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Perspectives in Cancer Research

The Paradoxical Association of Regression with a Poor Prognosis in Melanoma Contrasted with a Good Prognosis in Keratoacanthoma

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Abstract

Partial regression in cutaneous malignant melanoma has been reported by a number of observers, albeit not all, to be associated with a relatively poor prognosis; in contrast, a keratoacanthoma, which eventually regresses, does not metastasize. The "Hammond effect" could explain the possibly poor prognosis of the thin regressing melanoma. Hammond (W. G. Hammond *et al.*, Cancer J., *8*: 130–138, 1995) showed that the speed of biological progression to less differentiated phenotypes is directly related to the immunocompetences of the tumor hosts. If partial regression is a sign of an unusually strong immune reaction, then the melanoma that partially regresses might have a relatively poor prognosis because of the greater risk of biological progression among the surviving tumor clones.

A Hammond effect is not associated with regression of a keratoacanthoma. I postulate that the growth of this tumor is accelerated, rather than restrained, by the immune reaction and that the ultimate regression of the tumor is the result, not of immune cytotoxicity, but of a rapid terminal differentiation (a reverse Hammond effect); alternatively, very rapid growth might lead to an exhaustion of growth potential before progression to clonal immortality could occur.

Introduction

The biology of cutaneous malignant melanoma exhibits a seeming paradox: partial tumor regression in the radial growth phase, according to many (1–5) but not to all observers (reviewed in Ref. 6), is associated with a distinctly poor prognosis as compared with those melanomas that show no regression. It is my purpose in this report to present a heuristically appealing hypothesis that could resolve this apparent paradox and also explain the contrasting prognosis of the cutaneous keratoacanthoma (7).

Biology of Malignant Melanoma

There is much evidence, quite apart from the presence of lymphoid infiltrates, that immune reactions play a role in the biology of malignant melanoma. In mouse models, it is clear that melanomas, induced by UV light, arouse a complex immune reaction complete with the generation of suppressor cells (8). An understanding of this complex biology may, fortunately, not be necessary for the present purpose.

My understanding of the biology of the human melanoma is largely derived from reading the definitive works of W. A. Clark, Jr. (1, 9–14) rather than from personal observation. However, I do remember from my days as a resident in pathology that a nevus that showed, in the dermis, a heavy lymphoid infiltrate would be regarded with great suspicion as an incipient malignancy; *i.e.*, the dermal infiltrate was itself considered to be a reasonably good marker of malignancy. Earlier melanotic lesions, lacking a dermal infiltrate and having less or no dysplasia, frequently regress without harmful consequence and probably for nonimmunological reasons (11, 12, 15). Thus, in the nevus, a dermal infiltrate implies a relatively more dangerous lesion; the dysplastic nevus progresses almost imperceptibly into the "radial growth phase" melanoma. Owing to the observations that low levels of immune effectors tend to stimulate rather than inhibit tumor growth (16) and that these early melanotic lesions do not survive (unless treated with carcinogen) when transplanted within skin grafts to nude mice (9, 17), I think it probable that the early lesions may be stimulated by and be dependent upon the dermal infiltrate (18). This may also be the case in the early hyperplasia that precedes carcinoma of the colon (19). Perhaps the flux of effector lymphokines that diffuses into the epidermis from the dermis is not large and, as I will discuss later, there is some reason to believe that incipient tumors may be relatively resistant to inhibition by the immune reaction (*i.e.*, they may be more likely to be stimulated). Thus, regression in very early lesions might sometimes be caused by a diminution of the postulated lymphoid support which, in turn, may lead to differentiation (11); or perhaps regression occurs if they reach their "Hayflickian limit" before their progression to immortality (20).

Clark's extensive observations confirm that the early radial growth phase carries an excellent prognosis. Lesions at a still later stage of biological progression, the "vertical growth phase," are, of course, much more dangerous than the usual nonregressing radial growth phase lesion. The prognosis is seemingly unrelated to the magnitude of any dermal lymphoid infiltrate, but a "brisk" intratumoral lymphoid reaction is associated with an improved prognosis as compared with vertical growth phase tumors that have a lesser intratumoral lymphoid infiltration (1).

Cases of partial regression in the radial growth phase of a lesion may be dangerous (1, 2); this is the apparent paradox. These lesions that partially regress are associated with a lymphoid infiltration into the tumor *per se*, but the dermal infiltrate is reported to be unrelated to prognosis (1, 4).

