The immune system appears to play a key role in the carcinogenic process, but whether that role is a protective or harmful one is not clear. There is evidence that primary immunodeficiency is associated with an increased risk of specific neoplastic conditions, and the inability of the immune system to control certain viral infections (such as HIV-1, hepatitis B virus, and human papillomavirus) results in the well-known development of specific cancer types. The converse scenario of an inappropriately active immune response having an effect on the outcome of cancer brings us to a conundrum.

The natural mechanisms that suppress cancer development are both cell-autonomous (autophagy, senescence, apoptosis) and non-cell-autonomous (chemo-attraction or “find-me signals,” tumour senescence, tumour killing and clearance), with the latter involving interactions of cells with their microenvironment and especially with the immune system. It therefore seems apparent that inflammation is the host’s defense against any foreign protein, antigen, or cell. However, it is becoming increasingly apparent that, in most cancers, cancer-associated inflammation is a key determinant of disease progression and survival.

Numerous molecules that play a critical role in inflammation have been directly or indirectly related with parameters such as tumour necrosis factor, interleukins 1 and 6, chemokines, cyclooxygenase 2, 5-lipoxygenase, matrix metalloproteases, vascular endothelial growth factor, twist-related protein 1, and cell surface adhesion molecules. Each of the latter molecules has also individually been found to have prognostic value in at least one type of cancer. What is common to all the molecules is that they are regulated by the transcription factor nuclear factor κB. Nuclear factor κB is now known to be ubiquitous to all cell types and present in the cytoplasm during a cell’s resting stage. It is unclear whether the association between aggressive patterns of immunologic markers and poor overall survival in multiple cancer types is attributable to the effects of an intense immune response paradoxically working against the host or to the fact that the more hostile cancers are able to evade even an intense response from the immune system.

Immunotherapy has revolutionized cancer treatment. In 1975, Georges Köhler and Cesar Milstein of the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom, described a method of obtaining antigen-specific antibodies in large quantities. In 1997, with the approval of rituximab for targeting CD20 in patients with low-grade non-Hodgkin lymphoma, monoclonal antibody technology opened the door to the development of targeted cancer therapy. Rituximab was followed by trastuzumab for the treatment of breast cancer positive for human epidermal growth factor receptor 2 and by other agents for various cancer types. Interferon and interleukins have also been used as anticancer agents. More recently, potentiation of the naturally occurring immune response by blockade of the immune checkpoint inhibitors CTLA-4, PD-1, and PD-L1 has proved to be very successful in melanoma and seems promising for other cancers.

Inflammatory cytokines such as tumour necrosis factor α, interleukins 1 and 6, and interferon γ are implicated in maintaining the inflammatory response that leads to the wasting of structures constituting lean body mass. They are believed to be responsible for the cancer anorexia-cachexia syndrome (CACS). The proven role of immune-modulatory agents—for example, corticosteroids, thalidomide and eicosapentaenoic acid, nonsteroidal anti-inflammatory drugs, and statins—in the treatment of CACS supports that theory. The association of the aforementioned cytokines with CACS and the improvement of CACS with administration of immunomodulatory agents has brought about the notion of the immune response being ultimately harmful in cancer patients.

More recently, growth differentiation factor 15, a protein that belongs to the transforming growth factor β superfamily, was found to have a role in regulating inflammatory and apoptotic pathways.
in injured tissues and during disease processes. It is being investigated as a drug target for delaying the progression of CACS, and it has been found to be a predictor of benefit (overall survival, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival) from paclitaxel–platinum–5-fluorouracil chemotherapy in oral squamous cell carcinoma.\textsuperscript{11,12}

Multiple immunologic parameters have proved to have useful prognostic and assessment significance in cancer: for example, pretreatment serum albumin, C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio. Clinical trials have suggested using various combinations of clinical and laboratory parameters to predict recurrence or mortality, given the fact that the inflammatory response per se is associated with trends toward higher mortality in large population cohorts. The modified Glasgow Prognostic Score has been studied as mortality predictor in many cancers, and recently, its prognostic value was found to be improved with the addition of neutrophil and platelet counts and of high-sensitivity CRP. Another score involving CRP and a white cell count was recently published by Kasymjanova et al. in Current Oncology. Those authors prospectively assessed the association of baseline systemic inflammation with freedom from progression in response to chemotherapy and with survival in 134 patients having stage IV non-small-cell lung cancer. The proposed scoring system was the only significant factor prognostic for survival, even after adjustment for performance status, smoking, and weight loss.

In this edition of Current Oncology, Zeng et al. report a retrospective analysis suggesting that CRP at a cut-off 8 mg/L can have prognostic value for cancer-specific survival in patients with nasopharyngeal carcinoma. They also suggest that normalization of CRP levels after chemoradiation could similarly be a prognostic factor in such patients. Should their data be duplicated in a prospective and well-powered analysis, a new set of questions could arise, including whether further interventions to normalize CRP after chemoradiation might have further benefit, whether CRP or other markers could be used to monitor disease response in a subset of patients, and whether CRP as a marker could be applicable for other cancer sites. However, an important variable that has a proven strong prognostic value—human papillomavirus status—has not yet been considered in statistical models that address inflammatory markers.

The oncogenicity of human papillomavirus is relevant and intriguing from an immunologic standpoint, because that virus is associated with cervical cancer and with a type of squamous cell carcinoma of the head and neck that has a much better prognosis than its non-associated head-and-neck counterparts. The mechanisms of oncogenicity related to human papillomavirus and the role of the immune system in that respect remain unknown.

Although it is evident that the immune system has an ongoing interaction with the neoplastic process that starts with the very origins of that process, the factors that turn the response into a protective or harmful one is unclear. Although inflammatory biomarkers have proven prognostic value in various cancers, their usefulness in stratifying patients for therapeutic purposes is a field that has to be further studied.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

REFERENCES


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