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REVIEW

Cancer Immunoprevention: Current Status and Future Directions

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Abstract

Cancer is one of the most serious diseases affecting health and the second leading cause of death worldwide. Despite the development of various therapeutic modalities to deal with cancer, limited improvement in overall survival of patients has been yielded. Since there is no certain cure for cancer, detection of premalignant lesions, and prevention of their progression are vital to the decline of high morbidity and mortality of cancer. Among approaches to cancer prevention, immunoprevention has gained further attention in recent years. Deep understanding of the tumor/immune system interplay and successful prevention of virally-induced malignancies by vaccines have paved the way toward broadening cancer immunoprevention application. The identification of tumor antigens in premalignant lesions was the turning point in cancer immunoprevention that led to designing preventive vaccines for various malignancies including multiple myeloma, colorectal, and breast cancer. In addition to vaccines, immune checkpoint inhibitors are also being tested for the prevention of oral squamous cell carcinoma (SCC), and imiquimod which is an established drug for the prevention of skin SCC, is a non-specific immunomodulator. Herein, to provide a bench-to-bedside understanding of cancer immunoprevention, we will review the role of the immune system in suppression and promotion of tumors, immunoprevention of virally-induced cancers, identification of tumor antigens in premalignant lesions, and clinical advances of cancer immunoprevention.

Keywords Precancerous lesion · Precursor · Prevention · Tumor antigen · Immunosurveillance · Preventive vaccine · Prophylactic vaccine · Immune checkpoint blockade · Biomarker · Oral proliferative verrucous leukoplakia · Actinic keratosis · Colon polyp · Smoldering myeloma · Ductal carcinoma in situ of the breast

Introduction

Cancer is the second cause of death worldwide (Dwyer-Lindgren et al. 2016). Unfortunately, the global cancer incidence is rapidly increasing. It has been estimated that 14 million new cases of cancer will be diagnosed in 2035, while 6.7 million new cases were detected in 2012 (Pilleron et al. 2019). To respond to this critical problem, various therapeutic methods have been applied. Despite the improvement in overall survival of patients with cancer, that has been achieved through novel therapies such as immunotherapy and targeted therapy, the mortality rate is still high, and there is no definite cure for cancer (Bray et al. 2018; Farrow et al. 2020; Pishvaian et al. 2020). Therefore, cancer prevention could be a beacon of hope to decrease morbidity and mortality of cancer.

Different options such as surgery, chemotherapy, and immunotherapy could be applied to inhibit the progression of premalignant lesions (Degnim and King 2013; Kensler et al. 2016; Ravery 2007). However, less aggressive

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approaches are more acceptable for prevention, since the advantages of a preventive approach must outweigh the potential risks (Loveland-Cherry 2008). Immune-based interventions are believed to have fewer side effects than other available options. For instance, it has been reported that immunotherapy in solid tumors using immune checkpoint inhibitors (ICI) is accompanied by fewer side effects compared to chemotherapy (Magee et al. 2020). Also, vaccines and ICIs for non-small cell lung cancer showed better or indifferent safety profile compared to chemotherapy or placebo in a meta-analysis (Yu et al. 2017). In addition to fewer side effects, immune-based interventions can generate immunological memory inducing a long-term protection which is not achievable with other preventive approaches (Kirman et al. 2019; Varadé et al. 2020). Therefore, immune-based interventions seem to be attractive options for cancer prevention.

Recently, a deep understanding of the interplay between the immune system and tumor cells has paved the way toward employing immune-based interventions not only as immunotherapy but also as immunoprevention (Kensler et al. 2016). The notion of exploiting the immune system to fight cancer was initially reported in the 1890s by William Coley, who used Coley's toxins, containing killed Streptococcus pyogenes and Serratia marcescens, to cure recurrent sarcoma (Coley 1891; McCarthy 2006). Paul Ehrlich, who described the ability of the immune system to recognize and repress tumor cells had an important contribution to the promotion of cancer immunology in 1909 (Kasten 1996). In the 1950s, Macfarlane Burnet and Lewis Thomas provided a novel hypothesis known as immunosurveillance, which outlined the function of the immune system to destroy tumor cells. Considering the immune tolerance mechanisms, Burnet suggested that recognizing neo-antigens expressed in tumor cells can lead to the protection of the body against tumor cells (Burnet 1957, 1971). Thomas hypothesized that the mechanisms inducing tumor suppression are similar to those underlying homograft rejection (Thomas 1959). Altogether, current understanding of cancer immunosurveillance has been shaped based on principles found in the nineteenth and twentieth centuries.

