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SITC strategic vision: prevention, premalignant immunity, host and environmental factors

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ABSTRACT

Cancer immunotherapy has improved the survival of a subset of patients by harnessing the power of the immune system to find and destroy malignant cells. The immune system also protects the host by destroying developing premalignant and malignant tumors. Advancing our knowledge of premalignant immunity and immune changes seen in lesions that develop into invasive cancer versus those that regress offers an exciting opportunity to leverage the immune system for immune prevention and immune interception of premalignancy. Understanding the immune environment of premalignant lesions and how chronic inflammation plays a central role in the evolution of premalignancy is essential for developing effective immunoprevention and immune interceptions. Factors such as host genomics and environmental factors that affect premalignant immunity and the outcome of advanced cancers are equally important in determining the response to immunotherapy. The broad use of antibiotics and factors such as obesity can disrupt a healthy gut microbiome and drive chronic inflammation that suppresses preventive immunity or the antitumor immune response required for successful immunotherapy in advanced cancers. Modifiable lifestyle factors such as diet, obesity, smoking, and stress should be considered in designing immune prevention and interception studies, as well as for patients who receive immunotherapy for advanced cancer treatment. Other factors, such as the overall immune health of patients and existing comorbidities, affect both premalignant immunity and response to immunotherapy and, therefore, should be considered in managing patients with or without cancer. The Society for Immunotherapy of Cancer previously developed an overarching manuscript regarding the challenges and opportunities that exist in cancer immunotherapy, and this manuscript serves as an in-depth follow-up regarding the topics of premalignant immunity, immune interception, and immunoprevention, and the impact of the host on responding to immunotherapy.

INTRODUCTION

The Society for Immunotherapy of Cancer gathered a diverse group of experts across the cancer immunotherapy landscape to identify challenges and opportunities in cancer immunotherapy, which were outlined in the prefatory manuscript.[1] This manuscript serves to further define and address two of the outlined topics: (1) premalignant immunity, immune interception and immunoprevention and (2) the impact of the host on response to immune therapy and presents the current challenges and opportunities that exist. The immune system plays a vital role in screening and eradicating potentially neoplastic cells in the body and the evolution of premalignant and malignant tumors. Immunotherapy leverages the tumoricidal potential of immune cells, primarily T cells, in advanced and metastatic cancers. Furthermore, clinical trials of immune checkpoint inhibitors (ICIs) in the neoadjuvant setting in lung cancer, triple-negative breast cancer, and melanoma demonstrate the potential of immunotherapy in the treatment of early-stage cancers when the immune system is more intact and can be leveraged to prevent relapse in patients.[2 3] Understanding how host and environmental factors impact the immune system and how derangements in the immune system can allow cancers to develop is crucial to both preventing cancer and promoting optimal response to therapy in advanced cancers.

The emerging field of immunoprevention and immune interception investigates the immune response required to prevent premalignant tumors from developing into invasive diseases and establish protective immunity in high-risk healthy individuals to suppress or eliminate emerging tumors. The development of both effective vaccines to prevent virally induced cancers and effective biomarkers to identify premalignancy are areas with enormous potential to reduce

the economic and personal cancer burden on a global scale.

Chronic inflammation is a common factor in premalignancy and cancer. Various host and environmental factors contribute to chronic inflammation, including aging, inherited genomic alterations, lack of physical activity, unhealthy diet, obesity, dysbiotic microbiota, chronic stress, alcohol consumption, and tobacco use. All the aforementioned factors can negatively impact the immune system and induce a non-productive inflammation that contributes to the development of premalignant lesions and advanced cancers. These factors also impact response to immunotherapeutics. Although some of these factors, such as familial genomic mutations, are not modifiable factors, strategies that address the modifiable risk factors may prevent chronic inflammation or improve antitumor responses against premalignant and malignant lesions.

PREVENTION AND PREMALIGNANT IMMUNITY

The immune system plays a role in tumor development: detected premalignant lesions represent cells that escape from immune elimination.[4] Primary immunoprevention focuses on the immune response required to prevent cancer from developing in healthy individuals as well as how immunological processes such as age-associated chronic inflammation ("inflammaging") can drive tumor initiation and progression to invasive disease. Figure 1. The immune factors in premalignancy show the known factors governing the immune response in premalignancy. Examples of primary immunoprevention include

