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OPINION PAPER

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Harnessing host immune responses to preneoplasia: promise and challenges

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Abstract Preneoplastic lesions are more common than clinical cancer and define a population at increased risk for the development of malignancy. Recent studies suggest that the immune system has the capacity to recognize these lesions, and enrichment of preneoplasia-specific immune effectors can be detected in the tumor bed of some preneoplastic lesions such as monoclonal gammopathies. Here, I discuss the promise and challenges of harnessing the immune response against preneoplasia. Approaches to boost the natural host response to these lesions may have a major impact on reducing net cancer burden.

Keywords Cancer vaccines · Gammopathy · Myeloma · Prevention · Tumor immunity

Introduction

Carcinogenesis is a multistep process involving complex genetic and epigenetic changes in the tumor cells and their microenvironment [1]. In humans, this process takes several years/decades and remains clinically undetected for a large part of its life history. The process of cellular transformation and its key characteristics, including the alterations in oncogenes, anti-oncogenes, and expression of telomerase, are now much better understood [2]. However, the most common clinical outcome of clonal expansion of transformed cells in vivo in humans is not progressive cancer, but clinically indolent expansions in the form of preneoplasia. This is particularly evident in the case of some hematologic premalignancies such as gammopathies, wherein clonality can be easily established and surgical resection is not possible, thereby allowing the natural history of these lesions to be fully manifest.

Recent application of methods to study global gene expression signatures and interphase cytogenetics in human tumors have yielded the surprising finding that preneoplastic cells are a lot closer to their malignant counterparts than previously anticipated [3–5]. In many instances, the preneoplastic cells also have genetic instability and already carry many of the same chromosomal abnormalities or translocations seen in malignant tumors [6]. For example, nearly all of the chromosomal translocations initially identified in tumor cells in myeloma can also be observed in the tumor cells from its preneoplastic counterpart, monoclonal gammopathy of undetermined significance (MGUS) [5]. Why does the clinical behavior of MGUS then differ so much from that of myeloma? One possibility is that the clinical malignancy is regulated at least in part at the level of the interactions of tumor cells with their microenvironment [7]. In other words, host–tumor interactions in early tumors may have a profound impact on the clinical behavior of tumors. Several components of the tumor microenvironment including stromal cells, fibroblasts, new blood vessels, and immune cells play key roles in influencing carcinogenesis. Here, I will focus on the immune component of this microenvironment.

Natural host response in human preneoplasia

In principle, genetic and epigenetic changes in preneoplastic cells, as well as their microenvironment, can provide the source of antigenic targets for the immune system. The next key question therefore is whether the immune system can in fact recognize these cells. To address these questions in the context of a well-defined human preneoplasia, we turned to patients with MGUS.

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These patients have a clonal expansion of transformed plasma cells in the bone marrow, that often remains clinically stable for several years without the development of clinical malignancy [8]. An advantage of this model is that both preneoplastic and immune cells from the tumor bed can be readily isolated for study, without the need for ex vivo culture and enzyme treatments. In prior studies, we had observed that freshly isolated T cells from the myeloma marrow did not respond detectably to autologous tumor [9]. However, T cells from this microenvironment could be readily expanded using tumor-loaded dendritic cells (DCs), to kill autologous tumor cells in vitro. In contrast, when we studied patients with preneoplastic gammopathy, freshly isolated T cells from the bone marrow were enriched for T cells secreting interferon-γ in response to autologous tumor–loaded DCs [10]. This tumor-specific T-cell response could be detected without the need for ex vivo culture and consisted of both $CD4^+$ and $CD8^+$ T cells, with the former being the dominant population. Furthermore, the T cells were also capable of in vitro expansion and of recognizing preneoplastic cells in direct assays. Importantly, this response was specific for the pattern of antigens expressed by autologous preneoplastic cells, as DCs loaded with allogeneic preneoplastic cells were not recognized. Together, these data provide direct evidence that the immune system is capable of reacting to antigens on preneoplastic cells, and that the tumor bed of these lesions may be enriched for tumor-reactive killer T cells. It would now be of interest to test patients with epithelial preneoplastic lesions for similar enrichment of tumor-reactive T cells in the tumor bed. Presence of infiltrating T cells in other preneoplastic lesions (e.g., dysplastic nevi) has already been observed, although the specificity of these T cells was not tested [11].