After significant advances in the fundamentals of cancer immunology, a more complex interaction that can make the tumor cells resistant to immune-based interventions was recognized in the twenty-first century. The immunoediting hypothesis that describes the dynamic interaction between the immune system and tumor cells in three phases was first proposed by Robert Schreiber in the early 2000s (Dunn et al. 2004). Based on the immunoediting hypothesis, the immune system has essential functions not only in the elimination of tumor cells but also in shaping immunogenicity and promotion of cancer. The first phase of immunoediting, i.e., elimination, details the immune responses to identify and destroy early tumor cells. However, transformed cells can flee the immune system and undergo the equilibrium phase in which tumor outgrowth is yet restricted by innate and adaptive immunity but tumor cells with lower immunogenicity are selected to survive (Koebel et al. 2007). If the latent tumor cells can overcome the defensive functions of the immune system, they enter the escape phase and present a clinically detectable tumor (Khong and Restifo 2002). Given that, most of the initial studies reported evidence of immune escape in established tumors, this phase has been traditionally defined in malignant lesions (Dunn et al. 2004). However, recent investigations revealed evidence of immune escape in premalignant lesions (Laville et al. 2020; Mascaux et al. 2019; Pennycuick et al. 2020). This finding underlines the benefit of using immune-based interventions for premalignant lesions.

To assess the notion of cancer immunoprevention, we will first review the role of immune components in suppression or progression of malignancy. Afterward, examples of successful immunoprevention of virally-induced cancers, and the importance of identifying tumor antigens in premalignant lesions will be provided. Finally, recent preclinical and clinical studies on cancer immunoprevention will be discussed.

The Immune System and Malignancy

Immune Components to Suppress Cancer

Both innate and adaptive arms of immunity are essential for elimination and equilibrium phases. Dendritic cells (DCs) are professional antigen-presenting cells, responsible for uptake, processing, and presentation of peptide antigens released from tumor cells (Atkins et al. 2004). Initially, recruitment of DCs to tumor microenvironment (TME) occurs following secretion of specific chemokines and cytokines such as type I interferons released from tumor cells (Diamond et al. 2011; Nagarsheth et al. 2017). The maturation of DCs is induced by tumor antigens and damage-associated molecular patterns, which are released from stressed tumor cells and recognized by different pattern recognition receptors including Toll-like receptors (TLRs) (Fang et al. 2014; Sheen et al. 2017). The mature DCs migrate to the lymph nodes, where antigen presentation and T-cell priming occurs. The tumor antigen is presented by the major histocompatibility complex (MHC) class I on DCs, which interacts with the T-cell receptor (TCR) on T cells. Two more signals including the interaction of CD80/CD86-CD28 and secretion of proper cytokines such as interleukin (IL)-12 are necessary to activate T cells (Macatonia et al. 1995; Sharpe and Freeman 2002). Proliferation and migration of T cells activated against a specific antigen are

the subsequent steps. T cells infiltrated into TME are one of the key players to recognize and attack malignant cells (Mukherji et al. 1990). Cytotoxic $CD8^+$ T cells secrete cytotoxic agents, e.g., perforin-granzyme, and use the receptor-dependent destruction through Fas ligand (interacting with Fas on tumor cells) to destroy tumor cells. The secretion of cytokines including interferon (IFN)-γ and tumor necrosis factor (TNF)-α is also necessary for cytotoxic effects of T cells (Maher and Davies 2004). It is worthwhile mentioning the indispensable role of $CD4^+$ T cells, particularly T helper (Th1) cells, for development of a long-term effector $CD8^+$ T cell response, induction, and maintenance of immunological memory (Janssen et al. 2003; Ossendorp et al. 1998; Schoenberger et al. 1998). In addition to the conventional T cells expressing αβ TCR, γδ T cells expressing γδ TCR, not CD4 or CD8, also contribute to tumor elimination. They function through MHC-independent mechanism and secrete IFN-γ, perforin-granzyme, TNF, and TNF-related apoptosis-inducing ligand (TRAIL) to destroy malignant cells (Zhao et al. 2018).