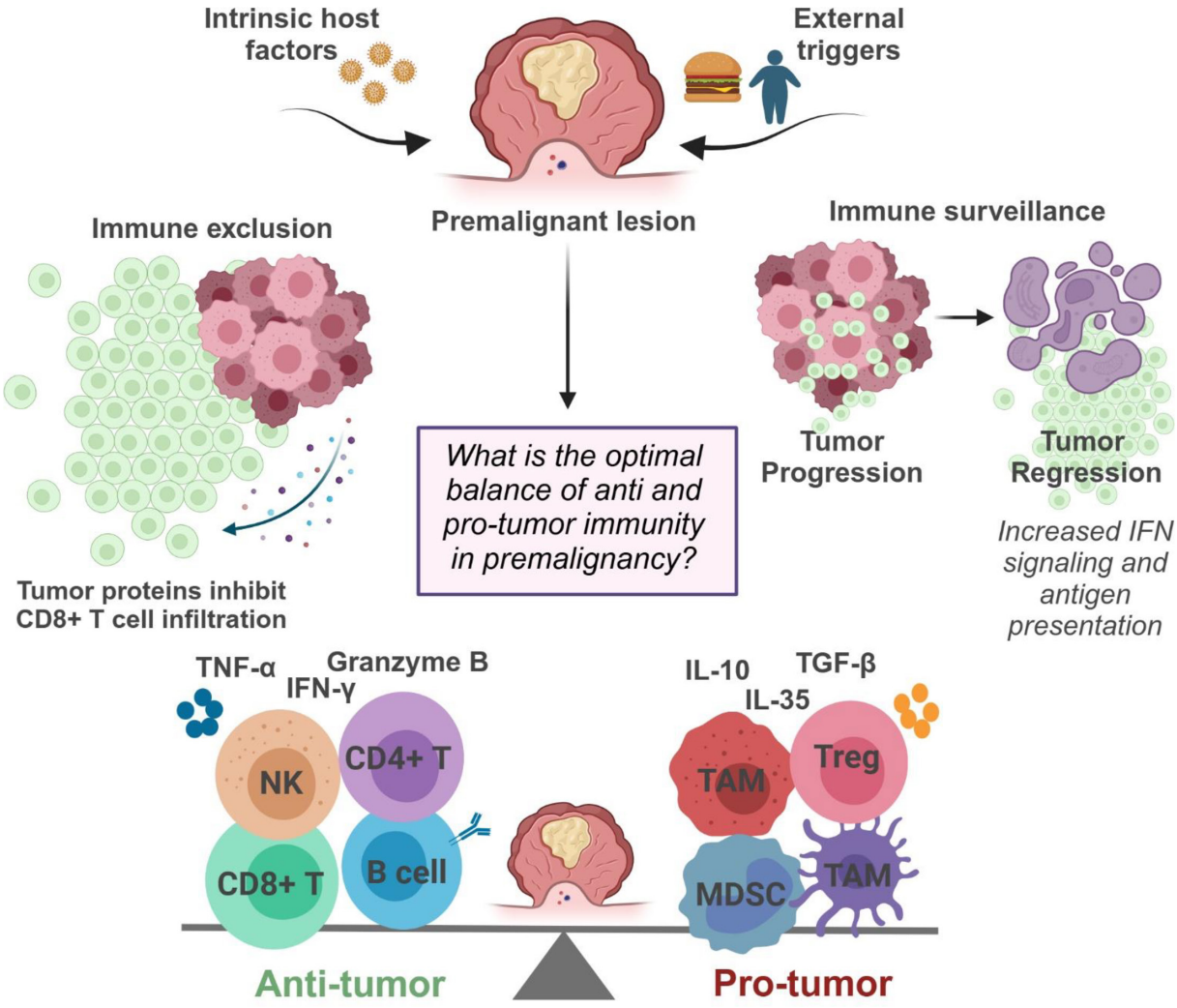

Figure 1 The immune factors in premalignancy. The many facets involved in progression to premalignancy are visualized: Intrinsic host susceptibility factors and negative external triggers are combined to lead to premalignant lesion development. The immune system monitors and eliminates premalignant and tumor cells; however, this can be a balance between inflammatory factors that inhibit tumor growth and immune factors that drive immune exclusion and immunosuppression allowing premalignant tumors to prevent immune cell infiltration. The host immune system balance resulting in cytokine signals that are protumor and antitumor determines whether the tumor will progress or regress. IFN, interferon; IL, interleukin; MDSC myeloid derived suppressor cells; NK, Natural killer cells; TAM (red), tumor associated macrophages; TAM (purple), Tumor associated myeloid cells (e.g. dendritic cells); TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, regulatory T cells.

sterilizing immunity from vaccination against hepatitis B virus (HBV) and human papillomavirus (HPV), which eliminate viral-induced precancerous lesions by inducing long-lasting memory T-cell responses.[5 6] This immunological phenomenon has already demonstrated a significant global health impact of decreasing hepatocellular carcinoma (HBV vaccine) and cervical cancer (HPV vaccine). Immune interception is the process of driving an immune response in patients with premalignant lesions that eradicates the existing lesions and induces immune memory to prevent invasive cancers. One example is using cancer-associated vaccines, such as human epidermal growth factor receptor 2 (HER2) vaccines to treat HER2$^+$ ductal carcinoma in situ (DCIS).[7] Immune interception and prevention strategies establish immune memory at a stage when antitumor immunity is not compromised by extensive immunosuppression and immune cell exhaustion to prevent the development of invasive disease, but successful implementation requires optimized screening methods and early detection of high-risk individuals for early immune-based interventions.

Immune environment of premalignant lesions

Tumor development is the result of a crucial interplay between a developing tumor and the immune system, so recent efforts have focused on understanding how the premalignant immune microenvironment evolves from chronic inflammation to immunosuppression.[8] Insights about the premalignant tumor immune environment in lung, colon, and breast premalignancies through the Human Tumor Atlas Network (HTAN) have shed light on differences in premalignant lesions that progress versus those that regress. For example, single-cell transcriptomic data and imaging studies of the two most common human colorectal polyps (conventional adenomas and serrated polyps) and their resulting colorectal cancer (CRC) counterparts (microsatellite instability-high (MSI-h) and microsatellite stable (MSS) cancer) demonstrated an evolutionary trajectory to CRC.[9] These studies showed an immune exclusion gene signature that prevents cytotoxic CD8$^+$ T cells from reaching tumors. Notably, three identified genes encode proteins secreted from cancer cells that are enriched in extracellular vesicles (EVs).[9] Since the secreted proteins can be detected in plasma, they may be informative biomarkers of immune exclusion in premalignancy. One of these genes is the discoidin domain receptor 1 (DDR1). DDR1 is a tyrosine kinase inhibitor which regulates the expression of extracellular matrix (ECM) proteins and collagen deposition. Overexpression has been inversely associated with CD8 T-cell infiltration in patients with breast cancer and, in preclinical studies, overexpression of DDR1 was associated with dense extracellular matrix.[10] Furthermore, the shed extracellular portion of DDR1 was sufficient to induce increased dense collagen fibers in the ECM leading to immune exclusion and decreased T-cell motility in MMTV-PyMT mice.[11] These studies have led to a clinical trial evaluating whether an antibody specific for DDR1 can overcome immune exclusion and reinvigorate CD8$^+$ T cells. A recent study also highlighted that MSI-h CRCs contain distinct non-metaplastic regions where tumor cells acquire stem cell properties and cytotoxic immune cells are depleted.[12] Using several multiomic techniques, a human precancer atlas is now being developed to identify patients at risk of developing both MSI-h and MSS CRC and evaluate novel prevention strategies.

