Schmucker DL, J Gerontol Geriatr Med 2018, 4: 022
DOI: 10.24966/GGM-8662/100022

HSOA Journal of Gerontology & Geriatric Medicine

Research Article

WI-38 Cells to Telomeres: 60 Years of Research on Aging

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Editorial

As the newly appointed Editor-in-Chief of the Herald Journal of Gerontology and Geriatric Medicine, I feel it imperative that potential authors have an insight into my background in aging research. Therefore, I would like to provide a synopsis of some of our studies. Hopefully, my comments may raise unanswered questions pertaining to aging that may stimulate future efforts in this exciting arena of basic and clinical research.

Sixty years ago, research on aging was primarily descriptive in nature and was focused on cataloging differences in organ and cell structure and function between young and senescent animal models. However, Hayflick's seminal observation that normal human diploid cells in culture exhibited a finite lifespan refuted the concept, based on cardiac myocytes, that cells in culture were immortal and provided the impetus for expanding both the breadth and depth of gerontological research. I first expressed an interest in aging as a NIH Postdoctoral Fellow at the University of California, San Francisco in the early 1970's. Our initial efforts culminated in the most comprehensive stereological analysis of the structural changes in the livers of rats at intervals between 1 and 30 months of age [1]. A particularly intriguing observation was a marked decline in the surface area of the smooth-surfaced endoplasmic reticulum, the primary subcellular locus of the hepatocyte Phase I drug-metabolizing enzyme system, as a function of increasing age [2]. This correlated with subsequent studies that demonstrated a significant decline in the efficacy of cytochrome P-450 dependent drug metabolism in this model [3-5]. Furthermore, we demonstrated that the specific activity, i.e., activity per microgram of purified protein, of a critical enzyme in this pathway, cytochrome P-450 reductase, was diminished by 50% in senescent versus young adult animals [6]. This observation fit nicely with the concept that the age-related diminution in enzyme activities reflected post-translational modifications to the enzyme molecules due, perhaps, to damage attributable to increases in intracellular free radicals. However, when we extended these studies to nonhuman primates and humans, we were unable to demonstrate significant and consistent age-related changes in either microsomal or specific activities of this enzyme [7-9]. We concluded that hepatic drug metabolism in senescent inbred rodent models did not accurately reflect this function in healthy, elderly humans [10]. We suspect that the documented age-related declines in drug metabolism in humans may reflect altered drug disposition and/or clearance rather than changes intrinsic to the hepatic Phase I pathway.

Significant age-related declines have been described in the humoral immune response to antigenic challenge. For example, there is ample evidence that elderly subjects exhibit a reduced immune response to vaccines [11]. Since our laboratory was primarily focused on the gastrointestinal tract and the liver, we had a particular interest in the effects of aging on the intestinal mucosal immune response. Our studies focused on the intestinal mucosal immune response to Cholera Toxoid (CTx) in both rat and nonhuman primate models. Our rodent model consisted of intraduodenal injections of CTx to young, mature and senescent Fischer 344 rats and the subsequent harvesting of intestinal washings and tissues to quantitate anti-CTx Immunoglobulin A (IgA) antibodies and CTx-specific plasma cells in the lamina propria [12,13]. We clearly demonstrated that impaired homing of IgA immunoblasts from Peyer's patches to the intestinal lamina propria following CTx immunization contributed to the diminished intestinal immune response in senescent rodents [14]. In subsequent studies we demonstrated that anti-CTx-specific IgA antibody levels were markedly lower in intestinal lavage samples of senescent versus young rhesus macaques, although total gut IgA concentrations were independent of age or immune status. Furthermore, flow cytometric analysis showed that the numbers of both IgA and CTx- positive lymphocytes in the peripheral blood were dramatically reduced in senescent macaques [15]. In an effort to identify factors responsible for this diminished mucosal immune response, we employed flow cytometry and quantitative immunohistochemistry to demonstrate age-related declines in lymphocytes expressing the homing integrin α4β7 and intestinal vascular endothelial cells expressing its specific receptor, the addressin MAdCAM-1 [16]. The reason for the age-related loss of integrin and receptor expressions is unknown, although the possibility of post-translational modifications diminishing their respective affinities cannot be dismissed.

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Citation: Schmucker DL (2018) WI-38 Cells to Telomeres: 60 Years of Research on Aging. J Gerontol Geriatr Med 4: 022.

Received: March 27, 2018; **Accepted:** October 05, 2018; **Published:** October 19, 2018

Gerontological and geriatric research has made dynamic progress in the past decades. The realization that telomere shortening may play a substantial role in the aging process, the identification of genes critical to the aging process, the enhanced focus on age-related diseases and the establishment of research institutions and private companies dedicated to the study of aging, e.g., the Buck Center, Geron and others, foment a marked increase in our understanding of the aging process. The Herald Journal of Gerontology and Geriatric Medicine is dedicated to publishing cutting edge research on aging that will advance our knowledge base to continue to improve the quality of life in the elderly subpopulation.

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