Antigenic targets in human preneoplasia

Our initial studies measured the immune reactivity at the level of the whole preneoplastic cells. Ongoing studies are trying to further characterize the nature of specific antigens recognized by preneoplasia-specific T cells. In principle, genetic and epigenetic changes in these preneoplastic cells can provide a plethora of antigenic targets, which may vary between different patients. However, most of the current effort at antigen discovery in human cancer has focused on established tumors. Systematic analyses of antigenic profiles in human preneoplasia have not yet been performed. Recently, this has begun to change. Preclinical studies have yielded some targets such as MUC-1, and cyclin-B1, which are expressed in human preneoplasia and can be targets of immune responses [12–14]. Most of the existing data in this regard are restricted to humoral responses, and evaluation of T-cell immunity to defined antigens in preneoplasia is needed. Application of existing methods of antigen discovery to human preneoplasia is an essential first step to designing rational approaches for immune prevention. To begin to address these issues, we and others have now begun larger collaborative efforts to prospectively correlate genomic and biologic features of tumor cells with host response in patients with preneoplastic lesions such as MGUS.

Immune surveillance, immune stimulation, or both?

The new studies of immune recognition of preneoplastic cells in humans raise important but yet unanswered questions about the biologic and clinical impact of immune recognition of preneoplasia on the natural history and biology of human tumors. The immune surveillance hypothesis postulated by MacFarlane and Burnet, including its critics and supporters, has occupied a central place in tumor immunology for the last 4 decades [15, 16]. Recent elegant studies in immune-deficient mice have provided support for the role of both interferon-γ and innate as well as adaptive lymphocyte-dependent mechanisms in immune control of cancers [15].

On the other hand, evidence has also accumulated that under some circumstances, chronic immune activation or inflammation may promote the persistence of tumor cells in vivo [17–19]. It is important to point out that these two possibilities are not mutually exclusive. For example, a low-level immune response may help suppress tumor growth but fail to eradicate it, depending on the proliferative rate and clonogenic potential of the targeted subpopulation, and the nature of tumor antigen being targeted. At the same time, growth factors/chemokines in the inflammatory microenvironment may promote genomic instability, for example by down-regulating p53 function, and eventually promoting tumor immune escape [19]. Immune recognition of preneoplasia may therefore be a two-edged sword, and contribute to sculpting of tumors with reduced immune responsiveness and a greater potential to grow independent of their microenvironment over time [15]. The dependence of early tumor growth on the microenvironment is now being increasingly appreciated [7]. This microenvironment also includes tumor-specific immune cells. The degree to which this immune element of the tumor environment modulates the biology or evolution of tumor and other cells in the tumor bed in vivo remains to be fully clarified.

Lessons from animal models

The difficulties with addressing some of the mechanistic questions directly in humans have encouraged the use of animal models to investigate immune-cancer interactions. Studies with tumor xenografts have been used to establish the ability of the immune system to reject tumors and clarify the nature of rejection antigens [20].

More recent studies have also emphasized the importance of tumor stroma or microenvironment as an important barrier for effective immunity [21, 22]. Both tumors and their microenvironment evolve during tumor progression. The latter in particular may represent a formidable challenge for therapeutic vaccination of advanced tumors.

Pioneering studies in animals have also provided some of the early proof of concept for immune prevention. For example, mammary carcinogenesis in transgenic mice over-expressing rat HER-2/neu protooncogene can be inhibited by vaccination with proteins or peptides, or by DNA plasmid vaccination [23–26]. Boosting natural immunity with IL-12 or IL-2 also hampers the development of mammary tumors, albeit less so than specific DNA immunization [27]. Immune control of preneoplastic lesions is substantially better than that of even small established tumors. Protection seems to depend on both interferon-γ–based delayed-type hypersensitivity and antibody responses [26]. Mice with spontaneous pancreatic cancers develop MUC-1–specific CTLs that do not protect spontaneous tumors. However, upon transfer to naïve mice, they can fully protect against challenge by MUC-1–expressing tumors [28]. Importantly, there was no evidence for toxicity against non-neoplastic tissues or enhancement of carcinogenesis in these experiments. A recent study extended immune prevention to genetic models of spontaneous preneoplasia. Hybrids of DCs with preneoplastic cells were shown to protect against colon polyps in a mouse model of spontaneous cancer [29]. Interestingly, tumor protection required both humoral and cellular immunity. Thus, a rapidly growing body of data in animals now supports the feasibility of targeting preneoplastic lesions for the immune prevention of cancer.

Limitations of animal models

One of the major limitations with many existing models is that they do not fully replicate human preneoplasia or cancer. Recent advances in mouse modeling of cancer, including inducible and tissue-selective targeting, are allowing for technologically much improved modeling of human cancer including preneoplastic lesions [30]. A recent elegant example is the mouse model for pancreatic cancer and preneoplastic lesions [31]. Such models may serve as valuable tools to study early tumor-immune interactions. However, improved mouse modeling of human cancer has also come with new insights into key biologic differences between human and mouse cells. For example, fundamental differences in telomerase biology and p53/Rb pathways in cellular senescence, and biology of the immune system in mouse and man may well impact the interpretation of experimental inhibition of carcinogenesis in mice, and its applicability to humans [32, 33]. Therefore, I feel that while mouse models are invaluable to establish certain principles, they must be complemented by carefully designed studies in humans to gain direct and fundamental insights into the interactions between preneoplasia and innate/adaptive immunity.