Premalignant lesions and chronic inflammation

RNA sequencing of premalignant lesions in endobronchial biopsies from high-risk smokers has identified four molecular subtypes with distinct differences in epithelial and immune processes that give rise to lung squamous cell carcinoma. A distinct proliferative subtype is enriched in bronchial dysplasia and exhibited upregulation of metabolic and cell cycle pathways. In this subtype, interferon (IFN) signaling and antigen processing and presentation pathways were decreased in progressive and persistent proliferative lesions compared with regressive lesions. Immunofluorescence staining of regressive and progressive lesions also demonstrated a decrease in CD8$^+$ T cells within progressive lesions.[13] Ongoing studies are now monitoring the progression of lung adenocarcinoma and squamous cell carcinoma using bronchial brushings to survey the immune microenvironment and genetic alterations in the involved and contralateral lung.

Chronic inflammation is important in the development of premalignancy and subsequent progression to invasive cancer. Innate inflammatory cytokines, including interleukin (IL)−1b, IL-6, and type I IFN (IFN-I), drive tumor initiation and treatment resistance.[14] Obesity and aging are also associated with chronic macrophage activation and accumulation of senescent cells that secrete pro-inflammatory cytokines ("senescence-associated secretory phenotype"), both of which drive cancer development.[15 16] Obesity has also been associated with elevated lipid levels, which is a risk factor for the development of hepatocellular carcinomas.[17] Chronic inflammation may be driven in part by the non-coding genome and the reactivation of expressed retro-transposable elements (EREs) and human endogenous retroviruses (HERVs), which have been described in many cancers.[18] Solid tumors reactivate EREs and HERVs that share nucleotide sequences with pathogens, and this viral mimicry activates IFN-I and other pro-inflammatory mechanisms. ERE and HERV transcripts (double-stranded RNA, double-stranded DNA, and RNA:DNA hybrids resulting from ERE-encoded reverse transcriptase activity) are disseminated in EVs, both in the tumor microenvironment (TME) and systemically, and can be taken up by immune and stromal cells and induce systemic inflammation.[19] EV-induced inflammation may also occur during "inflammaging" when ERE and HERV expression increases with age. However, the link between reactivation of HERVs and EREs and tumor initiation in premalignancy and malignant progression has not yet been conclusively demonstrated.[20] Previous clinical data from CANTOS of canakinumab (an IL-1b

inhibitor) aimed at decreasing vascular inflammation in cardiovascular disease also showed a decrease in total cancer mortality in the canakinumab group as compared with placebo (HR 0.49 p=0.0009 in the 300 mg group) and there were significantly fewer lung cancers in both the 150 mg (HR 0.61 p=0.034) and the 300 mg treatment groups (HR 0.44 p<0.0001). This would support a decrease in cancer recurrence with decreasing chronic inflammation.[21] However, the phase III trials CANOPY 1 and 2 that added canakinumab to chemotherapy in metastatic non-small cell lung cancer did not meet the primary endpoints of overall and progression-free survival.[22 23] This supports that there are different roles for IL-1β in premalignant and malignant tumors and in tumors that have received chemotherapy as compared with primary prevention and interception of premalignant disease suggesting that immune therapies that work well in prevention may not have the same effect once treating invasive disease. More studies are needed to understand how exposure to local and systemic chronic inflammation over extended time periods modulates cancer susceptibility and how precancerous lesions develop into invasive tumors. To this end, collaborations to build large tissue banks of precancerous lesions, malignant lesions, and associated blood samples, such as HTAN, are a priority in this area of research.

Immune prevention

Primary prevention aims to develop an effective antitumor immune response in healthy individuals that eliminates any atypical cells. The most successful primary immunoprevention therapies have prevented healthy individuals from developing virally induced cancers. Studies of young individuals in Finland, Denmark, Sweden and England show that HPV vaccination prior to becoming sexually active significantly reduces the incidence of cervical cancer.[24 25] HPV infection also causes other cancers, including head and neck cancer, and emerging data from a Costa Rican clinical trial (NCT00128661) demonstrated vaccine efficiency of 93.3% (95% CI 63% to 100%) in reducing HPV 16/18 infections in the oral mucosa in patients who received the HPV vaccine.[26] While these examples are success stories in primary immunoprevention, preventative vaccines against additional oncogenic microbial infections could have an enormous global impact. For example, the Epstein-Barr virus has been shown to increase the risk of nasopharyngeal cancer, Burkitt's lymphoma, Hodgkin's lymphoma, and stomach cancer and is associated with~200 000 new cancer cases per year worldwide[27 28] and *Helicobacter pylori* causes 95% of 1.1 million gastric cancers worldwide annually.[29]

However, most cancers are not caused by viral infections and produce few, if any, non-self antigens for priming robust antitumor immunity. Hereditary cancer syndromes (HCS) offer opportunities for early cancer detection and interception strategies. Individuals with HCS have inherited mutations in DNA repair pathways, so few additional mutations are necessary for malignant transformation to occur. A peptide vaccine against the tumor-associated antigen human telomerase reverse transcriptase (hTERT), commonly overexpressed in multiple subtypes of metastatic breast cancer, demonstrated safety and immunogenicity in patients with metastatic breast and prostate cancer. Only one patient had a partial response associated with increased intratumoral CD8+T cells.[30] Vaccinating 93 patients with locally advanced disease with IL-12 and an hTERT plasmid vaccine for secondary cancer prevention, 54.8% of patients had disease-free survival at 18 months. Patients with pancreatic cancer with an IL-12 and hTERT plasmid vaccine demonstrated an antigen-specific $CD8^+$ T-cell response associated with improved survival in those with localized disease.[31] Both of these studies have shown immunogenicity and safety but have not been tested for primary prevention or interception. Because breast cancer gene (BRCA) 1/2 mutation carriers experience a higher risk of developing breast and pancreatic cancer, a preventative plasmid vaccine of hTERT, Wilms tumor protein 1, and prostate-specific membrane antigen with or without the IL-12 plasmid delivered by electroporation is currently being tested for safety and efficacy in healthy BRCA 1/2 mutation carriers in a phase I trial (NCT04367675). Tumor-specific mutations that can function as neoantigens are effective in some advanced cancers, including melanoma,[32] but the neoantigen vaccines generated for advanced cancers are personalized to the tumor and, therefore, are not effective in prevention. In patients with Lynch syndrome, microsatellite instability leads to the accumulation of high numbers of DNA mutations, resulting in a high risk of developing colon cancer. Importantly, conserved mutations between patients with Lynch syndrome have been identified, offering an opportunity for preventative vaccination.[33] In a transgenic mouse model of Lynch syndrome, mice vaccinated with conserved frameshift mutations from patients resulted in reduced tumor burden and improved animal survival.[34] A vaccine with an adenoviral priming vaccine and modified vaccinia Ankara boost vaccine containing 209 recurrent frameshift peptide neoantigens is being tested in a phase Ib/II trial (NCT05078866) on 45 cancer-free Lynch syndrome carriers to evaluate vaccine safety and immunogenicity and to date, in 23 patients, it has been shown to be well tolerated and immunogenic in all patients.[35 36] While the number of cancer mutation carriers is low compared with individuals at high risk of developing cancer due to family history or exposure, insights from primary immunoprevention studies involving individuals with inherited cancer risk may be able to be extrapolated to a broader population for primary prevention if the vaccine is shown to be safe and effective.

