiency worsens some of the main hallmarks of AD, including low-grade chronic oxidative and inflammatory stress as well as exacerbated proteinopathy due, at least in part, to impaired macroautophagy. Moreover, our results reflect a positive correlation between the expression of NRF2 and macroautophagy in AD patients. We have also established the role of NRF2 in the basal and inducible regulation of CMA, based on the transcriptional regulation of the lysosomal receptor LAMP2A. This novel NRF2/LAMP2A axis may have important implications in the physiological response to stress and, consequently, be of interest for human pathology. In fact, data mining of The Cancer Genome Atlas showed a positive correlation between NRF2 an LAMP2 expression in gliomas and glioblastomas. Overall, this thesis describes a novel role of NRF2 in the regulation of macroautophagy and CMA, suggesting a new strategy to combat proteinopathies.

連絡先：器官・細胞生理学講座　　小松　雅明
（内線3511）