Immunonutrition: Enhancing Tumoricidal Cell Activity

Opportunities for Research

Susan S. Percival2,3 and John A. Milner*

Nutritional Sciences, University of Florida, Gainesville, FL 32611 and *Division of Cancer Prevention, National Cancer Institute, Rockville MD 20852

Direct evidence needed

There is little doubt that proper nutrition has a role in overall immune function. Although preclinical models provide rather compelling evidence that essential nutrients and other bioactive food components can influence tumoricidal cell activities, it is far less apparent how these changes relate to subsequent cancer prevention. While logically a change in tumoricidal cell activity would coincide with immunosurveillance, the direct-evidence linking this response to cancer prevention remains woefully inadequate.

Evidence that the observed in vitro tumoricidal effects are important for cancer prevention is scarce. While these tumoricidal properties may be important, more information is needed about the critical elements needed to bring about a response, appropriate models for predicting clinical outcomes, the importance of timing of exposure on the overall response, and vulnerable populations that might benefit or be placed at risk because of intervention. Future antitumor prevention efforts must induce and sustain the activity and survival of these cytotoxic white cells, optimize lymphocyte functions in the tumor microenvironment, and prevent immune suppression by inhibiting production or activity of tumor-derived suppressive factors and inhibiting generation or function of regulatory cells, such as CD4+CD25+ T cells. Determining the efficacy of nutrients to improve tumor-specific immunity in both normal and immunodeficient hosts must address all aspects of immune response to tumors, including tumor antigenicity, reduction of tumor-derived suppressor factors, and improvement of tumor-specific innate and adaptive immunity.

Basic biology of natural killer cells and γδ T cells

Overall, little is known about the basic biology of natural killer (NK)4 cells in fighting cancer or in eliminating aberrant cells. The highly polymorphic nature of NK-cell receptors for major histocompatibility complex (MHC) I molecules may provide a genetic explanation for why some mouse strains or human individuals are resistant or susceptible to various diseases. Systematic characterization of NK-cell receptors and their involvement in resistance to prevention or treatment strategies are warranted.

Several strategies for involving γδ T cells in cancer prevention include the use of various ligands to expand and activate γδ T cells in vivo. Some potential ligands that deserve consideration include synthetic phosphoantigens and aminobisphosphonates. In vitro cell culture as well as animal studies are needed to identify the antitumorigenic response mechanisms in γδ T cells, because, γδ T cells do not require antigen presentation as do the αβ T cells, a better understanding is needed about how they recognize stress and associated consequences. For example, additional research is needed to characterize heat-shock proteins and how they impact γδ T cell function. Furthermore, because no definitive description of γδ T cell antigens has been developed, the characteristics of these antigens including low-molecular-weight nonpeptide molecules, products of infection or cell stimulation, microbial metabolites, alkylamines, and aminobisphosphonates, deserve additional attention. Characterization of the importance of γδ T cell antigens is thus a critical area for investigation.

More information about the involvement of zinc in γδ T cells seems warranted. Zinc oxide has been used to promote wound healing, and zinc pyrithione has been used for psoriasis, but these treatments have been dropped, perhaps due to concerns about how they impact the immune system. Because the skin is known to deteriorate with age, could zinc inappropriately upregulate γδ T cells or is this just an effect of epithelial cell health?

A need for achieving immunobalance

By lowering cancer risk with excessive supplementation use, there may be ill consequences. Thus, it is conceivable that whereas cancer risk may be reduced, the risk of other diseases may be increased; for example, overstimulated γδ T cells may enhance the pathology associated with inflammatory bowel disease. Additional research is needed to determine the appropriate exposures of bioactive food components needed to bring

---

1 Published in a supplement to The Journal of Nutrition. Presented during a workshop entitled: “Immunonutrition: Enhancing Tumoricidal Cell Activity,” held in Bethesda, MD, March 23, 2005. This workshop was sponsored by the Division of Cancer Prevention, NCI, NIH, DHHS. Guest editors for the supplement publication were Susan S. Percival, John A. Milner, and Christopher A. Jolly. Guest Editor Disclosure: Susan S. Percival: no relationships to disclose; John A. Milner: no relationships to disclose; Christopher A. Jolly: received reimbursement for travel expenses from NCI.

2 To whom correspondence should be addressed. E-mail: Percival@ufl.edu.

3 The workshop was part of a sabbatical leave assignment for SSP.

4 Abbreviations used: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MHC, major histocompatibility complex; NK, natural killer; TGF-β, transforming growth factor-β.
about a beneficial response and to determine if there are vulnerable populations that experience such intakes. Additional studies are needed that involve enhancement of the immune system and how this might be coupled with autoimmunity. This example relates to the idea of balance—if one branch of the immune system is activated (or suppressed), how does this affect other branches?

In addition to how the immune system affects cancer, it is also necessary to consider the effects of tumors on the immune system. For example, tumors can secrete immunosuppressive agents. The effects of bioactive food components on this activity remain unresolved.

The cancer immunosurveillance hypothesis proposes that the immune system, through a 2-way interaction with tumors, is an important determinant of host resistance to cancer. Based on this hypothesis, studies using transgenic and immunodeficient animal models, as well as tumor-bearing human subjects are critical to understanding the ability of the immune cells to recognize and destroy tumors or resist tumor-induced suppression.