Repurposing known medications with immune roles for primary immune prevention has also been an emerging area of research. One example is aspirin, which has been attributed to multiple functions in cancer prevention, including impacting DNA repair and epigenetic changes, cell metabolism, and inflammation.[37] When evaluating patients with a history of colon cancer, those taking

aspirin showed increased tumor-infiltrating lymphocytes (p=0.02) and aspirin-mediated blocking of prostaglandin E2 decreased activation of type 2 immunosuppressive dendritic cells.[38] The CAPP2 trial (ISRCTN59521990) randomized 861 healthy Lynch syndrome carriers to aspirin versus placebo and demonstrated that individuals who took 600 mg of aspirin daily for 2 years had fewer colon cancers (HR 0.65, 95% CI 0.43 to 0.97, p=0.035) and protection was durable for 20 years.[39] Once the safety and immunogenicity of the viral 209 vaccine are established, trials for efficacy may be able to include the established benefits with aspirin for enhancing efficacy.

Immune interception

One of the earliest examples of successful cancer interception by immunization was the resolution of vulvar intraepithelial neoplasia (VIN) after vaccine administration of synthetic peptides derived from the E6/7 proteins of HPV. 20 patients with Grade 3 VIN were enrolled and vaccinated four times. At 12 months of follow-up, 15 of 19 patients had clinical responses (79%), with a complete response in 9 of 19 patients (47%). Those patients who developed clinical responses were more likely to have high-magnitude IFN-γ-secreting T-cell responses to the vaccinated antigens.[40] This success with a foreign antigen vaccine in clearing pre-invasive disease spearheaded vaccine development in non-virally mediated premalignancy.

A concern about the overtreatment of DCIS led to the exploration of vaccines targeting proteins expressed in DCIS, such as HER2, which is more frequently overexpressed in DCIS than in invasive breast cancer.[41] Investigators immunized 13 patients with HER2^{+} DCIS prior to surgery with four weekly vaccines of HER2 peptide-pulsed dendritic cells delivered intranodally. Peptides consisted of both class I and class II predicted epitopes. 7 of 11 evaluable subjects showed loss of HER2 expression in their DCIS lesions, suggesting the elimination of cells expressing HER2 may have resulted in antigen-loss variants responsible for the observed persistent DCIS.[7] Subsequent Phase II studies of the approach demonstrated that complete resolution of DCIS in 18.5% of patients could be achieved, which is only a modest response.[42] The development of vaccines targeting multiple antigens may reduce the frequency of antigen loss variants. A vaccine directed against HER2, insulin-like growth factor-binding protein 2, and insulin-like growth factor 1 receptor, which are commonly overexpressed proteins found in DCIS, lobular carcinoma in situ, and atypical hyperplasia, generated high levels of antigen-specific immunity in murine models.[43] Indeed, vaccination alone prevented the development of palpable mammary tumors in 60% of the TgMMTV-neu mice (50% spontaneous mammary tumor model) when immunizations were started at 18 weeks of age. Moreover, when the anti-proliferative bexarotene was given concurrently with vaccination, the development of cancer was prevented in 90% of mice as documented by pathologic examination of bilateral mammary fat pads.[43] The tri-antigen vaccine has recently completed safety/dose escalation studies (100, 300, and 600 mcg) in a phase I clinical trial in stage II and III HER2 negative breast cancer (NCT02780401). The majority of adverse events (AEs) (>95%) were grade 1 or 2, with the most commonly reported AE as injection site reactions, flu-like symptoms, fatigue, chills, and myalgia. All doses were immunogenic, with the greatest magnitude of antigen-specific type I immune responses observed in the low and intermediate doses. 80% of patients at the 300 mcg dose retained high levels of antigen-specific immunity up to 6 months after immunization, and responding patients had tumors exhibiting evidence of epitope spreading.[44] Phase II studies of the vaccine in DCIS patients are in development.

Colonic adenomatous polyps are lesions that predispose individuals to the development of invasive cancer. Mucin 1 (MUC1) is widely expressed in both colonic adenomas and colon cancers, and studies in murine models revealed that immunization against MUC1 prevents the development of colon cancer. In these studies, colon cancer was induced in MUC1 transgenic mice with azoxymethane injection and oral administration of dextran sulfate sodium.[45] A MUC1 vaccine has been tested for immunoprevention in a feasibility study in the premalignant setting.[46] Subjects with a history of advanced colonic adenomas were enrolled to receive a MUC1 peptide-based vaccine with a toll-like receptor 3 agonist as a vaccine adjuvant three times over 10 weeks with a booster dose at 1 year. The vaccine was safe and elicited high levels of MUC1-specific immunoglobulin G antibodies in 17/39 individuals. Investigators observed high levels of myeloid-derived suppressor cells in the peripheral blood of patients whose tumors did not respond to treatment, which may have inhibited the initiation of a productive antitumor immune response. Based on these encouraging results, the MUC1 vaccine was tested further in a randomized clinical trial.[47] 53 individuals with a diagnosis of advanced adenoma<1 year from randomization were assigned to receive either the MUC1 vaccine or placebo. Only 25% of vaccinated patients developed measurable immunity in this study. While no statistical difference in polyp control between the two groups was observed, individuals who did develop immunity with immunization appeared to have a reduction in polyp formation.