Hypotheses

The first hypothesis to consider is that the partial regression of a radial growth phase melanoma may be a marker of a lesion that is clonally heterogeneous and heritably unstable; the instability would account for the associated poor prognosis. This hypothesis, that partial regression is a marker of a uniquely unstable lesion, may not be an adequate explanation of the paradox because probably all cases of partial regression occur in radial growth phase melanomas that, elsewhere in the same lesion, show signs of progression to the thicker vertical growth phase (1). Thus, with or without partial regression, these lesions are demonstrably heterogeneous and unstable; the presence of a regressing clone may be unlikely to indicate a lesion of significantly greater clonal instability than is already indicated by the existence of a clone in the vertical growth phase.

Perhaps the most obvious hypothesis that might explain the paradox is to assume that the worsened prognosis associated with partial regression might be due to a greater possibility of metastasis that might be produced by the processes of tumor dissolution *per se*. I think this explanation is quite unlikely. For metastasis to occur, there

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must be vessel invasion. Current data suggest that the thin radial growth phase lesion, and that is the part of the lesion that is seen to undergo regression, is either avascular or poorly vascularized (21). The lesion develops vascularity only late in the process of regression, after widespread cell death has already occurred (22). This avascularity may make it somewhat unlikely that the process of regression *per se* would increase the risk of vessel invasion. Also, it is believed that metastases always originate from the thicker, vertical growth portion of the lesion. Furthermore, regression in other types of neoplasia has not been a marker of a poor prognosis (7).

Another possible way, and the one I favor, by which partial regression could lead to a poor prognosis depends on the "Hammond effect." Recently, Hammond *et al.* (23) have extended some previously reported hints in the literature to the effect that the immune capacity of the host is a determiner of the rapidity of biological progression. In the system reported by Hammond (the chemically induced bronchial carcinoma of the hamster), the greater the immune capacity of the tumor bearer, the greater the speed of tumor progression to less differentiated phenotypes, both in the primary host and during serial transplantation (23). I assume that partial regression in the radial growth phase melanoma is caused by an unusually vigorous immune reaction, as is suggested by the associated intratumoral lymphoid infiltrate (4). If the greater immune reaction leads, via the Hammond effect, to faster biological progression among the surviving tumor clones, it would be understandable that partial regression of melanoma might be associated with a poor prognosis. Although the Hammond effect is to me the most heuristic explanation, none of the possible explanations that I have discussed is mutually exclusive, and all could be correct to some degree.

The mechanisms that mediate the Hammond effect are unknown. If progression gives rise to clones that are more resistant to immune cytotoxicity, simple selection of resistant clones could account for the accelerated progression; immune macrophages can, under some conditions, accelerate growth and be mutagenic (24–26). Shapiro (27) has argued that any form of "stress" may promote "adaptive mutation." However, I will argue later in this report that tumors probably become, as a result of biological progression while in the primary host, more, rather than less, sensitive to the growth-inhibiting effects of immunity. Furthermore, the Hammond data suggest that progression may not have resulted in the spacial localizations that clonal selection of mutant clones usually engenders (28). Judging histologically, progression seemed to be spread rather uniformly across the entire tumor, and there were no noticeable intratumoral sampling-induced variations in the rate or character of the progression (23). Interestingly, there are reports of increased differentiation of human tumors grown in nude mice, suggesting, perhaps, a reverse Hammond effect (29, 30). Although the nature of the Hammond effect remains undetermined, the little available evidence suggests to me that it may entail an adaptive rather than a selective mechanism. It is interesting in this regard that, in tissue culture, growth restraint, albeit not by immunity, of the B16 melanoma (31) or of Rubin's 3T3 cells (32), produces progression. Noble also suggested that growth restraint of a hormone-dependent tumor *in vivo*, by withdrawal of the hormone, promoted progression (33). In the case of the reversible phenomenon observed by Rubin after growth restraint in tissue culture, adaptation rather than selection of mutants was almost certainly the mechanism. Although Hammond did not observe gross evidence of growth restraint, his tumors were probably highly immunogenic, so some restraint probably occurred (23). It is possible that any form of restraint, if not so severe as to cause complete tumor extinction, may accelerate tumor progression. If so, there might even be an analogy to the phenomenon of "punctuated equilibrium" in the evolution of plants and animals, as described by Eldredge and Gould (34).

