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EDITORIAL

Body composition as a modulator of response to immunotherapy in lung cancer: time to deal with it

Immune checkpoint inhibitors (ICIs), targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), are increasingly reshaping the therapeutic landscape of lung cancer.[1,2] Despite striking successes, only a limited proportion of patients achieve a relevant and long-lasting benefit with such treatments.[3] Individual patient response to ICI-based therapeutic strategies is currently unpredictable: besides the established (and still debated) role of PD-L1 expression, detection of putative tissue- and blood-based biomarkers (still in their experimental phase of development) is challenging both technologically and economically.[4] Thus, identification of clinical (and ideally modifiable) predictors of ICI efficacy represents a crucial goal in the immunotherapy era. To date, two opposite, potentially modifiable, body composition (BC)-related phenotypes have been suggested to potentially modulate immunotherapy outcomes in lung cancer patients: muscle wasting/sarcopenia and excess adiposity/obesity (Figure 1).

Muscle wasting is a prominent BC phenotype in lung cancer patients, which reflects increased protein degradation, reduced protein synthesis or a relative imbalance of the two, due to a complex interplay among cytokines, hormones and other humoral factors, change in energy and substrate metabolism and reduction in nutrient intake or availability, as well as in physical activity.[5] In this regard, recent evidence suggests a potential association between BC and weight loss and immunotherapy efficacy.[6] Clinical data on this topic are quite limited. Recently, a systematic review and meta-analysis concluded that baseline computerized tomography (CT) -assessed depletion of skeletal muscle mass and its onset or worsening during immunotherapy are associated with worse treatment response and shorter long-term efficacy in non-small-cell lung cancer (NSCLC) patients treated with ICIs, identifying sarcopenia as a potential negative predictive biomarker.[7] Among possible explanations for primary resistance to immunotherapy in sarcopenic patients, detrimental effects on the immune system mediated by chronic inflammation, suboptimal drug exposure and higher rates of adverse events and treatment discontinuation have been proposed.[8] Skeletal muscle cells may modulate immune response by interacting with immune cells, as non-professional antigen-presenting cells, expressing major histocompatibility complexes I and II and affecting T-cell function.[9] Additionally, proinflammatory cytokines released as part of the cancer-induced chronic inflammation, a major contributor to muscle breakdown, may also affect immune response, leading to immune escape. In this regard, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are implicated in the activation of several catabolic pathways, such as protein degradation and decreased synthesis, may promote increased angiogenesis and an immunosuppressive environment, characterized by the expression of immune checkpoints in effector T cells and the recruitment of immune suppressor cells.[10] Interleukin-1β (IL-1β) enhances tumor-infiltrating myeloid-derived suppressor cells (MDSCs), which inhibit T-cell and natural killer (NK) cell functions to promote tumoral growth and play an important role in ICI resistance.[11] MDSCs, in turn, activate Treg lymphocytes, which contribute to the immunosuppressive milieu, especially through the production of interleukin-10 (IL-10) which inhibits CD4+ and CD8+ T-cell function, leading to tumor progression.[12] Furthermore, M2 macrophages secrete transforming growth factor-β (TGF-β), a tissue-remodeling and potentially tumorigenic factor, which promotes angiogenesis and immunosuppression.[13] Such immunosuppressive events, observed in cachectic patients, can lead to immunotherapy resistance.[13] Overall, the release of cytokines involved in muscle catabolism and cachexia may also induce systemic inflammation and immunosuppression, associated with worse outcomes in cancer patients treated with immunotherapy.[14]

On the other hand, recent data showed an unexpected inverse relationship between obesity and the efficacy of ICIs, the so-called 'obesity paradox,' both in preclinical models and actual cancer patients.[15] In a large cohort of metastatic NSCLC patients with high PD-L1 expression receiving first-line pembrolizumab, obese patients had a significantly higher overall response rate (ORR), progression-free survival (PFS) and overall survival (OS); such correlation was not observed in the chemotherapy-treated cohort, suggesting that only patients who received immunotherapy had a clinical benefit related to obesity.[16] This concept becomes even more intriguing considering the relatively recent introduction of combinations of chemotherapy and immunotherapy as a new standard of care for NSCLC,[17] further highlighting the need to clarify the relationship between BC and chemotherapy and/or ICIs. A possible underlying mechanism justifying the benefit observed in obese patients might consist of the immune-suppressed phenotype caused by obesity-related chronic inflammation, characterized by a T-helper 1 (Th1) and