In some settings, premalignant lesions may be responsive to immune modulation. Oral leukoplakia is a precursor for oral cancer caused by chronic irritation from smoking and alcohol use and can be associated with T-cell infiltration. One particularly aggressive subtype, proliferative verrucous leukoplakia (PVL), has a 10% probability per year of transforming into invasive cancer. In a single-arm Phase II study, investigators treated 33 patients with PVL with four doses of nivolumab, 480 mg intravenously, once a month.[48] Biopsies of the lesions were performed before and after treatment. 12 patients (36%) experienced a complete response, while 4 had progressive disease. The study met its primary endpoint,

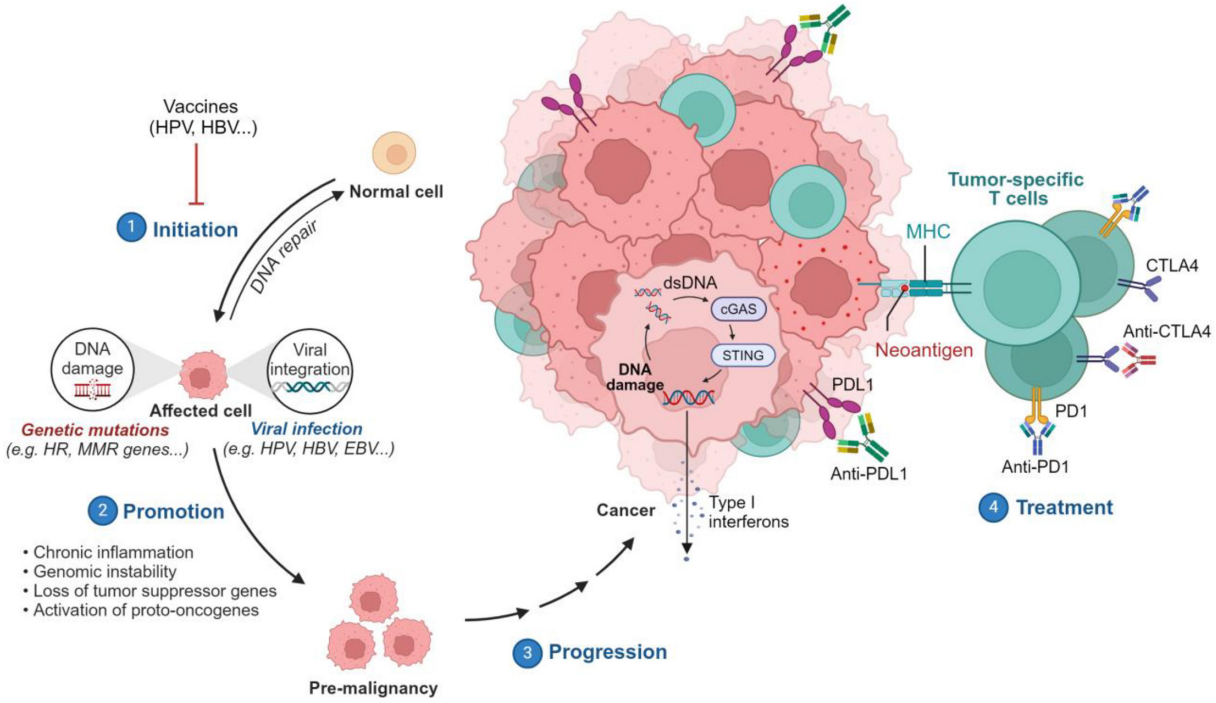

Figure 2 The genetic impact on cancer. Genetic alterations from intrinsic and extrinsic factors can affect the host's susceptibility to premalignant lesions and their progression to cancer. These alternations can also impact tumor immunogenicity, immune cell infiltration, and, ultimately, response to immunotherapy. cGAS, cyclic GMP-AMP synthase; CTLA4, cytotoxic T lymphocytes associated protein 4; dsDNA, double-stranded DNA; EBV, Epstein Bar Virus; HBV, hepatitis B virus; HPV, human papillomavirus; HR, homologous recombination; MHC, major histocompatibility complex; MMR, mismatch repair; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; STING, stimulator of interferon genes.

suggesting potential clinical activity of the approach in this hard-to-treat population. An increasing area of research is the repurposing of classic oral prevention agents for their immune stimulatory effects. Numerous agents that have been used for cancer chemoprevention may have some of their effects mediated, in part, by stimulation of the immune system.[49] For example, recent studies have shown that cyclooxygenase-2 (COX-2) regulates the expression of programmed death-ligand 1 (PD-L1) and COX-2 inhibitors such as naproxen and celecoxib are potent suppressors of PD-L1 on both tumors and antigen-presenting cells.[50] These drugs are not potent enough to be used as single agents but may be most effective when combined with immunoprevention regimens for cancer interception. Importantly, better development of interception/prevention vaccines will require new clinical trial paradigms to support long-term surveillance studies and improve biomarkers for prevention, including circulating tumor DNA or cell-free RNA tumor detection in blood biopsies and health systems to embrace new models of cancer care.

IMPACT OF THE HOST ENVIRONMENT AND IMMUNITY

Host genomics

While host genomics contributes to an individual's predisposition to certain cancers, these variants also impact tumor immunogenicity and treatment outcomes, as shown in figure 2. Mutations in genes involved in DNA repair pathways, including homologous recombination (HR) (eg, *BRCA1*/2, *ATM*, *BRIP1*, *CHEK2*, *PALB2*, and *RAD51C/D*) and the mismatch repair (MMR) pathway (eg, *MLH1*, *MSH2/6*, and *PMS2*) are well-documented to increase cancer predisposition.[51] Genomic instability resulting from DNA repair mutations can induce conserved neoantigens that may provide targets for immunoprevention. Genomic instability further modulates the TME by increasing tumor mutational burden (TMB), neoantigen load, and T-cell infiltration, which can be leveraged to improve responses to ICIs.[51] Consequently, the US Food and Drug Administration approved pembrolizumab for unresectable or metastatic solid tumors with MMR deficiency, high microsatellite instability, and high TMB. The utility and efficacy of ICI alone in HR-deficient cancers require further evaluation.[52]

