ASHBi SEMINAR

SETDB2 regulates sensory neuron survival and pain perception from flies to humans

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Professor, The University of Sydney

Date Monday, 4 March 2024

Time 16:00 – 17:00 [JST]

Venue Conference Room Onsite Only*

B1F, Faculty of Medicine Bldg. B

*Register via the right QR code

Abstract

Chronic pain affects hundreds of millions of people world-wide and current therapies do not adequately address pain for most patients. To identify core regulators of pain perception we combine functional screening in fruit flies with human exome sequencing of extreme pain patients. From this, we identified 99 conserved genes that control sensory neuron development or function, including the new conserved pain gene *SETDB2*. *SETDB2*, as a core regulator of pain perception and a new cause of congenital insensitivity to pain (CIP). We generated *SETDB2* KO mice and found they also exhibit defective acute pain perception, primarily mechanical nociception. We next generated humanized *SETDB2 CIP* mutant mice, and these animals also recapitulate the human CIP patients. While *SETDB2* is predicted to be a histone methyltransferase, we could not observe this activity. To identify the molecular cause of CIP in *SETDB2 CIP* mutant mice, we performed single cell sequencing, and identified ROS and translational stress signatures specifically in mechanical sensory neurons. Moreover, both isolated primary sensory neurons and *SETDB2* CIP patient iPSC-derived sensory neurons exhibit outgrowth phenotypes, and this could be rescued by the antioxidant AD4. Mechanistically, we found SETDB2 forms a complex with P53 and DAXX, and disruption of this complex may contribute to the observed pain phenotype. Overall, our conserved functional genomics approach highlights SETDB2 as a critical new pain gene, and treatment with antioxidants like AD4 may help *SETDB2* CIP patients or other individuals at risk of peripheral neuropathy.

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