Models and biomarkers needed

A critical need to adequately evaluate dietary modifications is the appropriate use of validated biological markers for predicting cancer prevention or therapy. Unfortunately, these indicators are not known with any degree of certainty. Undeniably, indicators are needed to effectively monitor modification of cancer risk in short-term studies. It is essential that attention is given to the physiological relevance of a change in immune cell number and which immune markers correlate with a good clinical outcome, i.e., cancer prevention.

Because diet and nutrition are frequently associated with the course of the disease, it is logical to assume that diet and proper nutrition can be used to help prevent or reduce the risk of disease. Leukemia-susceptible mice as a model system could be used to determine the ability of nutritional interventions to enhance cytotoxic cell activity, prevent tumor development, or prevent recurrence. Under some circumstances, bioactive food components may be as effective as drugs. If the site of action of food components could be identified, it would facilitate the identification of a population subset that might benefit most. Some potential targets that may be useful in strengthening tumoricidal activity and/or inhibiting tumor formation are IL-6, NFκB, and transforming growth factor-β (TGF-β). Blocking IL-6 or NFκB as a regulator of IL-6 may prevent cancer while TGF-β acts as a tumor suppressor in early disease and a tumor promoter and immunosuppressant in later stage disease.

Mouse models of malignancy are being used to investigate the mechanisms of action of γδ T cells and potential modulation of their responses for application to human disease. Knock-out models of both NK cells and γδ T cells would help determine biological function and may be useful in determining if proper nutrition can be used to support other immune branches and their subsequent tumoricidal activity.

Whereas it is clear that dietary components can have pronounced effects upon specific immunologic responses, it remains unclear whether dietary components influence tumor formation through modulation of immune responsiveness. T-lymphocyte transfer studies are an excellent model to investigate the direct effects of immunity on malignancy. Adoptive transfer studies demonstrate a direct role for immune cells to participate in cancer elimination.

Additional studies are needed that identify mechanisms for the physiological effects of dietary components when supplied as food or supplements to assist with articulating appropriate nutritional recommendations for individuals and/or target populations. While difficulty may occur in obtaining significant cell populations to perform ex vivo examination (i.e., Western blotting, biochemical assays), mechanisms can be understood with transgenic and knockout models, and these models will be very valuable in understanding tumoricidal activity.

Variability in test substances

Researchers must consider the microenvironments that modify the content and availability of bioactive food components, such as the season of harvest, geographical location, environmental conditions. Despite promising initial results, a significant obstacle for research is the difficulty in obtaining purified and reliable forms of bioactive food components. Researchers should be critical about which species of a specific bioactive food component is being examined, for example, long-chain vs. short-chain beta-glucans, or eicosapentaenoic acid (EPA) vs. docosahexaenoic acid (DHA) vs. fish oil vs. fatty, coldwater fish. Tea and mushroom were identified in the workshop as highly variable, and thus additional attention is needed to characterize these compounds’ important constituents within them and other potential modifiers of the immune system. Dose–response studies are hindered by differences in activity over the different batches. Prospective, double-blind, placebo-controlled studies may be difficult with the actual foods and thus isolated components may represent a viable option. Production of a capsule, which contains defined amounts of various extracts, may help solve this problem. Nevertheless, it is clear that, in most cases, the use of a single component does not result in a comparable response to consumption of the whole food. Thus, studies that use a traditional range of intakes of foods may offer a more realistic approach to unraveling the influence of diet on tumoricidal properties.

Vulnerable populations

The elderly frequently have a lapse in immune surveillance, increased cancer incidence, and increased nutritional deficiencies. Thus they may be a particularly important population for examining the effects of bioactive food components on tumoricidal activities. Clinical studies at preventing recurrence might also be a useful approach. The disadvantage of this population is this may not represent primary cancer prevention. Military personnel might also serve as a possible target population because stress may be expanded beyond that in civilian populations. Regardless of the group examined, the careful selection of at-risk populations should allow for smaller scale studies that would likely be less costly than wide-based population studies.

Prevention may have its effect during the early phase of the cancer process. Thus, it may be more appropriate to monitor dysphasia as a biomarker than cancers per se. Even when susceptible populations are used, trials still may need to continue for extended periods to determine whether a bioactive food component has an effect. Multiple end points may be needed to evaluate food components. Sample collection needs to be simple, because it is often too difficult to collect multiple samples from subjects, and it may jeopardize the success of the trial.

Building studies onto existing trials may help facilitate the discovery of the importance of some food components in modifying tumoricidal activities and cancer prevention. Be-
cause broad areas of cell biology, nutrition, and immunology will likely be needed to adequately evaluate diet, tumoricidal activity, and cancer prevention, there may be the need for a special study section or review panel to evaluate the approach and merits of interdisciplinary teams.

It is assumed that for those with a healthy immune system, nutritional intervention may have little or no impact. However, during periods of stress in the young and elderly, improved and enhanced immune function may be possible through diet or bioactive food components. These areas will require much more work to allow for an appreciation of the positive and negative effects and to allow a realistic cost–benefit analysis when research programs are designed. The need to understand genetic polymorphisms in nutrient requirements and in how the immune system responds will be critical in developing personalized nutrition for maximal cancer prevention.