The variability in response to ICI despite inherited genomic alterations can be attributed to unknown genetic and/or epigenetic differences between individuals. The accumulation of dsDNA resulting from MMR or HR deficiency can activate the cGAS/STING pathway, generating IFN-I that promote antitumor immunity and are implicated in response to ICI. Approximately 20% of the intratumoral variation in interferon signaling (*IFIH1*, *STING1*, and *TMEM108*) is heritable; therefore, knowledge of how these gene variants affect the TME can inform the development of personalized treatment regimens to increase ICI efficacy. Strategies targeting DNA repair pathways

to create a more pro-inflammatory TME, such as PARP1 inhibitors or transiently blocking the MMR pathway that induces IFN-I through cGAS/STING, are promising strategies to improve ICI response in immunologically cold tumors.[53 54]

Genomic characterization of tumors provides insight into oncogenic pathways, and implementing broader sequencing panels can mainstream genetic testing to guide treatment regimens and enable evidence-based investigational therapies in treatment refractory patients.[51] Despite the anticipated benefits of genomic profiling, its effective implementation faces challenges, including limited awareness about genomic medicine among patients and clinicians, delayed or inaccessible hereditary testing, regional disparities, inadequate funding, concerns regarding data security and privacy, limited laboratory services, and social determinants of health affecting accessibility.[55] Open-source repositories compiling information about the pathogenicity and responsiveness of genetic variants to specific treatments, such as the BRCA Exchange, along with artificial intelligence (AI) methods, present an opportunity to address some of these challenges. AI is already being integrated into clinical laboratory workflows, from identifying sequence variants to predicting variant effects on protein structure and function. AI approaches can further link tumor phenotypes, staging, and treatment. It can also extract information from existing research and support patient and clinician education.[56] Continued validation and thoughtful integration of AI into genomic profiling will support its broader use in evaluating TME and clinical care.

Lifestyle and environmental factors

The "exposome" refers to the cumulative measure of environmental influences and associated biological responses throughout a person's lifetime, encompassing all exposures from conception onwards. It plays a crucial role in cancer development by interacting with genetic predispositions to influence carcinogenesis. Primary contributing factors of the exposome are visualized in figure 3. *The premalignant exposome.* For instance, one

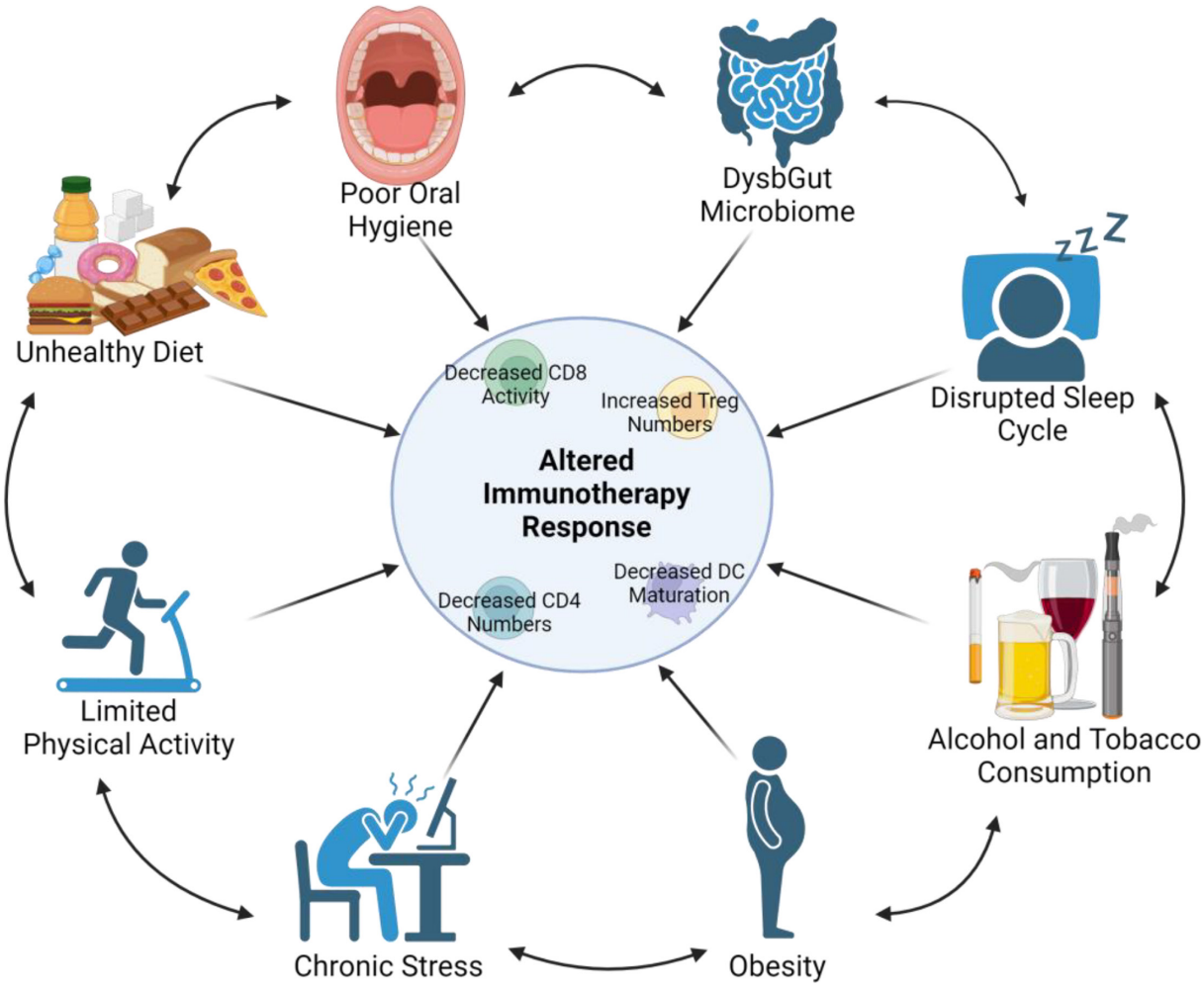

Figure 3 The premalignant exposome. The exposome is the sum of the lifestyle and environment and its effect on the immune response. Lifestyle choices and environmental factors displayed in this figure can negatively influence the function of the immune response, which when combined with host genetic susceptibility, can lead to premalignancy. DC, dendritic cell; Treg, regulatory T cells.

study demonstrated how air pollution contributes to lung cancer development, even in non-smokers, by causing mutations in the epidermal growth factor receptor gene associated with the activation of pulmonary macrophages producing pro-inflammatory cytokines such as IL-1b.[57] Additionally, the exposome affects immune regulation by modulating immune responses, potentially leading to heightened vulnerability to infections or autoimmune conditions. Its interplay with other comorbidities, such as cardiovascular diseases and diabetes, underscores the intricate web of environmental factors impacting overall health.

