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DISSERTATION

"Mapping Aging-associated Vascular ZIP-codes by Phage Display"

by

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1:00 PM

Cancer Center G1196

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ABSTRACT

The global population of adults aged 80 and above is projected to triple by 2050, carrying significant implications for health and the economy. As organisms age, they undergo damage accumulation from metabolic processes and environmental factors. While aging is a natural process, it significantly increases the risk of various chronic illnesses, such as cardiovascular diseases, stroke, neurodegenerative disorders, osteoarthritis, and cancer. Therefore, it is crucial to identify molecular markers that can predict damage accumulation or reduce the occurrence of age-related diseases. Our laboratory has pioneered the use of in vivo phage display technology to directly screen combinatorial peptide libraries. This approach has been extensively leveraged and optimized, and has led to the discovery of molecular markers that are selectively expressed and accessible to circulating ligands when administered intravenously. This study aimed to identify differential expression of markers in the vascular system during aging. Three rounds of peptide phage library selections were conducted in aged C57BL/6J mice (75-78 weeks old) followed by DNA sequencing techniques to identify universal and unique ligand peptides across seven target tissues. As a proof-of-concept, peptides isolated from the screening were cross-validated in young mice (6-8 weeks old) through biodistribution studies. The results revealed elevated levels of a specific peptide in the aged brain. While this peptide was also detected in other target tissues of both aged and young animals, it showed no association with aging except in the brain. This discovery of a peptide targeting a universal marker across tissues, which becomes exclusively relevant in the aging brain, opens new mechanistic possibilities for understanding age-related changes in the central nervous system. Furthermore, the tissue-specific molecular diversity of aged mice was assessed using customized bioinformatics analysis, evaluating over 4 million sequences obtained from high-throughput next-generation sequencing. These data represent a significant step towards constructing a molecular map of the aging vasculature. Once completed, this molecular map will offer insights into differentially expressed proteins, leading to a deeper understanding of the biology of aging.