Nutrition and Tumor Immunity: Divergent Effects of Antitumor Antibody

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Summary

Nutritional deficiency reduces antibody synthetic capacity. Antibody directed against tumor antigens, however, may serve either to heighten tumor immunity, as in antibody-dependent cellular cytotoxicity, or to diminish host resistance to cancer growth by “blocking” cell-mediated tumor immunity. Diets made deficient in specific amino acids are inimical to tumor growth, apparently through reduction of synthesis of blocking antibody. Thus, where tumor immune function is involved, complex and possibly paradoxical effects of nutritional status on tumor growth can be predicted.

Both the cellular and humoral arms of the immune system participate in tumor immunity, and increasing evidence of intimate interaction by the 2 classical components makes moot a discussion of the relative antitumor potency of either one. Malnutrition can affect both antibody formation (17) and lymphocyte-macrophage function (8, 18). Any effect of nutritional deficiency on these aspects of immunity can be predicted to manifest itself without regard to whether the target of the immune response is an environmental antigen or a neoantigen emerging as a component of a tumor cell. Evidence for tumor cell lysis occurring under the influence of antibody and complement without lymphocyte participation is sparse, but this potential mechanism of tumor destruction has not been ruled out. Macrophages, “armed” by contact with antigen or lymphocyte products, are also capable of lysing tumor cells (1). The lymphocyte, however, has come under more extensive study as an effector cell in tumor immunity, and several mechanisms of lymphocyte-mediated tumor cell cytotoxicity have been documented. The immune lymphocyte can destroy tumor cells directly or can do so by elaborating soluble substances that are cytotoxic (9) or that attract other cells to the site of immune stimulation (7). Even the normal lymphocyte, when linked to tumor-specific antibody by receptors for antibody Fc fragment, can kill tumor cells in a reaction known as ADCC (21, 22). This reaction requires no complement and but few antibody molecules per lytic event and can probably call into a play a larger proportion of circulating mononuclear cells to serve as effector cells than can, say, the classic lymphocyte-mediated cytotoxic reaction. In man, tumor immunity of the ADCC type has been demonstrated in transitional cell carcinoma of the bladder (10) and in choriocarcinoma (28). In addition, some studies of in vitro cytotoxicity of cancer patients’ lymphocytes for tumor cells have revealed an augmentation of cytotoxicity with addition of autologous serum (12), an effect possibly mediated by ADCC activity. Thus, an antitumor effect of antibody to tumor antigens is not only logical but is demonstrable, at least in the potentially important ADCC system. It would follow that malnutrition-induced interference with antibody synthesis would lead to accelerated tumor growth.

The now well accepted phenomenon of blocking antibody in tumor immunity (11) complicates this picture and sets the stage for apparently paradoxical effects of suboptimal nutrition on tumor growth. “Enhancement” of tumor

1 Presenting at the Conference in Nutrition in the Causation of Cancer, May 19 to 22, 1975, Key Biscayne, Fla.

2 The abbreviation used is: ADCC, antibody-dependent cellular cytotoxicity.
growth by antibody, first demonstrated by Kaliss and Bryant (16) during tumor grafting experiments in mice, has now been shown to occur in clinical cancer. The presence of blocking activity in serum correlates with the clinical course of cancer, persisting while cancer tissue is present and disappearing when tumor has been surgically extirpated (13). This aspect of the blocking antibody phenomenon is in contrast to lymphocyte-mediated cytotoxicity itself, which persists, once established, despite tumor removal, and suggests a diagnostic and prognostic value for assays of blocking antibody activity. The clinical significance of blocking antibody is not fully known, but instances have been reported (19) in which the appearance of blocking activity in serum has been associated with rapid progression of disease. The possibility that attempts to specifically or nonspecifically stimulate the immune system to antitumor activity may culminate instead in the induction of blocking antibody synthesis deserves full attention as modes of immunotherapy are developed and tested.

Blocking activity in serum occurs in the form of antigen-antibody complexes, rather than as free antibody. Sjögren et al. have convincingly shown (24) using acid dissociation and selective filtration techniques, that antigen and antibody components were inactive until they were recombined and that blocking immune complexes could be eluted from human solid tumor tissue (25).

