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"β-Tubulin Ser172 Phosphorylation Regulates Microtubule Remodeling in Duchenne Muscular Dystrophy Cardiomyopathy"

By

Delong Zhou
Cell Biology, Neuroscience and Physiology Program
MS 2018, Northeastern University, USA
BS 2016, China Pharmaceutical University, China

Thesis Advisors:

Diego Fraidenraich, Ph.D.
Department of Cell Biology and Molecular Medicine

Friday, May 8th, 2026
3:00 P.M.
Medical Science Building, G609B

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ABSTRACT

Duchenne muscular dystrophy (DMD) cardiomyopathy is a major cause of mortality in patients with DMD and is characterized by pathological remodeling of the cardiomyocyte microtubule network. Although dystrophin is well known for maintaining sarcolemmal integrity, the molecular mechanisms linking dystrophin loss to microtubule dysregulation remain incompletely understood. This dissertation examines the role of β-tubulin Ser172 phosphorylation in microtubule remodeling in DMD cardiomyopathy, including its contribution to cytoskeletal remodeling, its upstream kinase-dependent regulation, and its relevance to therapeutic applications. Cardiac tissue from mdx mice and patients with DMD showed reduced phosphorylation at βIII-tubulin Ser172 together with selective upregulation of *Tubb3*. In CRISPR-generated mdx mice carrying a phospho-mimic S172E mutation in βIII-tubulin, phospho-mimic replacement at Ser172 normalized microtubule organization and repolymerization, improved connexin-43 phosphorylation and localization, reduced isoproterenol-induced arrhythmias, and attenuated cardiac fibrosis and mononuclear invasion in mdx hearts, identifying β-tubulin Ser172 phosphorylation as an important regulator of dystrophic microtubule remodeling. Upstream phosphorylation/de-phosphorylation mechanisms were further investigated by focusing on DYRK1A and CaMKII as candidate kinases. Transcriptomic, proteomic, and computational analyses supported their association with microtubule regulation, and functional studies showed that perturbation of these kinases altered β-tubulin phosphorylation and microtubule organization through various mechanisms, supporting the notion that Ser172 is a critical regulatory site linking kinase activity to microtubule remodeling. Finally, this dissertation evaluated a dual AAV base-editing strategy designed to restore the DMD reading frame through exon skipping, and detectable, sequence-specific editing was achieved in human stem cell-derived cardiomyocytes, providing proof-of-principle for future optimization. Together, these studies identify β-tubulin Ser172 phosphorylation as an important regulator of microtubule remodeling in DMD cardiomyopathy and provide a foundation for future mechanistic and therapeutic investigation.

Key words
Duchenne muscular dystrophy, cardiomyopathy, dystrophin, microtubule remodeling, β-tubulin, phosphorylation, DYRK1A, CaMKII, connexin-43, base editing.