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EDITORIAL

Systemic inflammation and cancer-related frailty: shifting the paradigm toward precision survivorship medicine

Over the past few decades, multiple studies have tried to stratify cancer survivors according to their individual risk of treatment-related toxicities, particularly of persistent 'sequelae' and deterioration of health-related quality of life.[1] Nevertheless, a substantial part of the contributors to this inter-individual variability remains elusive. Seemingly similar patients may follow very different long-term patterns in terms of subjective toxicity to the same—or closely related—classes of drugs or treatment protocols.[2-4] This observation has catalyzed a need to improve the ability to accurately define predictors of cancer-related frailty at the individual level, and to personalize care pathways accordingly, from the moment a diagnosis of cancer is made. Such model of care would allow the implementation of early, tailored management interventions as well as of preventive and proactive supportive care strategies that could reduce morbidity and optimize the utilization of health care resources. Particularly, the identification of clinically actionable biomarkers for persistent cancer-related symptom burden is crucial to intercept optimized patient stratification with delivery of adapted interventions, and thus to successfully move forward the field of 'precision survivorship medicine'.[5,6]

Refined knowledge of physiological and cancer biology has allowed to unravel several mechanistic pathways that underlie the enhanced frailty of certain individuals along their survivorship trajectory,[7] and to identify some of its multiple risk factors, thus leveraging the holistic connection between biology, psychology, behaviors, and other socio-environmental mediators.[8] Among the biological risk factors that have been consistently proposed as linked to increased individual susceptibility to long-lasting treatment-related toxicities, particular empirical attention has been given to cancer-induced systemic inflammation, and, to a larger extent, to related mechanisms of accelerated aging, cellular damage, and stress.[7] The accumulating evidence that such mechanisms may act as physiopathological contributors to heterogeneity among cancer survivors set out the rationale to study their key pathway components and delve deeper into their molecular underpinnings, in order to discover potential biomarkers that may drive personalized clinical care.

Basic research focused on neural-immune signaling has suggested that stimulation of the central nervous system through the release of a pool of circulating cytokines and activation of the proinflammatory axis may herald the appearance of multiple physical, emotional, and cognitive manifestations, and, more broadly, of a number of inflammation-related 'sickness behaviors'.[9-12] Several studies, mostly focused on survivors of breast cancer, have described a wide range of symptoms that may stem from a common inflammatory substrate. For example, cancer-related fatigue, cognitive decline, sleep disturbance, emotional distress, and chronic pain are part of a constellation of usually concurrent and persistent 'behavioral' symptoms that are highly prevalent and distressful for cancer survivors, and for which a mutual etiology has been proposed, although a lot of its granularity still needs to be elucidated.[10,13-15] Along the same lines, data are available showing that the administration or induction of proinflammatory cytokines leads to increased symptomatology also in healthy humans[16-18] and that elevated inflammation is detected in non-cancer populations with emotional distress syndromes.[19,20] However, cancer-related inflammation seems to be linked with more prolonged and more severe symptoms among cancer patients compared to individuals without a history of cancer, suggesting a precipitating role for treatments (particularly chemo-, radiation-, hormone-, or immunotherapy and targeted agents), potentially triggering a hyperactivated cross-signaling and feedforwarding enhanced inflammatory cascades.[12]

Mounting evidence has also pointed at cancer-related inflammation as an accelerator of physiological aging through sustained cellular damage and stress.[7] While the accumulation of common impairments interfering with day-to-day function, such as cognitive deficit, increasing fatigue, and reduced physical performance, is typical of normative aging, leading to a physiological state of frailty in the elderly individual irrespective of a history of cancer, many cancer survivors report physical and cognitive decline that have an earlier onset and greater likelihood of becoming chronic, with substantial detriment on quality of life.[21-24] Pre-existing, predisposing factors including age at cancer diagnosis, comorbid conditions, and baseline psychosocial traits, coupled with precipitating, treatment-related factors, and with other perpetuating conditions, such as unhealthy lifestyles, may favor the accumulation of cells enriched with an inflammation- and stress mediators-biased 'secretome'.[12,15,25,26]