Preneoplasia: commotion in the tumor microenvironment

Studies of antitumor immune effectors in the myeloma/gammopathy model point to the dominant impact of tumor microenvironment on antitumor T-cell function in vivo. Indeed, tumor-reactive T cells are present and can be expanded ex vivo from the tumor bed in both myeloma and gammopathy, but differ greatly in antitumor effector function when freshly isolated. Several features of the tumor bed, including cytokines, tumor-derived shed molecules, or other immune regulatory cells (such as regulatory T cells), may contribute to the inhibition of tumor immunity in the tumor bed in progressive tumors [34, 35]. Tumor-derived cytokines or other factors may also inhibit the maturation of DCs in the tumor bed [36]. Inhibition of DC maturation may also shift the balance of immune recognition from immunity toward tolerance [37]. At least some of the potentially negative aspects of the tumor bed (e.g., angiogenesis) are known to be more evident in tumors versus in preneoplastic lesions. A major limitation of the current assays to measure antitumor T-cell responses in humans is that the T cells must be removed from the tumor microenvironment before study. Recent advances in measuring and visualizing immune responses in vivo, particularly in animal models [38], or methods to recreate the tumor bed ex vivo, may allow improved understanding of the differences between immune recognition of preneoplasia versus overt cancer.

Targeting preneoplasia for cancer prevention: challenges and opportunities

Patients with premalignancies are at an increased risk for the development of cancer, although only a proportion (but not all) will develop clinical cancer in their lifetime. This, coupled with the long natural history of these lesions, provides an opportunity to target these lesions for prevention of cancer. Much of this effort to date has focused on drugs. One example is cyclooxygenase-2 (COX-2) inhibitors, which are under active clinical investigation [39]. Another potential approach is to specifically harness the immune system's capacity to resist cancer [40]. Interestingly, COX-2 inhibitors may also modulate antitumor immunity in mice [41]; however, the degree to which this might occur in patients needs further study.

In principle, targeting the immune system for the prevention of cancer may involve both high-risk populations or those with precursor lesions. Both approaches are of value, but involve very different considerations in the clinic. Only the latter is the focus of this discussion.

One distinct advantage for targeting preneoplasia is that the clonal tumor itself can be a surrogate for efficacy. However these patients exhibit considerable heterogeneity, and therefore an important first step is to understand the clinical heterogeneity of these tumors. Those at higher risk for malignant transformation may then be suitable candidates for targeted prevention. The nature of host response to preneoplasia (e.g., identifying those with a blunted or altered response) may itself allow the identification of target high-risk populations. Another challenge will be to understand the antigenic (both intraclonal and interclonal) heterogeneity of these tumors. As discussed earlier, tumors and preneoplastic lesions in many ways represent specialized organs [42], and therefore local factors that impact the efficacy of preventive approaches may be tissue specific and differ between different tumors.

The field of tumor immunotherapy has provided the basis for several approaches to boost immunity, including peptides, DNA vaccines, viral vectors, cytokines, and DC vaccines [40]. In principle, these approaches can also be tested for boosting immunity for prevention of cancer. Our emphasis has been on the use of DCs as potent antigen-presenting cells for boosting immunity [43, 44]. An important aspect of DCs is their ability to acquire and cross-present antigens from tumor cells and efficiently stimulate both $CD4^+$ and $CD8^+$ T-cell responses [45]. In addition to boosting adaptive immunity, DCs are also particularly adept at stimulating innate lymphocytes such as NK or NKT cells [46, 47]. Recruiting both innate and adaptive immune effectors may be essential for effective immune prevention.

Optimizing trial designs for clinical testing of early therapeutic cancer vaccines is an area of active research [48]. Endpoints for these trials are generally based on short-term toxicity, measures of tumor regression (or lack of progression), and surrogate endpoints. The long natural history of preneoplastic lesions, often coupled with their appearance in otherwise healthy individuals, poses additional challenges for optimal clinical testing of preventive vaccines. Here, safety considerations need to include long-term effects. Improved surrogate markers for immune efficacy of preventive vaccines are therefore needed and will greatly facilitate the design of these studies. Such studies should also carefully consider host-related and disease-related features that may impact the outcome of immunologic interventions [49].

Conclusion

In this article, I have argued for increased attention to preneoplastic lesions as attractive targets for immune mediated prevention of cancer. While much remains to be learned in animal models, this change in focus for tumor immunology should also include direct immunologic study of patients with preneoplastic lesions. There is little doubt that there are several challenges that must be overcome. However, some of the greatest successes of immunology have come from prevention (e.g., small pox) rather than immune therapy of disease. Targeted immune-mediated prevention of cancer may therefore have a similar effect on human cancer burden, as with infectious diseases.

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