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Title of Thesis: Studies on post-translational modifications (acetylation and deacetylation) in endothelial Nitric Oxide Synthase (eNOS)

Findings

This thesis investigates the role of lysine acetylation and deacetylation in regulating endothelial nitric oxide synthase (eNOS), the enzyme responsible for nitric oxide (NO) production and maintenance of vascular homeostasis. Although eNOS catalytic mechanisms are well established, the molecular effects of post-translational modifications, particularly lysine acetylation, remain poorly understood. To address this, site-directed mutagenesis was used to generate acetylation-mimetic (K→Q) and deacetylation-mimetic (K→R) variants of conserved lysine residues, primarily Lys609 and Lys733, followed by comprehensive biochemical, biophysical, and computational analyses. The acetylation-mimetic K609Q variant significantly enhanced NO production, improved coupling efficiency, increased FMN-mediated electron transfer, and promoted conformational states favorable for catalysis, whereas K733Q produced minimal functional changes. In contrast, deacetylation-mimetic variants (K609R and K733R) reduced NO synthesis, impaired coupling efficiency, and disrupted FMN domain dynamics without affecting FAD-dependent electron transfer. Computational docking further demonstrated that lysine charge state influences calmodulin binding, domain orientation, and conformational flexibility, providing a structural basis for the observed functional differences. This study establishes lysine acetylation as a site-specific regulator of eNOS activity, identifies Lys^{609} as a critical regulatory hotspot, and provides mechanistic insight into how metabolic signaling modulates endothelial NO production. These findings offer a foundation for

developing therapeutic strategies targeting eNOS acetylation to restore endothelial function and reduce cardiovascular disease.