Cancer-related cognitive impairment (CRCI) is now widely recognized as a significant clinical problem that can negatively impact quality of life for many survivors long after completion of curative treatments (1,2). Less well appreciated is accumulating evidence that CRCI exists prior to initiation of chemotherapy. Emerging research strongly suggests that the common characterization of this phenomenon as “chemobrain” is a misnomer and highlights the need for new conceptualizations of the underlying mechanisms, which can then be targeted for intervention.

In this issue of the Journal, Patel and colleagues examined the relationship between neurocognitive performance on standardized tests and circulating proinflammatory cytokine levels in newly diagnosed breast cancer patients (3). In their sample of 174 postmenopausal patients, higher plasma levels of sTNF-RII (used as a marker of TNFa production) were associated with poorer memory performance. Relative to 88 age-matched control patients, newly diagnosed breast cancer patients demonstrated impaired verbal memory performance (but not impaired executive functioning or processing speed) and had higher levels of IL-1ra (but not sTNF-RII or IL-6). While several previous investigations have examined cognitive function prior to adjuvant cancer treatment, Patel and colleagues are the first to examine neurocognitive performance in breast cancer patients prior to any cancer treatment (including surgery). Patel and colleagues adjusted their statistical models for a number of key factors that may predict neurocognitive performance, including age, education, fatigue, and, importantly, comorbid medical conditions such as diabetes or hypertension, which are common in older people but are infrequently considered as possible contributors to CRCI. Their results suggest that elevations in proinflammatory cytokines (eg, TNFa) elicited by the underlying disease may be sufficient to cause decrements in memory performance. Given the correlational approach used in this initial clinical study, as the authors note, one cannot rule out the contribution of additional factors (eg, diet, medications, physical activity) that were not assessed.

Strong support for causal links between tumor growth and cognitive deficits in the host is beginning to emerge from preclinical research that has demonstrated effects of both experimentally induced and transplanted tumors on well-established behavioral tests of cognitive function in rat and mouse models (4–7). In one such study, tumor-induced memory impairment was found to be accompanied by increased expression of hippocampal TNFa mRNA in the brain (though not upregulation in peripheral plasma TNFAs). Interestingly, mice bearing tumors in that study also developed increases in depression-like behavior, as well as higher plasma levels of the stress-related hormone corticosterone (7). This and other preclinical observations suggest that the effects of cancer on cognitive function might best be considered from the perspective of the broader literature on “sickness behavior” symptoms in cancer (8). Sickness behavior symptoms include cognitive impairments, but also depressive symptoms, fatigue, pain sensitization, and sleep disturbances, among others (Figure 1). These symptoms often cluster together in cancer patients over time and have been correlated with circulating inflammatory cytokines (9), with causal evidence from animal and human experimental studies that inflammatory stimuli can trigger these behavioral changes (8). Sickness behavior symptoms reflect an evolutionarily adaptive motivational state in which rest and recovery are prioritized over other biological functions. While Patel et al. adjusted for fatigue and anxious mood in their analyses, they did not assess depressive symptoms or sleep disturbance, both of which are common in the immediate aftermath of a cancer diagnosis. Future research that considers the broad constellation of behavioral symptoms related to inflammation rather than focusing on single symptoms such as neurocognitive performance may help to clarify whether interrelated neurovegetative symptoms have distinct biological mechanisms (10,11).

Cancer-related stress is another psychological process that was not considered in the study by Patel and colleagues. A recent paper in the Journal reported that posttraumatic stress symptoms related to cancer accounted for differences in cognitive function between breast cancer patients (assessed prior...
to chemotherapy) and control patients (12). In newly diagnosed cancer patients, acute psychological stress is often elevated as patients undergo staging and other medical testing, make treatment decisions, cope with current or anticipated physical symptoms, and grapple with existential concerns. These stressors may not only affect performance on neurocognitive tests but may themselves activate proinflammatory pathways (13). Indeed, psychological stress may interact with inflammatory pathways to synergistically increase cognitive changes and other behavioral symptoms (14). Psychological stress may also have direct effects on the central nervous system, including decreases in neurogenesis and hippocampal volume (15), that could be exacerbated by additional biological insults of cancer and its treatment. These potential interactions between psychological and physiological reactions to cancer warrant further research.

With regard to potential interventions to reduce CRCI and other sickness behaviors, peripheral blockade of TNF (eg, with infliximab) would have to be used with considerable caution given the important and complex role of TNF in tumor immune surveillance (16,17). Additional options may include targeting IL-1 and IL-6, both known to promote Th17 immunity (18), involved in multiple aspects of neuropathology (19). A behavioral intervention might offer hope of a more nuanced engagement with the regulatory circuitry linking the brain and the immune system (20). Physical exercise has broad psychological and physiological benefits, including improvements in cognition and brain function in aging adults (21), reductions in fatigue and depressive symptoms in cancer patients and survivors (22), and reductions in inflammatory biomarkers (23). Given emerging evidence that exercise may also increase the efficacy of chemotherapy by reducing tumor hypoxia (24), exercise in the context of active cancer treatment may be especially beneficial. Because exercise has been demonstrated to reduce both the biological mechanisms of sickness behavior symptoms (eg, inflammation) and the symptoms themselves with minimal side effects, exercise interventions may dramatically alter the trajectory of cancer-related neurocognitive impairments. This hypothesis requires testing in randomized control trials.

The innovative study by Patel and colleagues in the Journal points the way to important areas for future longitudinal, translational, and intervention research. These multidisciplinary efforts will improve basic scientific understanding of how activation of proinflammatory cytokine networks by cancer cells may increase behavioral symptoms and will also guide clinical interventions to reduce these cancer-related symptoms and improve patient quality of life.
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References