Apocalyptic horsemen of geriatric oncology

Considering the processes we encounter and must overcome to reduce the burden of Geriatric Oncology, I am reminded of the scriptural description of the Four Horsemen of the Apocalypse, War, Pestilence, Famine, and Death. All are synergistic and portend devastating outcomes. The Apocalyptic Horsemen that we must engage and thwart in Geriatric Oncology, include Genomic Infidelity, Cellular Senescence, Inflammaging and Diabesity.

Genomic Infidelity, including DNA mutagenesis, rearrangement and epigenetic changes, continuously increases over the lifespan. It provides the enabling, disruptive background for almost all malignant transformation (1,2). These processes essentially throw the switches that result in oncogene activation and inactivation of tumor suppressor genes. While extensive DNA Damage Response Pathways and Epigenetic Regulatory Systems exist to counteract these changes, their inexorable progression leads to cancer as a common disease of older adults (3).

Cellular senescence, which may be associated with mutagenesis, as well as with cumulative environmental influences, leads to a number of age-associated phenotypes that significantly impact geriatric oncology. These include immuno-senescence, myo-senescence, sarcopenia, and the senescence associated secretory phenotype (SASP). Immuno-senescence results in loss and/or alterations in the immune system that may contribute to age-associated declines in immuno surveillance leading to a permissive milieu for tumor growth and increased susceptibility to infectious organisms. Senescence of muscle satellite cells accompanied by inadequate nutrition and physical activity, may contribute to decreases in skeletal muscle mass resulting in age-associated sarcopenia (4). The latter can lead to frailty, falls, functional decline, and death (5). At the same time, sarcopenia can interfere with patient tolerability of cancer therapies (6). Yet another consequence of senescence is the SASP, in which cells lose their proliferative capacity, and increase their secretion of inflammatory cytokines, many of which may amplify tumor growth supportive factors in the tumor microenvironment (7-9).

Inflammaging has been identified as age-associated chronic, sterile, low-grade inflammation that occurs in response to endogenous cell debris and metabolic errors. It may particularly occur in pathways that mediate gut-liver, gut-brain, and/or gut-adipose tissue communication and interactions (10). Unlike classic acute inflammation, which is usually targeted at destroying foreign pathogenic organisms, and then terminates once the pathogens are eliminated, inflammaging is low-grade and ongoing (11). Consequences, of inflammaging include synthesis and release of cytokines including TNF, IL-1, IL-6, and IL-8, as well as epigenetic changes leading to accelerated biological aging as demonstrated by altered patterns of DNA methylation (10).

Diabesity denotes the expanding worldwide prevalence of obesity, its association with increased incidence of diabetes and the pandemic proportions of this problem in the older adult population (12-15). The consequent metaflammation (metabolic triggered inflammation), as well as the accompanying hormonal dysregulation may promote tumor growth and impact its trajectory (11). Like inflammaging, metaflammation is a low-grade, chronic, sterile inflammation, brought about mostly by expansion of adipose tissue with macrophage infiltration and activation (16).

In addition to releasing the cytokines noted above, adipocyte-macrophage interactions release a host of adipocytokines, which may further promote tumor growth in older obese adults (17). Diabesity also contributes to hormonal changes, such as increased insulin and insulin-like growth factors, as well as increased conversion of androgens to estrogens, all of which may accelerate tumor growth (18). Moreover, metaflammation further contributes to inflammaging, both of which contribute to sarcopenia and sarcopenic obesity.

Certainly, all of these processes are redundantly interactive and synergistic. Importantly however, their rates of development can be controlled and their effects can be at least partially mitigated by limiting exposure to mutagens, such as tobacco, alcohol, talc, and irradiation. In addition, lifelong adherence to recommended guidelines for diet, nutrition, and physical activity appear to slow many of these processes (19). Notably, Diabesity appears to be the most controllable by behavioral modification.

This issue of *TCR* features a series of articles on the impact of obesity, diabetes, and cancer in the older adult population, focuses on providing a better understanding of the processes noted above, how they may influence cancer promotion and progression, and how they may be mitigated to reduce cancer incidence and its comorbidities. The article by Muss, Smitherman, Wood *et al.*, provides an assessment of P^{16} as a marker of biological aging (20). Hassan, Queen, and Cao, detail the impact of enhanced environment on cancer development and its mediation by a hypothalamic-sympathoneural-adipocyte axis (21). Xu and Rogers, address immune regulation of cancer and how it is impacted by physical activity and energy restriction (22). The article by Qiang, Lipscombe, and Lega, provide important insights into mechanisms and consequences

of diabesity (23). Finally, Ligibel, Schmitz, and Berger, describe mechanisms and consequences of sarcopenia, particularly those that accompany cancer and suggest the need for studies for its more effective treatment (24). Overall, these articles provide an important outline of the need for increased translational research to mitigate the impact of cancer in the geriatric population.

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