CAREER: Emergence of cellular aging from gene networks in Saccharomyces cerevisie

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Aging is a fundamental question in biology, yet its mechanism remains elusive despite decades of research. Cellular aging, the basis of physiological aging, can be studied using the model organism of *S. cerevisiae*. Yeast cells from a single colony live to different ages despite their genotypic homogeneity. At the population level, the conserved Strehler-Mildvan correlation in multicellular organisms can also be observed in yeast populations. This coexistence of individual plasticity and universal demographic characteristic is one of most puzzling features of aging. As a model organism, life span of hundred of yeast mutants have been measured. Paradoxically, not a single gene can be claimed as a direct cause of aging. To complicate things even further, when yeast aging is measured in different ways, different and sometimes opposite changes in gene networks can be observed. This seemingly complicated picture of yeast aging is addressed by the core idea of this proposal – cellular aging is an emergent property of gene networks, a principle that will be demonstrated mathematically and then studied by simulations, empirical analysis and experiments.

In contrast to failures of complex machineries, mortality rate increases exponentially during biological aging. This key feature of biological aging can emerge from Qin’s network models with stochastically interacting non-aging components. Key predictions of Qin’s model include the effect of network robustness on the rate of cellular aging, the Strehler-Mildvan correlation, and the role of stochastic noises in biological aging. These theoretic predictions are corroborated by our initial empirical studies of the effects of robustness, tolerance to oxidative stress, and genetic capacitors on cellular aging. Building on these conceptual and empirical findings, PI Qin proposes the following three integrated components to gain in-depth understanding on cellular aging and gene networks: (1) Theoretical component: A sophisticated theoretic framework on network theory of cellular aging will be developed. Major thrusts here include studying how power-law network configuration, network robustness, and interaction dynamics influence aging dynamics and how network approach can influence aging as quantitative traits. (2) Empirical component: The main focus here is how robustness influences aging and age-related traits. Mutational robustness, morphological robustness, expressional robustness, and oxidative robustness will be computed, network modules/interaction patterns with strong effects on aging will be identified. The effect of these network modules and interaction patterns will then be verified experimentally using yeast genomic resources and by association studies in sequenced strains. (3) ducational component. Activities of this project will provide a great opportunity of interdisciplinary educations to minority undergraduates, and will bring investigation-based learning to classrooms.

Intellectual merit of this project lies in the novel mechanistic model of cellular aging based on gene networks, its unique insights, and close integration of mathematical modeling, computational genomics, and experimental genetics. The proposed model demonstrates that cellular aging can emerge from gene interactions and stochastic heterogeneity of interaction is a key factor in shaping the dynamics of the aging process. With respect to year aging, the proposed network model will also provide a unifying theory to explain both aging in both dividing and non-dividing cells. Gene network is the basis of many other pleiotropic traits, and cellular aging is a fundamental concept in biology. Hence, this proposed project would not only lay the foundation for PI’s scientific career, but would also contribute the general understanding of emergent properties of gene networks.

Broad impact will be achieved through integrating research into teaching, interdisciplinary training of African American students, faculty workshops, dissemination of educational materials through social media, and outreaching effort to K12 schools in poor neighborhoods. A significant component of this project is an educational component to provide inter-disciplinary training to under-represented undergraduate students on mathematics, computing, and systems biology. In addition to undergraduate independent research projects, the proposed research activities will be partitioned into modules and small projects that can be carried out by undergraduates in three courses – in a manner of crowd-sourcing. PI will organize computing workshops for faculty in local colleges to establish a community of scientific computing. Video tutorials will be generated and distributed through social media. Hands-on laboratory modules will be developed to teach basic concepts of computational think and genomics to K12 students.