Refined biological knowledge has brought to highlight the role of specific markers of systemic inflammation. Several cytokines,[27-53] particularly interleukin (IL)-1b, IL-6, and tumor necrosis factor-alpha (TNF-a), seem to have

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implications in orchestrating local and systemic effects leading to a wide spectrum of host-defense responses in cancer survivors, such as on energy levels and mood.[11,44-46,53-56] The proinflammatory activity of these mediators has been linked with higher susceptibility to cancer-related symptoms across the disease continuum, from before primary surgery throughout long-term treatments.[11,57,58] Downstream products of cytokine activation also play a relevant role in the proinflammatory response and can contribute to cancer-related frailty. Among these, C-reactive protein (CRP) is an acute-phase protein synthesized by hepatocytes in response to proinflammatory cytokines during inflammatory or infectious processes and is also a marker of immune diseases and cardiovascular risk.[59-61] Higher levels of CRP also have clinical meaning, as suggested by some studies that have associated elevated levels (>3 mg/l) of CRP with cognitive disturbance among elderly cancer survivors.[60]

Furthermore, the identification of associations between genetic variants and a range of treatment-related toxicities has shed optimism on the possibility of identifying germline or acquired genetic indicators of individual susceptibility to cancer-related frailty and improve the predictive ability of models based on clinical characteristics.[5] For instance, in the setting of cancer-related inflammation, germline variants that often take the form of single-nucleotide polymorphisms in the promoter region of genes implicated in oxidative stress or proinflammatory cytokines have been associated with several treatment-related toxicities, particularly with behavioral-like symptoms.[19,27,28,62-67] Additional polymorphisms, some of them in genes associated with cellular response to stress, have been suggested to be implicated in increased predisposition to other common toxicities, such as contributing to cardiomyopathy following anthracycline-based chemotherapy,[68,69] or oxaliplatin-associated neurotoxicity.[70]

How is it then possible to leverage the link between systemic inflammation and cancer-related frailty to inform clinical practice and reduce cancer-related symptom burden? Some of the aforementioned inflammatory markers are easily detectable in the serum and may inform patient stratification if adequately incorporated in screening tools that build on clinical risk factors.[71] Novel technologies may also allow for continuous monitoring of systemic inflammation as a potential 'dynamic biomarker', aiming at anticipating the clinical appearance of inflammation-related symptoms.[72,73] For example, although the inflammation cascade is complex, it was suggested that CRP trajectories could be a proxy of chronic low-grade inflammatory status, and therefore may be useful for early detection, monitoring, and management of cancer- and inflammation-related conditions.[74,75]

Understanding the mechanisms behind the association between inflammation and cancer-related frailty can also pave the way for the development of novel therapeutic strategies that target inflammation to prevent symptomatic deterioration. With improved knowledge of key players of cancer-related inflammation and of their cross-talk at the local and systemic level, potential modifiers and modulators have also been identified. In this setting, a strong and consistent link has been described between inflammation and some behavioral traits. For example, individuals with higher adiposity and lower levels of physical activity, and those who are active smokers, usually have increased levels of systemic inflammatory markers.[12,76] Similarly, a bidirectional association between sarcopenia (i.e. loss of skeletal muscle) and markers of systemic inflammation such as neutrophil-to-lymphocyte ratio has been described in some tumor types.[77-79] This observation led to the hypothesis that inflammation both underlies and is enhanced by muscle breakdown, pointing at another important component of cancer-related frailty.[77] Compelling evidence shows that interventions that act on behavioral modifications of obesity, physical inactivity, unfavorable energy balance, altered body composition and nutritional impairments, alcohol and tobacco use, psychosocial stress, and poor sleep can target inflammation, and thereby can be useful to manage a spectrum of inflammation-associated symptoms, and can thus positively affect both life span and health span among cancer survivors.[7,80-89] Importantly, many of these behavioral interventions can be delivered remotely and digitally.[90] A conceptual framework showing the link among systemic inflammation, cancer-related frailty and its risk factors, and modulating interventions is displayed in Figure 1.

