Inheritable Longevity Programming: First Epigenetic Mechanism and Proof-of-Concept for Transgenerational Therapies to Prevent Multiple Aging-Related Diseases with Single Molecules

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My 2015 project was to establish the first animal model, enabling studies to identify epigenetic mechanisms underlying transgenerational inheritance of nutrition-programmed longevity. My current study was to examine whether E(z)/EZH2-dependent H3K27me3 may be one such epigenetic mechanism, and EZH2 inhibitors (e.g., EPZ-6438) may extend longevity by preventing multiple aging-related diseases (ARDs) across generations. Integrative methods were employed for longevity analysis, western blotting, disease and behavioral characterization after various post-eclosion treatments. First, post-eclosion treatment with a low-protein (LP) diet shortened longevity across generations, while upregulated only in the F0 flies the protein level of E(z), an H3K27-specific methyltransferase, leading to higher H3K27me3 levels in the F0 and F2 generations. This observation suggested that H3K27me3 may be transmitted across generations and underlie transgenerational nutrition-programmed longevity. Supporting the idea, post-eclosion RNAi-mediated knockdown of E(z) or its functional inhibition with EPZ-6438 in the F0 flies improved longevity while rendering H3K27me3 low across generations. Importantly, EPZ-6438 alleviated LP-induced longevity reduction via preventing ARDs across generations, establishing increased E(z)-dependent H3K27me3 and consequently early onset of ARDs as its main cause. Finally, the efficacy of EPZ-6438 was more substantial when delivered earlier in adult life. My results 1) revealed E(z)-dependent H3K27me3 as the first such epigenetic mechanism, 2) identified EPZ-6438 to extend longevity and prevent multiple ARDs, and 3) provided the first-ever proof-of-concept for transgenerational epigenetic therapy with individual molecules for simultaneous prevention of multiple ARDs.