Abstract

Proteostasis collapse and the progressive accumulation of misfolded proteins constitute central pathological features of neurodegenerative disease, yet the systemic and inter-organismal mechanisms governing proteostatic decline remain incompletely defined. Using a genetically tractable host-microbe model, we demonstrate that individual commensal bacterial isolates exert strain-specific effects on aggregation propensity and organismal physiology. Feeding *C. elegans* monoxenic diets of defined bacterial isolates spanning distinct phylogenetic lineages revealed marked strain-dependent modulation of polyglutamine aggregation kinetics, lifespan, and neurodegenerative phenotypes, with a subset of isolates conferring robust protection against aggregation and downstream neuronal dysfunction.

Untargeted metabolomic profiling coupled with functional validation indicated that protective bacterial exposure reprograms host metabolism at a systems level, rather than acting through simple caloric or nutrient provision, with differential abundance detected across multiple interconnected metabolic axes. Among these, one pathway emerged as a previously uncharacterized regulatory node coupling microbial metabolic activity to host proteostatic capacity. Pharmacological supplementation of pathway intermediates and orthogonal genetic perturbation of discrete pathway components yielded divergent, flux dependent effects on aggregation and organismal fitness, indicating that the balance and directionality of metabolic flux, rather than pathway activity alone, determines aggregation outcome. Quantitative proteomic analysis further revealed selective enrichment of mitochondrial and stress responsive proteostasis networks, consistent with a model in which metabolic adaptation confers resilience to proteotoxic insult rather than promoting direct aggregate clearance.

Cross-species validation in human cellular models corroborated conservation of this regulatory mechanism, with both pharmacological and RNAi mediated perturbation of the homologous pathway component modulating aggregation phenotypes. Collectively, these data establish microbiome driven metabolic rewiring as a conserved, systems-level determinant of host proteostatic capacity, implicating a previously unrecognized metabolic axis as a candidate therapeutic target in neurodegenerative disease.