Whatever the mechanism of the Hammond effect, it is necessary to try to explain how the effect could cause a poor prognosis in association with the partial regression of a radial growth phase tumor, but that an immune reaction, as judged by an intratumoral lymphoid infiltrate, is associated with a better, not worse, prognosis of melanomas that are in the vertical growth phase (1). One possibility is that extensive progression has already occurred in the vertical growth phase so that an increased rate of progression and a worsened prognosis produced by a Hammond effect might be small and outweighed by competing growth-modulating effects of the immune reaction. Another possibility is that the immune response may tend to change qualitatively with time to become less stimulatory (relatively more inhibitory). In accord with both of these ideas, there is some suggestion that the earlier in the progression sequence immunity-induced regression occurs, the more dramatic may be the worsening of the prognosis. Thus, in those rare cases in which regression of a thin lesion occurs with only minimal evidence of progression to the vertical growth phase, the prognosis may be exceedingly bad (2).

Keratoacanthoma and Cutaneous SCC[2]

Regression of a keratoacanthoma, in contrast to the partial regression of a radial growth phase melanoma, does not imply a poor prognosis; apparently, regression of the acanthoma does not trigger a Hammond effect, and the regression goes to completion.

A keratoacanthoma has been described as a well-differentiated SCC with the striking peculiarity of exceedingly rapid growth and, after a period of weeks or at best a few months, complete regression (7). Others, who think it distinct from the SCC, seem to do so largely because it regresses, and it is my opinion that were it not for the attribute of regression, there would be little hesitancy in classifying the keratoacanthoma as an SCC, or at least as a variant thereof. The body of the acanthoma is infiltrated, as is the regressing radial growth phase melanoma, with an "activated" lymphoid infiltrate in which CD4+ cells are prominent; this infiltrate is much more pronounced than is that in the slower growing but nonregressing SCC (22). In the SCC, as in the vertical growth phase melanoma, the denser the intratumoral infiltrate, the better the prognosis. As in the melanoma, a heavy dermal lymphoid infiltrate, in contrast to the intratumoral, does not seem to alter the prognosis (22).

Most authors logically assume that the regression of the keratoacanthoma is mediated by a cytotoxic immune reaction. In support of this supposition, they point out that the acanthoma, which is going to regress, has a heavier intratumoral lymphocytic infiltrate than does the SCC (22). However, I am impressed by the fact that, at the time the heavy infiltrates were noted, the acanthomas had not regressed; the heavy lymphoid infiltrate was itself considered one sign of histological regression and helped, prior to regression, to distinguish the acanthomas from the SCCs (22). Can the immune response, *i.e.*, the lymphoid infiltrate, have a long lag before its effects are seen? Why would such a strong immune reaction not activate the Hammond effect and produce a bad prognosis? Can one explain the rapid growth of the acanthoma?

The simplest explanation of why the regression of the keratoacanthoma, in contrast to regression in melanoma, is not associated with a poor prognosis is really no explanation at all; one could simply posit that the keratoacanthoma cells, in contrast to those of the melanoma, lack an inherent tendency to progression; therefore, immunity-mediated regression cannot produce a Hammond effect. Although I cannot disprove the hypothesis that the keratoacanthoma regresses as a direct result of the cytotoxicity of the lymphoid infiltrate, I will offer

[2] The abbreviation used is: SCC, squamous cell carcinoma.

a possible alternative that may be more congenial with some other observations in the literature and then see how or if the alternative fits with the information concerning melanoma.