Given these examples of divergent if not frankly antagonistic effects of antibody on tumor immunity, what will be the ultimate effect of malnutrition-induced reduction in antibody synthesis on tumor growth? Jose and Good (15), using an experimental tumor system in which splenic lymphocytes from rats immunized with mastocytoma cells served as effector cells, studied the effect of dietary manipulation on serum factors affecting the cytotoxic reaction. Results showed that serum from immunized animals kept on a diet fully adequate in protein and calories, when included in the in vitro antitumor cytotoxic reaction, was associated with markedly reduced lysis of the mastocytoma cells. On the other hand, when dietary protein was reduced to 8% of the caloric intake, a highly significant degree of tumor cell killing occurred when the serum of the animal was included in the sensitized lymphocyte-mastocytoma target cell system. When an adequate or nearly adequate (22%) protein diet was instituted in the serum donor animals but only one-half the total calories were provided, it was again seen that tumor cell killing was much less than in the presence of serum from protein-deficient animals. As control, the serum from a nonimmunized normal animal allowed lymphocyte-mediated tumor cell killing to proceed at a normal rate. The conclusion from these studies seems to be that the ability of tumor-bearing or tumor-immunized animals on a normal diet to synthesize serum factors that interfere with cell-mediated tumor immunity outweighs the ability of these animals to develop effective cell-mediated immunity. Conversely, provision of a diet deficient in protein precludes the development of such blocking factors, thereby allowing lymphocyte-mediated antitumor immunity, which is relatively unaffected in this system by dietary deficiency, to proceed in a normal fashion. Jose and Good have looked more specifically at the dietary components responsible for this paradoxical effect on antitumor immunity of dietary deficiency. Using the same system but instituting, instead of broad protein deficiency, specific deficiencies in the amino acids threonine, valine, and tryptophan to amounts between 10 and 50% of normal concentration, these workers noted profound effects on blocking activity. Threonine, valine, and tryptophan in amounts from one-half to two-thirds normal were associated with the appearance in serum of factors that nearly completely blocked lymphocyte-mediated cytotoxicity for mastocytoma cells. When these 3 amino acids were separately reduced in amount from 10 to 25% of standard, these serum factors that blocked normal cell-mediated antitumor immunity either failed to occur or developed in the serum in very small amounts. It appears then that blocking antibody activity, a counteracting force in tumor immunity that is correlated with enhanced tumor growth, is more susceptible than is basic lymphocyte cytotoxic activity to the effects of dietary deficiency, a finding that would seem to be at variance with our established prejudices regarding nutrition and cancer.

What are the factors that determine whether a given host's tendency to resist or to enhance tumor growth shall predominate? Baldwin (4) has approached the problem experimentally by altering the immune complexes generated in vitro by combining rat hepatoma D23 antigen and its associated antibody. Results showed that the nature of the immune complex determined the degree of blocking activity, with complexes prepared in antigen excess being nearly devoid of blocking activity. If such data can be extrapolated to the in vivo tumor-host relationship, it is apparent that the amount of tumor antigen entering the circulation during tumor tissue turnover, in relation to the amount of antibody produced, will have divergent effect on the functional result of the antitumor response.

There are other factors that bear on the relationship between nutritional status, antibody formation, and tumor growth. In conclusion, and without a desire to discourage work in this important area by dwelling on complexities and potential pitfalls, some of these can be simply stated. (a) The ADCC reaction, although mediated by antibody linking effector and target cell, can also be rendered ineffective by other antibody molecules (20), devoid of antitumor activity but possessing Fc fragment affinity for the effector cell and presumably under nutritional influence of the type described by Jose and Good. (b) Tumor antigen alone, uncomplexed with antibody, can also block the immune response, particularly its lymphocyte-mediated component (2). (c) Studies of peripheral blood lymphocyte antitumor activity may not reflect immune events at the site of the tumor; circulating and mesenteric node lymphocytes have in fact shown antithetical responses (3). Finally, evidence exists (6) that nutritional deficiency may differentially affect an immune response according to the requirement of a particular antigen for T- and B-lymphocyte cooperation in the induction phase, a phenomenon that, if confirmed, will add an additional measure of complexity to the nutrition-tumor immunity interface. Awareness of these
counterbalancing aspects of the immune response to cancer should be of value to both nutritionists and immunologists, aiding in the design of appropriate experiments to elucidate a fascinating potential relationship.

References

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