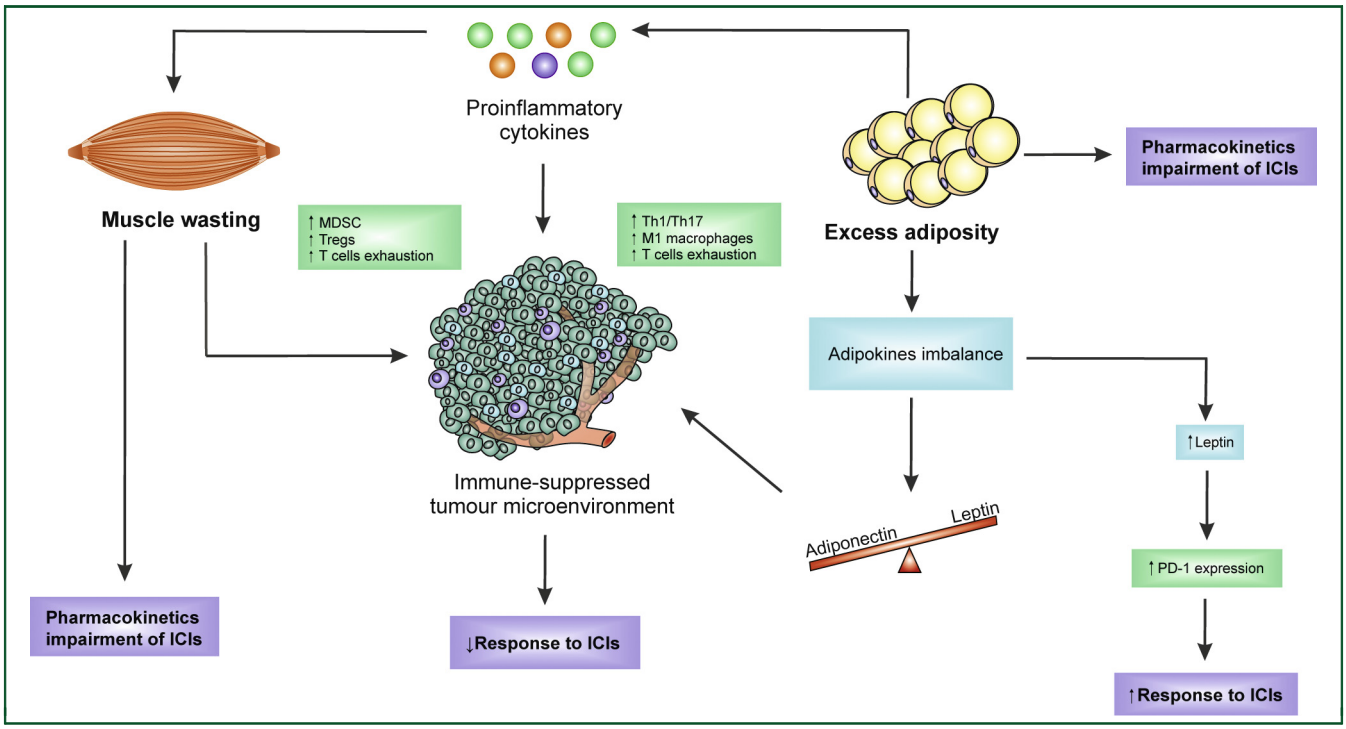

Figure 1. Body-composition-related phenotypes involved in the modulation of ICI response.
ICIs, immune checkpoint inhibitors; M1 macrophages, classically activated macrophages; MDSC, myeloid-derived suppressor cell; PD-1, programmed cell death protein 1; Th1, T-helper 1 cells; Th17, T-helper 17 cells; Treg, regulatory T cells.