Natural killer (NK) cells are crucial players in tumor elimination. NK cells act either through direct cytotoxicity, i.e., perforin-dependent pathway, or indirectly via the production of TRAIL (Krasnova et al. 2017). They are able to attack tumor cells that downregulate their MHC-I. They contain the NK group 2 member D (NKG2D) receptor and recognize transformed cells through binding to some ligands such as MHC class I polypeptide-related sequence A (MICA), MICB, and UL16-binding proteins (Fernández-Messina et al. 2012).

Natural killer T (NKT) cells are the next immune cells that attack tumor cells. They contain characteristics of both NK and T cells and exert tumor lysis through perforin and granzyme. The recognition of lipid antigens is feasible by NKT cells. Non-polymorphic MHC class I-like CD1d molecules present these antigens to TCRs, which are not similar to those that belong to T cells (Terabe and Berzofsky 2018).

Immune Components to Promote Cancer

The immunosuppressive microenvironment is a common characteristic of cancer immune escape. Various components of TME provoke this state: (a) malignant cells; (b) immune cells including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), regulatory T cells (Tregs), NKT cells; (c) mesenchymal stem cells; and (d) cancer-associated fibroblasts (Beatty and Gladney 2015; Bianchi et al. 2011). Immune cells play different roles to induce immunosuppression. For instance, MDSCs are immature cells that disable T-cell activation (Raber et al. 2014). They also enhance frequency and activity of Tregs and TAMs, support conversion of $CD4^+$ T cells into Tregs, and cause recruitment of Tregs (Schlecker et al. 2012; Serafini et al. 2008). There are also several functions for Tregs to promote immune escape: (a) secretion of inhibitory cytokines such as IL-10, and transforming growth factor (TGF)-β; (b) interfering and inhibiting the functions of effector T cells; and (c) upregulation of cytotoxic T-lymphocyte-associated protein (CTLA)-4 to induce tolerogenic DCs (Facciabene et al. 2012). In addition, TAMs infiltrating TME have a central role in the induction of inflammation. The classic or M1 macrophages have an anti-tumor function by production of cytokines such as TNF-α, IL-12, and IL-6, while the alternative or M2 macrophages foster the outgrowth of tumor cells by production of IL-10, and TGF-β, and a shift to a Th2 immunity (Martinez et al. 2008). M2 macrophages also promote induction and accumulation of the abovementioned immunosuppressive immune cells (Nishikawa and Sakaguchi 2010). Altogether, inhibitory immune components foster tumor outgrowth and escape.

Tumor immune escape has also another undeniable player called immune checkpoints. Inhibitory immune checkpoints include CTLA-4, programmed cell death protein 1 (PD-1), lymphocyte activation gene-3, and T-cell immunoglobulin domain and mucin domain three (reviewed in Donini et al. 2018), and CTLA-4 and PD-1 are the most studied immune checkpoints. CTLA-4, competitively binds to ligands of CD28 (i.e., CD80/CD86) to inhibit T-cell priming, while PD-1 causes T-cell apoptosis and hampers effector activities of cytotoxic T cells by binding to its ligands (i.e., PD-L1/PD-L2) on tumor cells (Blank et al. 2006; Dong et al. 2002; Schwartz 1992; Tirapu et al. 2006). Both of the abovementioned functions lead to tumor escape by attenuation of T-cell activities.

It has been reported that immune dysregulation in TME precedes the progression of premalignant lesions to malignancy. Malignant specimens compared to their precursors have a lower frequency of specific immune subsets, playing roles in elimination and equilibrium phases, including $CD8^+$ T cells, mature DCs, and NKT cells, while they have a higher frequency of Tregs and MDSCs (Chaves et al. 2019; Dhodapkar et al. 2003; Jang 2013; Ma et al. 2018; Wu et al. 2013; Yuan et al. 2008). Therefore, it is rational to use interventions that strengthen effector immune cells or hamper inhibitory components for cancer immunoprevention.

Immune-based Interventions for Cancer Prevention

Considering dynamic interaction of the immune system and tumor cells, various immune-based interventions have been designed to either empower the anti-tumor properties or inhibit pro-tumor functions of the immune system (Schreiber et al. 2011). The major immune-based interventions for cancer include vaccines, ICIs, adoptive cell therapy,

monoclonal antibodies, and non-specific immunomodulators. Although these interventions have primarily been used as immunotherapy, some options such as vaccines, ICIs, and non-specific immunomodulators have also been tested for cancer immunoprevention.

