第1回 国際先導研究セミナー

日時：6 月 4 日（火）17:00–
場所：順天堂大学 7号館 1階カンファレンスルーム

Selective autophagy as an anti-ageing programme

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Abstract:
The talk will summarise several ongoing research projects in the laboratory, primarily focussing on the selective degradation of dysfunctional mitochondria by autophagy. We investigate how this homeostatic process, termed mitophagy, is regulated at the molecular and cellular levels and how it plays an essential role in multiple aspects of cellular physiology. The talk will highlight our efforts to elucidate molecular mechanisms allowing autophagy receptor proteins to detect damaged mitochondria producing elevated levels of reactive oxygen species (ROS). These mechanisms include oxidation of redox-sensitive cysteine residues in p62 and NDP52 triggering their oligomerisation mediated by disulphide bonds. We propose that the ability to sense elevated levels of ROS by these proteins has been acquired during human evolution. Furthermore, we posit that the acquisition of this mechanism contributed to the improved stress resistance allowing for longer lifespan of our species. Indeed, the talk will illustrate how the loss of mitochondrial quality control by mitophagy results in an accumulation of damaged mitochondria, elevated and persistent activity of stress-response pathways, as well as the metabolic dysfunction associated with the depletion of nicotinamide adenine dinucleotide (NAD) pools, triggering an energetic crisis. Mitophagy and metabolic, particularly NAD, deficits are evident in ageing and our data indicate that the loss of mitochondrial quality control is a key driver of age-related perturbation in cellular physiology culminating in either cell death or senescence. As a proof of concept, we demonstrate that small molecules identified in our screens for novel mitophagy activators can protect against age- or disease-related senescence and cell death. Based on our data, we propose that selective autophagy pathways, and specifically mitophagy, are promising targets for interventions aiming to reverse age-related dysfunction and improve viability of cells, including human neurons, in diseases associated with the autophagy deficit.

Selected Publications:
Kelly et al., *Dev Cell*. 2024, Victorelli et al., *Nature*. 2023, Sun et al., *Cell Rep.* 2023, Kataura et al, *EMBO J*. 2022, Kataura et al., *Dev Cell*. 2022, Rabanal-Ruiz et al *J Cell Biol*. 2021, Carroll et al.,. *Nat Commun.* 2018

【後援】 基礎研究医養成プログラム、順天堂大学大学院医学研究科

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