T-helper 17 (Th17) dominated environment, an increase of M1-like macrophages[18] and T-cell dysfunction and exhaustion, with a consequent increase of PD-1 expression on CD8+ T cells. A recent study demonstrated that these features lead to higher responsiveness to ICIs in obese tumor-bearing mice, data corroborated by the clinical observation of improved outcomes in obese patients affected by a wide range of cancers, without an increase in immune-related adverse events. As reported by the authors, the increase of PD-1 expression and T cells aging could potentially be mediated by leptin through the STAT3 pathway.[19] Leptin, whose plasma levels correlate with obesity, is an important inflammatory mediator adipokine, able to promote cytokine release, activate Th17 proliferation, impair NK cytotoxicity when increased and contribute to MDSCs induction.[8] Another important adipokine involved is adiponectin, normally reduced during obesity, which has been shown to regulate macrophage proliferation, plasticity and polarization (toward an M2-phenotype), innate-like lymphocyte activity and other innate immune cells functions.[20] The definition of the physiological role and impact on immunity of these adipokines may be crucial for the definition of targeted therapeutic strategies.

Another key point to be considered is that BC phenotypes may contribute to determining drug pharmacokinetics and predicting drug-related toxicities in cancer patients. In the case of ICIs, the lack of data about their pharmacokinetic profile in patients with high body mass index (BMI) and the use of flat-dose administration further increase the complexity of the correlation between BMI and immunotherapeutic agents.[21] Cachexia has been associated with primary resistance to immunotherapy because of suboptimal drug exposure, and anorexia/cachexia-related metabolic wasting has been hypothesized to accelerate the clearance of circulating antibodies, resulting in worse clinical outcomes.[22] Intriguingly, the combination of low muscle and high adipose tissue (sarcopenic obesity), an emerging abnormal and occult BC phenotype in oncology, may help identify a subgroup of patients who may actually not gain any benefit from immunotherapy. A recent study among patients with metastatic melanoma receiving ICIs suggests that patients with higher muscle and low or intermediate fat content seem to have better outcomes than those with high fat/low muscle.[23] In light of currently available data, we may speculate that, although the balance between muscle and fat mass seems to be crucial, the 'relative prognostic weight' of skeletal muscle mass compared with adiposity is likely to be superior.

Overall, the evaluation of BC is likely to become crucial in the clinical decision-making process when starting an ICI-based treatment and for effective patient selection and stratification for future clinical trials employing this class of anticancer agents. In this context, CT scans, routinely acquired for cancer diagnosis and staging, represent an easy modality to provide a careful assessment of BC at specific and relevant time-points throughout the entire course of the patient's treatment, across different body weight, and hence BMI, spectra.[24] In detail, a single axial CT image for regional BC analysis at the third lumbar vertebra has been described to be associated with the whole BC.[25] Using a

commercially available image analysis software, muscle and different adipose tissue deposits can be estimated based on the Hounsfield unit (HU) tissue-specific thresholds.[24]

The abnormal BC phenotypes are prevalent and often hidden conditions in clinical practice, which may be neglected by the use of 'standard' anthropometric measurements such as weight, BMI and weight loss. In the new era of precision medicine, early assessment and monitoring of BC should be routinely carried out in lung cancer patients, despite normal or heavy body weight, since its intrinsic prognostic meaning and, more importantly, in order to offer the patient a tailored therapeutic intervention with the potential of implementing the expected outcome and/or tolerability of available therapies. Baseline and ongoing modifications of circulating cytokines and inflammatory biomarkers along with longitudinal BC detection could give more insights into the mechanisms linking metabolic signatures to immunotherapy response. Moreover, the possibility to explore strategies aimed at optimizing BC (such as tailored nutritional counseling, exercise programs and pharmacological approaches) toward a more immunoresponsive phenotype is extremely intriguing for promoting ICI efficacy and potentially reversing resistance in a proportion of lung cancer patients.

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