Vaccines

Vaccines are the most commonly applied immune-based interventions in preventive settings. They are capable of inducing endogenous effector and memory T-cell responses through enhanced tumor antigen presentation. They have some advantages, such as induction of long-term immune responses, simple delivery, and limited side effects, which make them a great candidate for cancer prevention (de Vos van Steenwijk et al. 2014; Kimura et al. 2013; Mukherjee et al. 2007).

Up to now, various vaccine constructs including peptide-based, cell-based, and genetic vaccines have been produced. Each vaccine construct has its own advantages and disadvantages. For instance, peptide-based vaccines, including short peptides and polyvalent synthetic long peptides, are low-cost, and easy to produce (Kenter et al. 2009; Kimura et al. 2013; Skwarczynski and Toth 2016). Whole tumor cell vaccines are made using allogeneic or autologous tumor cell lines, consisting of both known and unknown tumor antigens (Chiang et al. 2010). Immune cell vaccines are another type which uses DCs loaded with a specific tumor antigen, tumor-derived mRNA, or tumor cell lysate (Kantoff et al. 2010; Pandha et al. 2004; Su et al. 2003). Genetic vaccines, which could be delivered directly or by viral vectors, use DNA or RNA to express both desired tumor antigens and adjuvant (DiPaola et al. 2006; Jorritsma et al. 2016). Peptide-based, DC, and DNA vaccines have been tested as preventive measures in clinical settings.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors, which are approved for treatment of many types of cancer, has recently been applied to the field of cancer prevention in clinical settings. Although they have the risk of developing immune-related adverse events (irAEs) in multiple organs (Martins et al. 2019), preclinical evidence has supported their clinical application for cancer prevention. A number of precancerous lesions showed the expression of PD-L1 correlating with malignant transformation. For instance, evaluation of monoclonal gammopathy of undetermined significance, and asymptomatic monoclonal gammopathies (AMGs) which precede multiple myeloma (MM), and oral precancerous lesions revealed that the expression of PD-L1 on precancerous lesions associated with malignant transformation (Dave et al. 2020; Dhodapkar et al. 2015; Yagyuu et al. 2017). Besides, the blockade of PD-1/PD-L1 pathway led to enhanced anti-tumor immunity in AMGs in vitro, and the blockade prevented progression of carcinogen-induced oral premalignant lesions in a mouse model (Dhodapkar et al. 2015; Wang et al. 2017).

Non-Specific Immunomodulators

Non-specific immunomodulators are various types of drugs capable of either activating or suppressing the immune system in a general non-specific way, without directing immune activity against a specific target. Some non-specific immunomodulators including BCG, IL-2, and imiquimod have been approved for cancer immunotherapy (Bhatia et al. 2009; Morales and Nickel 1986; Roozeboom et al. 2012). Imiquimod, a TLR7 agonist, has also been approved for the treatment of actinic keratosis which is the precursor of skin squamous cell carcinoma (SCC) (Quist and Gollnick 2011). There is a broad range of non-specific immunomodulators which have the potential to be tested either alone or in combination with other interventions for cancer prevention. Some examples of non-specific immunomodulators which are under clinical investigation will be discussed in the last section.

Immunoprevention of Virally-Induced Tumors

The ambition of cancer immunoprevention has initially been fulfilled in the context of virally-induced tumors. Up to now, vaccines have been available to prevent two virally-induced cancers, i.e., cervical cancer associated with human papillomavirus (HPV), and hepatocellular carcinoma (HCC) associated with chronic hepatitis B virus (HBV) infection (Kao 2015; Schiller et al. 2012). There are also other important cancer-inducing pathogens, including hepatitis C virus (HCV) causing HCC, Epstein-Barr virus causing Burkitt's lymphoma and nasopharyngeal carcinoma, human herpesvirus 8 causing Kaposi's sarcoma, human T-cell lymphotropic virus causing adult T-cell leukemia/lymphoma, and *Helicobacter pylori* causing gastric cancer (Chang et al. 1994; Farinati et al. 2007; Parsonnet et al. 1991; Yoshida et al. 1982; zur Hausen et al. 1970). The abovementioned pathogens have not been prevented by vaccines yet. However, robust treatments could be used to eradicate some of these pathogens. Overall, infection-induced cancers account for one-sixth of all human cancers and are great potentials for cancer prevention (de Martel et al. 2012).

