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Mini-review

Redirecting the focus of cancer immunotherapy to premalignant conditions

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ABSTRACT

Much progress has been made in introducing immunological treatment approaches for cancer, with lessons learned from both the successes and failures of immunotherapy. Among the challenges of immunotherapeutic approaches for cancer are the multitudes of mechanisms by which cancers are known to subvert the immune defenses. This has led to the incorporation into the immunotherapeutic arsenal strategies by which to overcome the cancer's immunological blockades. What has been only superficially explored is the immunological milieu of premalignant lesions and the possibility of immunological approaches for the treatment of premalignant lesions so as to prevent secondary premalignant lesions and their progression to cancer. This review discusses the immunological environment associated with premalignant lesions, and the possible missed opportunity of utilizing immunological treatment strategies in the less hostile environment of premalignant lesions as compared to the immune subversive cancer environment.

Introduction

The survival rates for patients with cancer have been steadily improving with the introduction of a broader armament of treatment options. In addition to surgery, chemotherapy and radiotherapy, several different immunotherapeutic approaches are being used. Such treatments include antibodies such as trastuzumab targeting HER2, cetuximab targeting EGFR or bevacizumab targeting VEGF [1–4]. Non-specific immune-augmenting cytokine treatments such as with IL-2 or IFN-α have been FDA approved and others are in clinical trials [5–7]. Tumor-specific immune treatments have also been tested both alone and in combination with other treatment approaches. These include peptide vaccines and cell-based tumor vaccines [8–10]. While a number of these immunotherapies have seen successes in the treatment of cancer patients, common obstacles to immunological cancer treatment are the multitudes of immune subversive and immune evading approaches that cancers possess.

The mechanisms that cancers have to avoid immune defenses are both direct and indirect. Cancers can directly inhibit immune reactivity by secreting soluble immune inhibitory mediators such as PGE_2, TGF-β and IL-10 [11–13]. They also express checkpoint inhibitory ligands such as PD-L1 that block immune reactivity [14]. Indirect immune inhibition by cancers is mediated by their induction of host immune inhibitory cell populations. These include macrophages, Treg cells, Th2 skewed T-cells, myeloid-derived suppressor cells (MDSC) and the less mature $CD34^+$ progenitor cells [15–19]. Within the tumor milieu, there are not only inhibitory immune cell populations, but also immune inhibitory endothelial cells and fibroblasts [20,21]. Some of these immune inhibitory mechanisms can readily be overcome such as by treatment with COX-2 inhibitors to overcome the immune suppressive activity of PGE_2 [15,22]. Treatment with antibodies to checkpoint inhibitory proteins can also overcome a suppressive mechanism [23,24]. This has included clinical use of antibodies targeting checkpoint inhibitory proteins such as CTLA-4, PD-1 and its ligand PD-L1 [25–27].

Despite the introduction of immunological treatment approaches aiming to stimulate anti-cancer immune reactivity and to overcome the immunological blockades imposed by the cancer, the multiplicity of mechanisms by which cancers can subvert these immunological treatment approaches continues to challenge immunotherapeutic efforts. This heterogeneity of tumor-induced immune suppressive mechanisms may warrant more than blockades of individual immune inhibitory routes to allow for effective

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immunological treatment for cancer. An alternative that is explored in this review is immunological treatment against precancerous lesions that are at high risk for secondary occurrences or progressing to cancer. It is not uncommon for multiple premalignant lesions to develop at various times due to the field effect of areas exposed to substances such as carcinogens [28]. These precancerous lesions are morphologically atypical and, while not yet malignant, are poised to progress to cancer. Unfortunately, the immunological status of the premalignant lesion environment is not well understood and similar observations in a number of instances have resulted in very differing interpretations. This review summarizes the immunological impact of premalignant lesions, both locally and systemically, the deficiencies in what is understood about the role of the immune infiltrate within premalignant tissues, and summarizes studies that have explored the feasibility of immunological treatments to prevent secondary occurrences of premalignant lesions and to prevent premalignant lesion progression to cancer. This could highlight a missed opportunity of preventing cancer by immunological treatment in presumably a less immune subversive environment than in the more challenging immune-hostile cancer environment.

Immunological milieu of premalignant lesions

Substantial efforts have been exerted on cancer prevention such as through lifestyle modifications to include improved diet, smoking cessation and reduced sun exposure. Less emphasis has been placed on immunological approaches to prevent cancer development or progression prior to when cancers subvert immune defenses. An advancement toward this effort is the relatively recent availability of HPV vaccines, which aim to prevent cervical cancer, but also can become effective in preventing other HPV-associated malignancies such as squamous cell carcinomas (SCC) of the head and neck [29,30]. However, there remain non-HPV-associated malignancies that might also be preventable in individuals that are at high risk for development of cancer.