The alternative hypothesis suggests that the growth of the keratoacanthoma is stimulated, rather than inhibited, by the lymphoid reaction. This possibility is supported by the numerous observations showing that the immune reaction can be stimulatory to tumor growth (16), and the keratoacanthoma grows exceedingly fast in the presence of a heavy lymphoid infiltrate. Others have also suggested that the keratoacanthoma may be supported by the inflammatory stroma and stimulated by the lymphoid infiltrate (35). However, past experimental work has suggested that it is a quantitatively low or intermediate immune reaction that is stimulatory and that tumor growth is less vigorous if the reaction is either larger or smaller than some modest level that is optimal for tumor growth (16). The optimal level for growth will, however, be different for different types of tumor and even for different tumors of the same type. The level of lymphoid infiltrate that is postulated to stimulate growth of the keratoacanthoma seems to be even higher than levels that, in the SCC, would be associated with slower growth and a better prognosis (22). Therefore, I must assume that, regardless of the density of the lymphoid infiltrate, from the perspective of the cells of the acanthoma, the immune reaction is weak and in the stimulatory rather than the cytotoxic range. Inasmuch as the acanthoma has undergone minimal progression, this phenomenon suggests that the sensitivity of tumor cells to the immune reaction may change during progression; early in the process, the cells may usually be more stimulated and less inhibited by a given density of lymphoid infiltrate. This same type of progression probably applies to melanoma also.

Is there a logical explanation for the postulated change, during biological progression, in the tumors responsiveness to the immune reaction? If the level of the antitumor reaction declines with time, selection would insure that tumors would gradually become less dependent upon, but more stimulated by, whatever low level of immune reactivity remained. There is much evidence that tumor-bearing animals are indeed generally immunodepressed, and effective antitumor responses, for a variety of reasons, seem to wane with time (36–38); perhaps an anti-(stimulatory T cell) suppressor cell reaction occurs. The progression to independence from immune dependency would thus be analogous to the hormone-dependent tumor that becomes independent when deprived of the hormone (39).

The postulate that the keratoacanthoma is relatively stimulated rather than inhibited by the effects of the immune response could explain why the Hammond effect is not seen. As far as the immune-resistant cells of the acanthoma are concerned, the level of immune reaction may be functionally low; consequently, stimulation of growth (and differentiation?) rather than biological progression results; the Hammond effect presumably requires a less stimulatory and relatively more inhibitory level of immunity (23). The contrast with the partially regressing, radial growth phase melanoma is striking; although both are infiltrated by lymphoid cells, the result is apparently growth stimulation in the keratoacanthoma and growth restraint accompanied by progression in the melanoma.

The rapid growth of the keratoacanthoma usually eventuates in regression, and since I have postulated that the cells are resistant and actually stimulated to rapid growth by the immune reaction, why do they eventually regress? I can offer speculations. It is possible that cells stimulated rather than inhibited by an immune response may tend to differentiate (29, 30) and/or perhaps the cells of the acanthoma are stimulated to rapid growth before they have achieved immortality. Regression might then occur when tumor clones reach their "Hayflickian limit" (20). The more immunologically sensitive cells of the SCC, being less stimulated or actually inhibited by the immune response might, especially with the aid of the Hammond effect, achieve immortality, a facet of progression, in time to survive. Alternatively, regression of the keratoacanthoma may occur when and if the stimulatory immune reaction evolves and changes qualitatively into a nonstimulatory type of reaction and the immuno-dependent tumors, therefore, regress.

Skeptics of the hypothesis I have presented, who prefer to believe that the regression of the keratoacanthoma and other relatively benign tumor types is caused by immune cytotoxicity, should consider a tumor in the mouse that is analogous to the human keratoacanthoma. In the classical experiments in which mouse skin is "initiated" with a subcarcinogenic dosage of a hydrocarbon carcinogen and papillomas appear as a result of subsequent "promotion" with a nonspecific chemical or physical irritant, the papillomas almost always regress. just as is the case with human keratoacanthoma. The immune capacity of the mouse can influence the incidence and duration of the papillomas, which are demonstrably immunogenic (40, 41); a modest host immune capacity aids oncogenesis more than a greater or a lesser capacity (42). However, it was shown by Andrews (43) that when the promotion was provided by grafting the initiated skin to immunodepressed allogeneic recipients, regression of the resulting papillomas still occurred, and occurred despite the fact that there was sufficient immunodepression to permit the survival of the papilloma-bearing skin allografts. This degree of immunodepression suggests that papilloma regression may not have been caused, in this case, by an immune reaction. Possible alternatives are that regression of the mouse skin papillomas was due to a lack of immortal clones, or perhaps rapid growth led to differentiation, or perhaps regression occurred because of the extinction of a tumor-stimulating immune reaction; the essential point is that, whatever the mechanism, rapid growth, initiated in this case by the trauma of skin grafting, resulted in eventual regression without a Hammond effect and probably without cytotoxic immunity.

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