



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

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July 15, 2024

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 γ -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/ γ -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 α -crystalline on ageing. We hypothesized that α -crystallin (HSPB5), a small heat shock protein (sHsp), will stabilize γ -spectrin and shield it from *clp-1* proteolytic degradation during ageing. I ectopically expressed the constitutively active 3E mutant of α -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 α -crystallin animals. We speculate that constitutively active α -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)

Thesis Director: Prof. Dr. Michael Krieg

Hosted by: Prof. Dr. Michael Krieg