Premalignant lesions are tissues that are not yet malignant, but can progress to become malignant. Examples of these precancerous tissues include polyps in the colon, actinic keratosis of the skin, dysplasia of the cervix, metaplasia of the lung, and leukoplakias of the mouth. Premalignant lesions of the oral cavity, including leukoplakias and erythroplakias, are now routinely screened for during dental examinations [31]. Also routine are colonoscopies to detect colon polyps to, in turn, reduce colon cancer [32,33]. Dysplasia of the cervix is screened for by Pap smears [34]. While standard treatment for these premalignant tissues often includes their excision, such treatment does not remove premalignant cells that have not yet been detected and often does not prevent development of secondary lesions. Very few studies have examined the possibility of adapting immune therapeutic approaches for individuals with premalignant lesions that are at high risk of developing cancer. In fact, few studies have examined the immune environment of premalignant lesions or when, in the course of their progression to cancer, the immune inhibitory environment that is so prominent in cancer becomes established.

One study that compared the immunological microenvironment of intraepidermal carcinomas and SCC showed an increased content of T-cells, and in particular $CD8^+$ T-cells, within the lesions compared to the levels of these cells in cancer tissue [35]. In a separate study, premalignant oral leukoplakias were shown to be infiltrated by $CD3^+$ T-cells, with those containing lower numbers of $CD3^+$ cells having a higher incidence of progression to cancer [36]. It has also been shown that leukoplakias with dysplasia and oral SCC have a higher dendritic Langerhans cell and T-cell content than leukoplakias without dysplasia [37]. The conclusions of such studies suggest that the higher level of immune cell infiltration is indicative of ongoing immune reactivity against premalignant lesions and against cancers. However, additional studies are needed to determine whether this immune reactivity is a beneficial response that aims to protect against tumor development or whether the response could promote tumor development. Supportive of conclusions that immune cell presence within lesions could be an attempt to limit lesion progression are results of studies showing premalignant oral lesion tissues of patients and of a mouse model of premalignant oral lesions that progress to cancer contained increased levels of Th1 and inflammatory cytokines compared to levels within oral cancers [38].

Studies have, however, shown pro-tumorigenic effects of the immune response in precancerous lesions. Such studies have often focused on precancerous states of the gastrointestinal tract. Barrett's esophagus is a premalignant condition that is considered to arise from chronic inflammation and carries a high risk of progression to esophageal adenocarcinoma. Studies of the immune phenotypes in this progression have shown Barrett's esophageal tissues contain an elevated pro-tumorigenic Th2 immune phenotype, but this shifts once cancer has developed to a less activated T-cell phenotype that consists of a mixed Th1 and Th2 cytokine profile [39]. In addition, infiltration by M2 macrophages and Treg cells was suggested to contribute to esophageal cancer development in a rat model of chronic duodenal content reflux esophagitis [40]. Similarly, studies with *Helicobacter pyroli*-infected patients having precancerous gastric lesions and *H. pyroli*-infected mice concluded that increased myeloid cell infiltration and increased IFN-γ expression could be contributing to progression of lesions toward a more cancerous state [41]. This progression of lesions toward cancer in spite of an increase in IFN-γ is paradoxical since IFN-γ is typically considered to be important in the defense against cancer. Gene expression profiles of colon polyp tissues and unaffected colon mucosa of patients having colon polyps showed significant overlap of changes in gene expression compared to gene expression profiles of healthy patients [42]. A large proportion of these alterations in gene expression were associated with immune inflammatory responses, leading the authors to suggest that the pro-inflammatory expression can promote the development of additional polyps in the unaffected colon mucosa of patients with polyps. However, in contrast with this suggestion of inflammation-promoted development of polyps, patients with ulcerative colitis were shown to have a similar frequency of developing polyps as did healthy controls, although, the histological types of polyps differed with an increase in inflammatory (pseudo) polyps [43]. This study also showed no increase in the incidence of adenomas among Crohn's colitis patients.

Studies indicating immune involvement in progression of premalignant states toward cancer have also been conducted in non-gastrointestinal tract sites. Using the TRAMP mouse model that, upon puberty, progressively develops hyperplasia, prostatic intraepithelial neoplasia and carcinoma, the presence of T-cells was shown to facilitate that the progression process [44]. The requirement of T-cells for this progression was demonstrated through multiple means, including using T-cell-deficient crosses or T-cell receptor-deficient crosses of the TRAMP mice, and with T-cell reconstitution studies of these immune deficient mice. Studies with a different murine model of prostatic hyperplasia similarly suggested immune involvement in stimulating prostatic epithelial proliferation, but in this model, the inflammatory reaction was mediated by macrophage-derived IL-1 [45]. Macrophage recruitment was also suggested to promote the formation and progression of pancreatic premalignant lesions [46].

As described above, substantial information is now available about the immune content within precancerous tissues. Overall, inflammation along the gastrointestinal tract appears to have a