In order to be disruptive and practice-changing, survivorship research focused on dissecting and predicting variability in cancer-related frailty requires a shift toward a deeper understanding of biological underpinnings. This would facilitate the interception of cancer-related frailty through screening and continuous monitoring of biomarkers, and implementation of targeted interventions, and stimulate patient's engagement with their own care. To do so, it is necessary to overcome major shortcomings in the current way we design studies and collect data in this research domain. Historically, toxicity and quality-of-life evaluations have represented secondary endpoint analyses of larger clinical trials. However, the development of multidimensional prediction models requires prospective, *ad hoc* designed and adequately powered clinical studies that incorporate appropriate measurements of the target toxicity phenotype [including combining objective metrics, such as clinician-assessed toxicities via NCI CTCAE, with self-reported data using patient-reported outcome measures (PROMs)[91]]. In addition, standard clinical data linked with biospecimens are required for a comprehensive assessment of multiple biological dimensions, including cytokine multiplex for systemic inflammation, as well as markers of aging and stress. Assessments should be longitudinal and include long-term evaluations extending for years after completion of primary treatment. Healthy controls should also be available for comparison. Finally, while the bulk of survivorship research has been traditionally conducted on population of survivors of very common neoplasms such as breast cancer, efforts to expand this knowledge and research models to other cancer types, including less prevalent ones, are strongly needed.