Social determinants of health also impact cancer risk/carcinogenesis. Emerging data have now implicated modifiable lifestyle factors, such as obesity, diet, stress, and sleep patterns in immunotherapy responses and overall cancer outcomes. While some social determinants of health are non-modifiable, including age, sex, and socioeconomic status, it is important to recognize that many of these factors coexist. Therefore, patients should be approached using a holistic method that acknowledges all social determinants of health and their possible impact on immune function.

Smaller scale studies have begun to investigate the effects of consumable products on ICI therapy, where decreased ICI success correlates with the use of tobacco products, marijuana, and alcohol consumption due to alterations in the population and function of immune cells in the TME.[58–60] In addition to affecting immune cell populations and function, cannabis, alcohol, and tobacco use are associated with changes in the microbiome.[61] Preliminary clinical work on circadian rhythm effects has demonstrated the time of day of infusion significantly impacts median progression-free survival and median overall survival rates among various cancers in patients receiving ICI therapy.[62] Preclinical studies have found that enrichment of clock gene pathways and an abnormal circadian clock can increase PD-L1 expression in the TME and enhance T-cell exhaustion.[63] Similarly, a preclinical animal model of chronic mild stress found increased infiltration of regulatory T cells, decreased $CD8^+$ T-cell numbers, and reduced levels of tumor-associated cytokines in tumors of mice treated with an anti-PD-L1 antibody.[64] These early studies indicate the importance of lifestyle effects on the success of immunotherapy treatment and warrant further investigation.

Obesity and diet interventions are currently being investigated for their role in ICI activity across various cancer models. Preclinical obesity models revealed increased prevalence of intratumoral myeloid cell populations. A high-fat diet preclinical model of obesity demonstrated that myeloid-derived suppressor cells facilitated breast cancer tumor growth by limiting the activation of tumor-reactive $CD8^+$ T cells.[65] The availability of nutrients in the TME can also alter the immune environment of the tumor and tumor growth. The increased nutrient availability observed with obesity promotes tumor cell proliferation and an increase in exhausted $CD8^+$ T cells.[66] Dietary interventions altering nutrient availability, such as ketogenic, high-fiber, or caloric restriction, may use metabolic vulnerabilities in tumor cells to decrease tumor progression and enhance the efficacy of ICI.[67 68] Fiber has also been associated with increased gut bacterial diversity and higher dietary fiber intake is correlated with enhanced ICI response and decreased risk of immune-related AEs (irAEs).[69] One large clinical trial utilizing a fasting-mimicking diet among various cancer types found decreased levels of immunosuppressive immune cells and an increase in $CD8^+$ T cells, indicating diet content could be used to alter the TME.[70] Notably, recent epidemiological studies have examined the rates of cancer in individuals taking GLP-1 agonists for weight loss. For example, a recent study found that these GLP-1 targeting agents may reduce CRC risk in patients with type 2 diabetes, who are overweight/obese partially mediated by weight loss and other mechanisms.

Despite the widespread use of immunotherapy, the impact of changeable lifestyle factors on the therapeutic efficacy of ICI remains unclear. For instance, in the "obesity paradox", obesity has been reported to increase responses to ICI treatment despite conflicting results between studies.[71] Therefore, further investigation into the direct effect of obesity on ICI response is warranted. Large-scale observational studies on the effects of dietary intake on ICI therapy in cancer have not been done. Dietary intervention studies often use differing nutritional modifications and contrasting data collection methodologies, making data harmonization and comparison difficult. AEs from ICI therapy may also cause patients to struggle to adopt new lifestyle habits or participate in interventional diet-related research studies. Standard guidelines for study implementation and patient education may reduce variability between centers and increase patient retention in lifestyle-focused trials.

Another challenge for the field remains the lack of preclinical models that recapitulate humans' genetic diversity and infectious disease history for environmental and lifestyle studies. While preclinical models offer invaluable mechanistic insights, standard pathogen-free animal models do not reliably predict clinical responses to treatment. Therefore, developing more clinically relevant animal models to study environmental factors affecting ICI response should be prioritized. Altering the living conditions of laboratory mice including housing mice at thermoneutral temperatures in animal facilities influence tumor growth, gut microbiome, and antitumor immunity and may lead to greater concordance between preclinical and clinical studies.[72] However, not all institutions have the comparative medicine facilities required for these studies.

Microbiome

The gut microbiome plays a key role in the development and progression of cancer, as well as antitumor immunity and tumor responsiveness to ICI. Antibiotics or diet changes can disrupt the gut microbiome. The cross talk

of the host immune system with the gut microbiota maintains intestinal homeostasis and is essential in preserving healthy immune functions.[73] Despite research indicating the link between dysbiosis and increased inflammation leading to the development of cancer, it remains unknown whether this is caused by pathogen-specific or bacterial-community effects. Increased gut microbial diversity and the use of antibiotics during ICI treatment have been shown to improve or negatively impact patient outcomes, respectively.[74 75] Therefore, establishing a favorable microbiome in patients with cancer is an active area of research. In addition to research on specific bacteria, work is underway investigating the role of the metabolites produced by bacterial species and their impacts on ICI efficacy.[76] Recent clinical trials have demonstrated microbiome interventions such as probiotics or fecal microbiome transplantation (FMT) offer unique opportunities to alter patient microbiomes and potentially improve outcomes of ICI treatment.

