Immunonutrition: Enhancing Tumoricidal Cell Activity

How Can We Best Directly Show that Immunity Influenced by Diet Modifies Cancer: Studies with Dietary Fat in a UV-Carcinogenesis Model

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EXPANDED ABSTRACT

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UV is the primary causal agent of nonmelanoma skin cancer. UV is also a potent immunosuppressive agent, diminishing the ability in animals to mount T-cell-mediated immune responses and it abrogates an animal’s capacity to reject transplanted, highly antigenic UV-induced skin tumors. The latter effect results from the development of suppressor T lymphocytes, the presence or the absence of which also determines whether primary cancer develops in UV-irradiated skin (1). Indeed, T cell involvement with UV-induced immunosuppression was demonstrated by the adoptive transfer of splenocytes from UV-irradiated mice into normal mice, rendering them tumor susceptible (2). Whereas solar UV is an environmental factor difficult to avoid, other extrinsic factors, notably diet, might influence skin-cancer development and thus hold promise in skin-cancer prevention strategies.

Dietary fat was first shown to influence UV-carcinogenic expression in 1939 (3). More recent studies have shown that the level of dietary omega-6 fatty acid influences UV-carcinogenic expression in the hairless mouse model, with increasing levels of lipid reducing the tumor latent period and increasing tumor multiplicity (4). On the other hand, a diet containing omega-3 fatty acids increased the tumor latent period and reduced tumor multiplicity (5). Using a crossover feeding design, the point along the carcinogenic continuum at which dietary omega-6 fatty acids exerted their maximum effect was shown to be principally on the postinitiation or promotion stage (6). When a high-fat diet was fed during the initiation stage and then was replaced with a low-fat diet immediately after UV radiation was halted, animals exhibited the same tumor parameters as having been fed the low-fat diet throughout the study. These findings suggested that dietary modification, even after a cancer-causing exposure to UV, might represent a potentially important intervention strategy in the prevention of nonmelanoma skin cancer and posed the question of how dietary fat could influence such a response.

Earlier studies had suggested that the promotion stage of carcinogenesis might be modulated immunologically, and, indeed, the systemic alteration induced by UVB radiation that suppresses an animal’s ability to reject highly antigenic UV-induced skin cancers occurs during the promotion stage of carcinogenesis (7). In addition, it had been reported that UV-carcinogenesis could be inhibited by feeding mice an essential fatty acid (EFA)3 deficient diet and that the inhibition could be overcome by replacing the diet with one of adequate EFA levels or treatment with chemical promoters (8). These studies confirmed not only the relationship of dietary lipid to the postinitiation stage of UV-carcinogenesis but led to the suggestion that the induced EFA deficiency was associated with protection from UV-initiated tumor outgrowth. These investigators, by way of explanation, suggested that a lack of eicosanoid precursors, as occurs in EFA deficiency, might prevent UV induction of the immune-suppressed state. Indeed, it was demonstrated that suppressor T-cell function is prostaglandin E2 (PGE2) dependent and that UV-induced suppression of contact hypersensitivity, an immune response that may share pathways with tumor rejection, is abrogated by treatment with an inhibitor of prostaglandin synthesis (9). Subsequently, it was shown that PGE2 levels were directly related to the level of omega-6 fatty acid intake, with the highest concentrations occurring at a dietary lipid level in which the greatest exacerbation of UV-carcinogenic expression occurs (10). It was also demonstrated that delayed-type hypersensitivity (DTH), a T-cell mediated response, was markedly (P = 0.01) suppressed in animals fed high levels of omega-6 fatty acids compared with those fed low levels of omega-6 fatty acids or comparable levels of omega-3 fatty acids that contained adequate levels of EFA (linoleic acid). When the influence of high/low omega-6 fatty acid on specific immune parameters was examined, it was found that DTH was significantly suppressed in the high-fat group in the run-in feeding period, even before UV radiation was administered (11). Although both high- and low-fat groups ex-

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3 Abbreviations used: DTH, delayed-type hypersensitivity; EFA, essential fatty acid; PGE2, prostaglandin E2.
hibited UV-induced suppression of this response, the high-fat group was totally suppressed after 3 wk of UV, whereas the low-fat group exhibited reactivity through week 8. When UV-induced tumors were transplanted to recipient animals receiving various periods (0, 6, 11 wk) of UV, no significant differences in median tumor rejection times between the 2 dietary groups occurred at 0 or 6 wk. However, after 11 wk of UV, the low-fat group exhibited a tumor rejection time that was comparable with that of nonirradiated animals, i.e., 21 d, whereas the rejection time for the high-fat group was >63 d. Suppression of tumor rejection by high fat occurred at a time when high fat had been shown to exacerbate carcinogenic expression.

Whereas it was clear that dietary fat could have pronounced effects upon specific immunologic responses, the question still remained whether dietary fat influenced primary UV-induced tumor formation through modulation of immune responsiveness. T lymphocyte transfer studies were undertaken with animals receiving isocaloric diets containing high or low dietary fat and irradiated for 11 wk. At weeks 9 and 12, enriched T cells from high-fat donors that had received 11 wk of UV were transferred intravenously to low-fat recipients. Median tumor times for high-fat, low-fat recipient, and low-fat groups were 15.8, 18.5, and 21.6 wk, respectively. The significantly (P < 0.03) shortened primary tumor latent period in the low-fat recipients clearly demonstrates that the influence of dietary fat upon UV-carcinogenic expression is, at least partially, mediated via immunologic mechanisms (12). Furthermore, when a soluble cell fraction, prepared from a cell line derived from a UV-induced squamous-cell carcinoma in the hairless mouse, was used to “immunize” animals receiving a high-fat diet and a cancer initiating dose of UV, a significant increase in the tumor latent period occurred in comparison with the nonimmunized control. This observation suggests the existence of either a tumor antigen common to both the tumor-cell line and UV-transformed host cells or the elicitation of a general immune response that influences primary tumor formation.

Regardless of specific mechanism(s), it is clear that a major mode of action of dietary fat on UV-carcinogenic expression occurs via modulation of immune pathways; this effect is manifested at a time when the host animal has already been immunocompromised as a result of UV radiation; and the magnitude of this post-UV fat effect may, itself, be modified through immunologic manipulation.

LITERATURE CITED