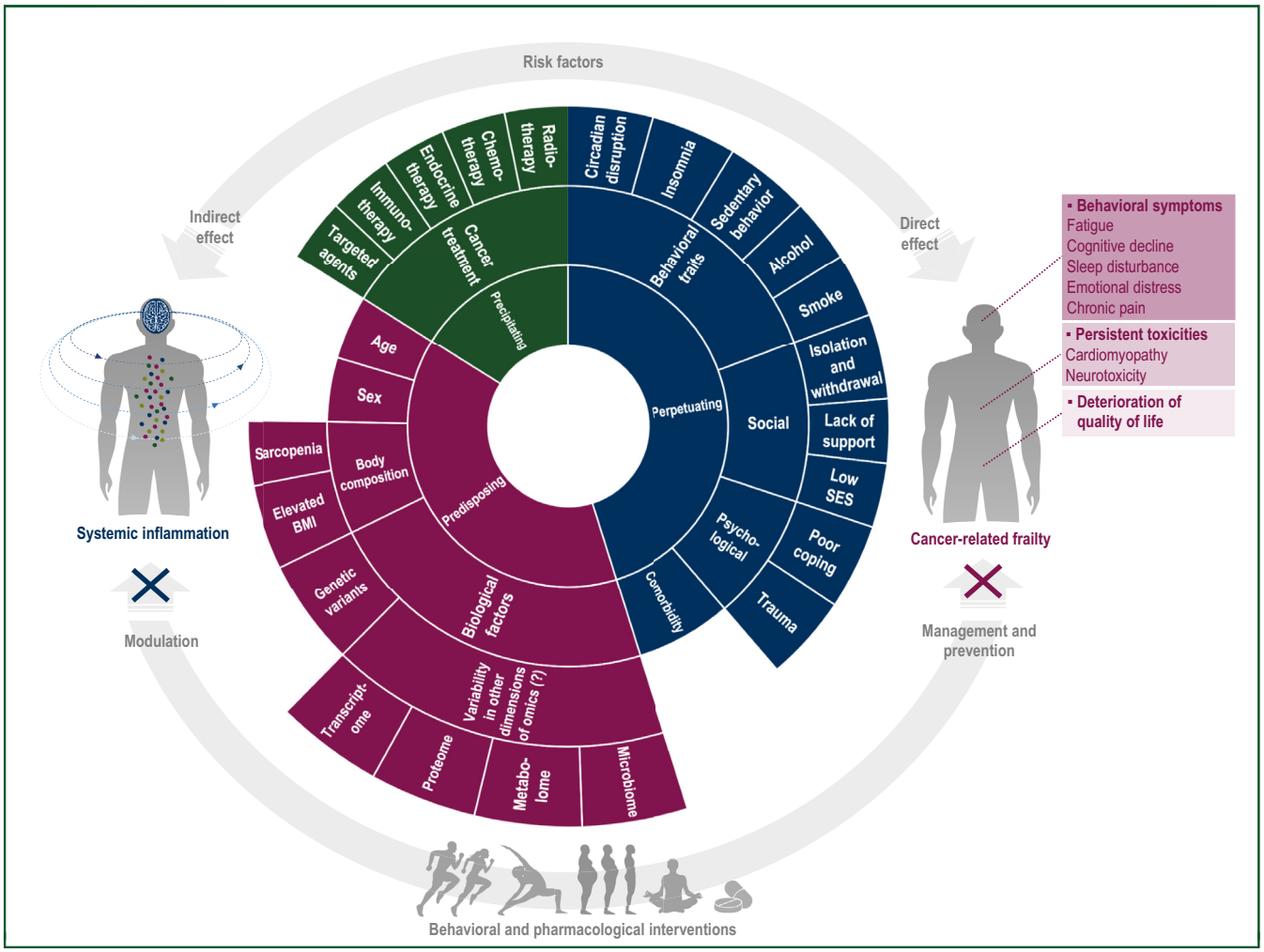

Figure 1. Framework of systemic inflammation and cancer-related frailty.
Risk factors exerting a direct and/or indirect (inflammation-mediated) effect on cancer-related frailty are shown hierarchically in the sunburst chart. Potential risk factors emerging from ongoing and upcoming research are also included (i.e. variability in -omic dimensions). Examples of behavioral interventions (i.e. physical activity, mind—body interventions, weight loss interventions, and maintenance of a healthy weight) are displayed in the lower portion of the figure. These interventions can exert a direct and multi-target effect in the management and prevention of multiple phenotypes associated with cancer-related frailty and are thought to act also on frailty through an indirect effect provided by the modulation of the inflammasome. Lists of risk factors, phenotypes of cancer-related frailty, and interventions in this theorical framework are intended to be illustrations and may be not fully representative of all the spectrum of conditions associated with cancer and cancer-treatments.
BMI, body mass index; SES, socioeconomic status.

In addition, a discovery approach, going beyond the 'hypothesis-driven' evaluation of markers of systemic inflammation, may help identify additional contributors that act as predisposing, precipitating, or perpetuating factors of cancer-related frailty. So far, decades of biomarker research—particularly including large genome-wide studies trying to identify germline genomic predictors of cancer treatment-related toxicity—have yielded only few clinically relevant biomarkers, mostly focused on acute effects, and the majority of studies did not extend to long-term toxicities that may impair patients' quality of life for years after treatment completion.[5] The agnostic study of various dimensions of '-omics', including transcriptomics, proteomics, metabolomics, and the microbiome, may further inform this complex, multifaceted framework.[92-95] However, while high-dimensional 'omic' data hold the promise to provide additional mechanistic knowledge and hopefully some clinically useful biomarkers, research exploiting such dimensions in the cancer survivorship domain is still relatively immature. Rigor and standardization are required in sample collection and processing, and methodologies for training and validation of analytic algorithms still need refinement. In addition, 'new omic' dimensions will soon start to be increasingly available, including data structured directly from health medical records using natural language processing, automated extraction of imaging, and passive capture of patient-generated data through wearables and biosensors.[96-99] Managing these complex high-dimensional data will warrant dedicated research effort.[100]

In conclusion, there is an emerging realization that systemic inflammation, both pre-existing and treatment-induced, plays a critical role in shaping long-term treatment burden, by being a major driver of cancer-related frailty. It is now needed to move toward focused research

that demonstrates how the interception of biological traits can lead to optimized precision survivorship care, through refined identification of survivors at higher risk of cancer-related frailty, individual screening and monitoring pathways, personalized management interventions and systematic pre-habilitation programs, including those based on behavioral strategies and health promotion, and development of targeted therapies that modulate inflammatory responses and other relevant biological pathways.

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