To date, the bacterial species attributed to favorable or unfavorable microbiomes are controversial, further complicated by the complex differences in cell types and immune profiles of various cancers. For example, oral bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have been found within various cancers, including oral squamous cell carcinoma, CRC, and pancreatic cancer.[77 78] Despite research indicating a role of *P. gingivalis* and *F. nucleatum* in chronic inflammation and recruitment of tumor-infiltrating immune cells, the causation between the presence of specific bacteria and tumor development still needs to be investigated.[79] Further complications include standardization of microbiome sample collection, processing, and sequencing methods across institutions and countries and the extravagant costs for metagenomic sequencing that can result in difficulty obtaining consistent results between institutions running data sets. Additionally, there are no standard practices for testing patient microbiomes or guidelines for therapeutic microbiome interventions to guide clinician's treatment decision-making. The creation of novel microbiome therapeutics such as full spectrum consortiums, super probiotics or methods to create central large-scale FMT operations would be beneficial for all oncology stakeholders from researchers to clinicians to patients. The development of novel and practical analyses for microbiome populations or their metabolites in patients could improve the success of immunotherapy in various cancers. While commercial kits for fecal metabolomics are in development, the use of quick and straightforward point-of-care metabolite analyses from various patient sources including breath, stool, urine, and blood in clinical settings may rapidly inform immuno-oncology decision-making.[80]

Immune health and comorbidities

Roughly 50% of patients with cancer are candidates for immunotherapy treatment.[81] Despite immunotherapies having a different toxicity profile than traditional chemotherapies, irAEs can occur and carry risks of disability and/or fatality for patients. To reduce a patient's risk of developing immune toxicities that may decrease quality of life, treatment decision-making teams consider the presence of comorbidities, which are clinically classified as autoimmune, immune neutral, and immune dampening diseases. Immune neutral diseases such as dyslipidemia and gastroesophageal reflux disease are classified as such because the effect or relationship these comorbidities have with the immune system is not fully understood and requires further study.

Notably, up to two-thirds of patients diagnosed with cancer have at least one comorbidity. Across all patient with cancer cohorts, hypertension (HTN), chronic obstructive pulmonary disease (COPD), diabetes, cerebrovascular disease, congestive heart failure, and peripheral vascular disease were among the most common comorbid conditions.[82] 60% of cancers are diagnosed after the sixth decade of life,[83] and immunosenescence (aging-related changes to the immune system) correlates with reduced efficacy of treatments aimed at enhancing endogenous immune responses, such as ICI therapy.[84] Comorbidities such as HTN, diabetes, and COPD that cause features of biological aging may also cause varying degrees of immunosenescence, mimicking the effect of aging on the immune system. Thus, patients with comorbidities are expected to experience blunted efficacy of immune-stimulating immunotherapies.

Patients with comorbidities, chronic viral infections, varying degrees of organ dysfunction, and autoimmune diseases are commonly excluded from clinical trials.[85 86] In the case of autoimmunity, patient exclusion occurs even though many patients present with low severity disease based on symptoms and require minimal systemic treatment. Although understudied, multiple retrospective reviews indicate that patients with immune dampening or autoimmune comorbidities do not necessarily have worse outcomes or irAEs with immunotherapy treatment.[87] Clinical trial protocols rarely describe parameters for inclusion or exclusion with respect to autoimmune comorbidities; thus, trials may unnecessarily exclude patients who could benefit from treatment. Indeed, strict eligibility criteria exclude up to 70% of patients with lung cancer from immunotherapy clinical trials,[88] and patients 65 years of age and older are under-represented in clinical trials.[89]

Moving forward, more data from immunotherapy-treated patients with autoimmune diseases, such as sarcoidosis, thyroid disease, Crohn's disease, rheumatoid arthritis, transplant patients on immunosuppressants, and psoriasis are needed to reconcile conflicting clinical observations. For example, some studies have suggested that patients with autoimmune diseases have an increased risk for systemic adverse events post-treatment with immunotherapy.[90] However, some combination treatments, such as metformin and antibody or cell-based immunotherapies for patients with both cancer and diabetes, have shown evidence of an improved response

to immunotherapy.[91] Patients with different comorbidities may also benefit from additional exploration of novel combinations, vaccines, and other therapeutics that increase the robustness of the endogenous immune system or strengthen a patient's overall immune health. As clinicians continue to treat patients with cancer with immunotherapy and as treatments succeed in prolonging life, there is an increasing need to better understand the significance of immune health and immunosenescence. Studies are greatly needed that can (1) distinguish the effects that immune-influencing diseases have on irAEs and response to immunotherapy, (2) identify which patients are at higher risk for adverse events, (3) determine how to safely include patients with comorbidities in clinical trials so they are not precluded from receiving beneficial treatments, and (4) provide guidance regarding how to modify treatment plans according to comorbidities.

CONCLUSION

Using the immune system for cancer interception in patients with premalignant lesions is an attractive approach as the progression of premalignancy to invasive cancer takes place over decades allowing the immune system time to respond to and eradicate the lesions. Further, immune suppression in preinvasive lesions is reduced compared with invasive cancers, leading to a more effective cellular immune response both locally in tissues and systemically. There are many examples of immune modulatory approaches advancing to the clinic for cancer interception. These include active immunization with vaccines directed against premalignant lesions, the use of other forms of immune modulators such as ICI, and the repurposing of classic oral prevention agents for their immune stimulatory effects or controlling chronic inflammation.

Some of the current challenges for primary prevention include identifying the appropriate targets for cancers that are not inherited or virally induced. Also, the toxicities for primary prevention must be considered because these agents will be administered to healthy individuals. The benefits of immunoprevention of cancer cannot be understated, particularly in preventing the morbidity and mortality of both the cancers that develop and the treatments of those cancers as well as the cost savings for society and the individual. Furthermore, the impact of immune-based cancer therapies in a population with more robust immune health compared with patients with advanced cancers may allow for higher efficacy of immunotherapeutics.

Environmental factors such as diet, lifestyle, and gut microbiota, along with host factors including age, sex, and overall immune health status, can impact response to immune-based treatments, and more prospective studies are required that consider these factors in the efficacy of immunotherapy for patients in the premalignant stage or those with advanced cancers. We are now able to evaluate these complex factors more than we ever have in the past due to advancements in technology, such as genomic sequencing coupled with multiomics approaches and AI analysis to provide a comprehensive understanding of the immune status of the patient or the immune phenotype of the developing tumor to develop more effective preventative vaccines and immunotherapeutics.

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