HBV- and HCV-Associated Hepatocellular Carcinoma

Chronic HBV and HCV infections are the major risk factors for HCC development and account for over 80% of

HCC cases globally (McGlynn and London 2005). In the late 1980s, HBV vaccination was launched in several Asian countries. The program led to a significant decrease in vertical transmission of infection and subsequent chronic hepatitis (Venook et al. 2010). As expected, the incidence rate of HCC was also reduced. As an example, after around 6–10 years of starting the national vaccination program in Taiwan, the incidence rate of HCC in 6–14 year old children was declined from 0.70 per 100,000 in 1981–1986–0.36 per 100,000 in 1990–1994 (Chang et al. 1997). This means prevention of viral infection has led to decreased malignant transformation.

Although efficient vaccines have been developed against HBV to decrease the incidence of virally-induced HCC, designing an effective vaccine against HCV has encountered a number of challenges. The most important barriers are the presence of at least seven genotypes of HCV with a broad genetic diversity and an elevated chance of error in viral replication (Walker 2017). Likewise, complexity of immune responses against HCV made some failures to develop an effective vaccine acting through either T-cell-dependent or antibody-dependent immunity (McConnell and Lim 2018). Therefore, efficient drugs for treatment of HCV infection are necessary to prevent HCC associated with HCV.

HPV-Associated Cancer

The next virally-induced cancer subject to immunoprevention is HPV-induced cancer. HPV infection accounts for the induction of almost all cases of cervical cancer. Two high-risk HPVs, i.e., HPV16 and 18, are responsible for approximately 70% of cervical cancers (Lowy and Schiller 2012). HPV is also responsible for other types of malignancies including vulvar, anogenital, and oral cancer (De Sanjosé et al. 2013; Rautava and Syrjänen 2012; Serrano et al. 2015). Both prevention and treatment of the viral infection could prevent HPV-induced cancer in several organs, and HPV-induced cervical cancer has potential to be the first eradicated cancer worldwide.

Immunoprevention of HPV-induced cervical cancer could be achieved by vaccines aimed at prevention of the infection. Gardasil and Cervarix are vaccines already approved to prevent HPV infection in populations without a history of viral infection (Fig. 1). Both vaccines contain virus-like particles of the L1 protein of HPV16 and 18, the major capsid protein playing a role in the virus entry. Gardasil is a quadrivalent HPV vaccine which also covers HPV6 and 11 to prevent genital warts. The new generation Gardasil 9 is a nonavalent HPV vaccine which covers seven more high-risk genotypes as well (Buck et al. 2013; Toh et al. 2017). Based on results of a recent meta-analysis, an 83% reduction

