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Journal of Cancer Immunology Editorial

Cellular Response to Stress: At the Crossroads between Immunosenescence and Cancer

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Received date: June 01, 2020, **Accepted date:** June 01, 2020

Keywords: Aging, Cancer, Stress, Immunosenescence, Innate immunity

Aging is a complicated process not yet fully understood. Driven by a variety of stressors such as infectious agents, radiation, intracellular stress, and stressing metabolic conditions, molecular damage occurs over time [1]. Among many consequences, age-related unchecked molecular damage leads to immunosenescence, a hallmark of aging. Traditionally defined as a declining function of the immune system, immunosenescence is a term that includes the effect of aging on adaptive and innate immunity [2]. Loss of homeostatic control of the immune system leads to higher incidence and mortality due to infection, and diseases including cancer, in the elderly.

Most recently, immunosenescence has been operatively redefined so it can be better measured and characterized. Robust measures of immune markers differently expressed in younger and older individuals are key [2]. For example, circulating levels of inflammation-related molecules such as pro and anti -inflammatory mediators, not only can anticipate mortality risk in the elderly, reviewed in [3,4], but are predictors of poor outcome in age-related disorders [5].

On its side, the presence of some of the components of the senescence-associated secretory phenotype (SASP) overlap with those of immunosenescence. SASP represents tumor micro environmental interactions between different cellular and molecular players [6]. SASP components such as cytokines released by senescent cells actively modify the micro environmental milieu and drive the oncogenic process [7]. We, therefore recognize the connection between immunosenescence and the cellular microenvironment. Cytokines, chemokines, and high energy metabolites are not only drivers of immunosenescence, also they contribute to cancer initiation and promote its progression.

Among molecules with expression affected by stress and aging, heat shock proteins (HSP) are an interesting matter for discussion. Stress-related change in the expression of HSP facilitate cellular recovery. Changes in the expression of HSP modulate protein homeostasis, and affect the progression of age-related pathology [8]. On this matter, a couple of topics are relevant and need more investigation. There is no general agreement on the adaptive response of cells in the way they modify HSP expression with advancing age. Another intriguing theme pertains to hormesis (the salutary effect of repeated short periods of mild stress) and how it affects the synthesis of HSP. To promote discussion, we can speculate that context-dependent function of HSP is relevant. On this regard, the concentration of HSP, the timing of exposure to HSP, the cellular milieu, and the cell-intrinsic rate of aging determine how these molecules contribute to immunosenescence and cancer. Within the TME, HSP promote features of immunosenescence as well as hallmarks of cancer [9]. For example, chronic inflammation, through tissue injury drives proliferation of cancer cells and components of the stroma such as fibroblasts, and immunocytes. By doing so, HSP trigger inflammatory signaling which in turns increases expression of numerous pro- and anti-inflammatory cytokines, chemokines, and chemokine receptors, known to promote tumor progression.

As result of aging, changes in cell intrinsic and extrinsic factors modify the response to stress, the immune responses, and altered the normal tissue milieu. These conditions drive immunosenescence and tumor progression. Not only intracellular communication involved in immune responses is important. Also, one should be aware of other variables such as cell-to-cell communication, antigenic presentation, and immunoescape. To understand how these complex variables intertwine is not only relevant to understand the effects of aging on the immune system and oncogenic transformation, is needed to enhance our

chances of developing better therapeutic strategies to treat cancer in the elderly.

Not until recently, the fields of biology of aging and age-associated pathologies were unconnected. One emergent approach aims to address the role of aging as a major contributing factor for most chronic diseases, including cancer. Throughout understanding of aging biology, will help us to improve health span and delay age-related chronic pathology. We and others [10] advocate that research on responsiveness to stress, immunosenescence, epigenetics, metabolism, macromolecular damage, proteostasis, and stem cells drive the aging process are worth to consider as potential anticancer therapeutic targets. Fine adjustment of mediators of immunosenescence towards homeostatic levels could have beneficial outcomes in lifespan, cancer, and other various pathologies.

Funding

This study was supported in part by Center for Clinical and Translational Science (CCTS), School of Pharmacy, University of Mississippi; Office of Research, University of Mississippi Medical Center; National Center for Natural Products Research, School of Pharmacy, University of Mississippi.

Acknowledgements

The author wishes to thank Amit Reddy, Hali Peterson, and Isabella Gomez-Espinoza for thoughtful discussions and for collating the manuscript.

Conflicts of Interest

The author declare that he has no conflicts of interest.

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