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Review article

Evaluating the physiological reserves of older patients with cancer: The value of potential biomarkers of aging?

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ABSTRACT

Aging of an individual entails a progressive decline of functional reserves and loss of homeostasis that eventually lead to mortality. This process is highly individualized and is influenced by multiple genetic, epigenetic and environmental factors. This individualization and the diversity of factors influencing aging result in a significant heterogeneity among people with the same chronological age, representing a major challenge in daily oncology practice. Thus, many factors other than mere chronological age will contribute to treatment tolerance and outcome in the older patients with cancer. Clinical/comprehensive geriatric assessment can provide information on the general health status of individuals, but is far from perfect as a prognostic/predictive tool for individual patients. On the other hand, aging can also be assessed in terms of biological changes in certain tissues like the blood compartment which result from adaptive alterations due to past history of exposures, as well as intrinsic aging processes. There are major signs of 'aging' in lymphocytes (e.g. lymphocyte subset distribution, telomere length, p16INK4A expression), and also in (inflammatory) cytokine expression and gene expression patterns. These result from a combination of the above two processes, overlaying genetic predispositions which contribute significantly to the aging phenotype. These potential "aging biomarkers" might provide additional prognostic/predictive information supplementing clinical evaluation. The purpose of the current paper is to describe the most relevant potential "aging biomarkers" (markers that indicate the biological functional age of patients) which focus on the biological background, the (limited) available clinical data, and technical challenges.

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Chitinase
CRAMP
Aging genes

Despite their great potential interest, there is a need for much more (validated) clinical data before these biomarkers could be used in a routine clinical setting. This manuscript tries to provide a guideline on how these markers can be integrated in future research aimed at providing such data.

Contents

1. Introduction

The incidence of most malignant diseases increases with age.[1] Data from the Surveillance, Epidemiology, and End Results (SEER) database show that approximately 55% of all newly diagnosed cancer cases and 70% of cancer-related deaths occur in patients aged 65 years or older.[2] Median age at death for the major tumors common to both males and females (lung, colorectal, lymphoma, leukemia, pancreas, stomach, urinary bladder) ranges from 71 to 77 years.[2] Thus, as the world population ages, it is expected that the number of older patients with cancer will increase and therefore clinicians will be frequently confronted with older patients with cancer and treatment decisions in this population.[3]

Aging may contribute to carcinogenesis in two ways: first the passage of time simply leads to accumulations of cells with different molecular aberrations, eventually resulting in overt tumors; second, aging is associated with substantial alterations in internal homeostasis, especially in immune and endocrine systems that play a significant role in cancer control. Hence, aging is associated with numerous events at the molecular, cellular and physiological levels that increase susceptibility to carcinogens, promote carcinogenesis and decrease protective mechanisms.[4]

Cellular senescence is a fundamental cellular program that can be activated by different mechanisms. Deoxyribonucleic acid (DNA) damage is considered one of the most important triggers. If the amount of DNA damage after exposure to either endogenous or exogenous toxins is beyond the capacity of repair mechanisms, but fails to initiate apoptosis, the cell can activate a DNA damage response,[5] ultimately leading to permanent cell cycle arrest, i.e. senescence.[6,7] A second, in some ways related, trigger of cellular senescence is replicative exhaustion, i.e. cells can only undergo a finite number of divisions under some sort of genetic control, most often shortening of the repeats at the ends of the chromosomes (telomeres). When these reach a critical low number after numerous cell divisions, a signaling cascade is initiated (a DNA damage cascade — hence the similarities with the first mechanism above) and the cell is driven into a state of irreversible growth arrest.[5] Third mechanism is excessive exposure of the cell to oxidative stress can also lead to a similar response to that observed with replicative exhaustion, resulting in a permanently growth arrested senescent status.[8] Finally, another mechanism that can lead to activation of the senescence pathway and result in cellular senescence is the activation