PhD THESIS DEFENSE: Deciphering the Role of Mechanical Stress during Aging and in Neurodegenerative Diseases

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15:00
Auditorium and Online (Teams)

The locomotion of Caenorhabditis elegans (C. elegans) offers a unique platform for studying complex postures and motor behaviors. In this study, I investigated locomotor patterns across different ages and genetic backgrounds of C. elegans, utilizing customized tracking systems and advanced analysis techniques. A comprehensive examination of locomotion behaviors was conducted using the eigenworm approach. Eigenworms are the principal components of the animals' posture space. I identified specific eigenworms associated with forward movement, turning, and exaggerated bends. Notably, spectrin-mutant animals showed a strong correlation between their bending movements and a specific eigenworm for

turning in wild-type animals. These findings suggest that eigenworms offer a universal framework to compare different types of worm movement and assess the effects of mutations. This paves the way for a more informative analysis of worm behavior, especially when combined with studies of neuronal networks.
Additionally, I explored the role of proprioception in coordinating motor activities within C. elegans, employing genetic and modeling approaches. The focus of my research was to elucidate the mechanisms underlying proprioceptive feedback, including mechanical stress and neuronal signaling, with a focus on age-related deficits. My findings elucidate that the spectral network associated with a singular proprioceptive DVA interneuron, which modulates tension and compression states, serves as a critical determinant of body posture. Intriguingly, a striking resemblance was observed between animals of early ageing and the mutant animals for ?-spectrin, where both animals crawled with exaggerated body bends. Moreover, I show that proprioceptive neurons are found to encode body posture and exhibit age-dependent structural and functional alterations, including protein aggregation and decreased mechanical tension. Notably, spectrin, a cytoskeletal component, emerges as a key player in maintaining proprioceptive integrity during ageing.
Furthermore, I investigated the molecular pathways underlying age-associated proprioceptive defects, more specifically, the role CLP-1 protease in the cleavage of UNC-70/?-spectrin in ageing animals. Conditional knockout of clp-1 in DVA interneuron revealed altered locomotor behaviors, along with the pan-neuronal knockout of clp-1. Given the role of spectrin in proprioception through DVA interneuron suggests that clp-1 regulates spectrin in age-related neurodegeneration. Lastly, I explored the effect of ectopic expression of human ??crystalline on ageing. We hypothesized that ??-crystallin (HSPB5), a small heat shock protein (sHsp), will stabilize ?-spectrin and shield it from clp-1 proteolytic degradation during ageing. I ectopically expressed the constitutively active 3E mutant of ??-crystallin pan-neuronally or specifically in DVA. Through locomotion analysis of animals from young adult to adult day 6, I observed a modest rescue in the locomotion behavioral pattern in both DVA specific and pan-neuronally expressed ??-crystallin animals. We speculate that constitutively active ??-crystallin may bind to proteolytically vulnerable domains/residues of the UNC-70 protein, providing protection against proteases such as clp-1. Collectively, these findings contribute to our understanding of proprioceptive mechanisms in ageing and offer insights into potential therapeutic targets for age-related neurodegenerative diseases.

Monday July 15, 15:00 h. ICFO Auditorium and Online (Teams)
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