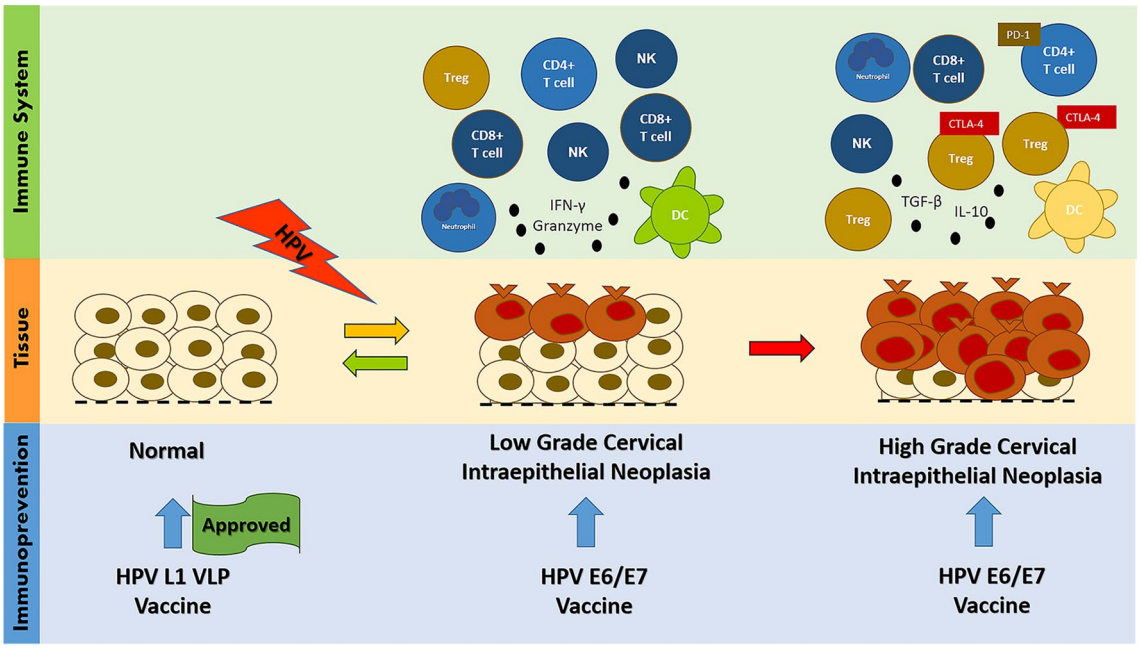

Fig. 1 Immunoprevention for HPV-induced cervical cancer. Two types of vaccines could be used to prevent HPV-induced cervical cancer. For individuals without HPV infection, the approved HPV L1 VLP vaccine is used to prevent infection and possible subsequent intraepithelial neoplasia. Individuals infected with high-risk HPV types might develop low-grade intraepithelial neoplasia. In this state, predominant cytotoxic cells play a key role to eradicate the lesion. If the immune system is capable to destroy transformed cells, the lesion will be regressed. Otherwise, it progresses to high-grade intraepithelial neoplasia. To prevent progression of low- and high-grade intraepithelial neoplasia to cervical cancer, the HPV E6/E7 vaccine could be applied. *HPV* human papillomavirus, *VLP* virus like particles

in the prevalence of HPV16 and 18 infections, as well as a 51% reduction in cervical intraepithelial neoplasia grade 2^+ ($CIN2^+$), were observed after 5–9 years of vaccination among girls under age 20 (Drolet et al. 2019). Therefore, prevention of HPV infection by vaccines administered only to girls under age 20 halved the frequency of premalignant lesions. Interestingly, a recent study showed the direct effect that prevention of HPV infection reduces the risk of invasive cervical cancer, which had not been assessed before. The study showed application of the quadrivalent HPV vaccine to the girls between 10–30 years old, not only decreases risk of premalignant lesions but also associates with a lower risk of invasive cervical cancer (Lei et al. 2020). If the vaccine coverage for girls is not high, vaccinating both girls and boys might be beneficial for prevention of HPV-induced cervical cancer (Brisson et al. 2020).

Immunoprevention of HPV-induced cervical cancer could also be achieved by vaccines aimed at the treatment of infection/premalignant lesion. They are not only a therapeutic approach but also a preventive modality, because they can inhibit the progression of premalignant lesions to malignancy (Fig. 1). These vaccines, still only in clinical testing, target the oncoproteins E6 and E7, which inhibit p53 and Rb tumor suppressors, respectively (Buitrago-Pérez et al. 2009; Jabbar et al. 2018).

In the first study on efficacy of preventive vaccines in virally-induced tumors, a peptide vaccine consisted of long peptides originated from HPV16 oncoproteins E6, E7 and incomplete Freund's adjuvant were tested. Nineteen patients suffering from grade 3 vulvar intraepithelial neoplasia were recruited to the study, and nine patients experienced complete eradication of lesions. The complete responses maintained after 24 months of follow-up and correlated with adaptive immune response (Kenter et al. 2009).

To inhibit development of cervical cancer associated with HPV, the HPV16 synthetic long-peptide vaccine containing E6 and E7 was tested on women with low-grade CIN in an early randomized controlled trial. As a result, a robust Th1 type response was induced, lasting for at least one year. On the other hand, the booster vaccine administered after one year induced a Th2 type response which necessitated using an adjuvant to induce Th1 response (de Vos van Steenwijk et al. 2014). Prior to this study, the vaccine was tested for patients with high-grade CIN in an early clinical trial which incompletely terminated, because the patients were not motivated enough to take the vaccine and postpone the standard of care, i.e., the loop electrosurgical excision procedure (LEEP). Nevertheless, nine patients that received the vaccine showed an improved T-cell immune response (de Vos van Steenwijk, Ramwadhdoebe et al. 2012). Altogether, vaccines for the eradication of established CIN showed promising results in early clinical trials; however, convincing patients to continue the vaccine instead of undergoing LEEP remained the main concern. The inclusion of individuals with positive high-risk HPV DNA test and normal cervical biopsy might also be helpful to determine efficacy of the vaccine to prevent development of premalignant and malignant cervical lesions.

Tumor Antigens in Premalignant Lesions

Preventive approaches have also been assessed for non-virally-induced tumors by targeting tumor antigens. Tumor antigens are divided into two main categories: (a) tumor-associated antigens (TAA), which are expressed in normal cells and are overexpressed in malignant cells; (b) tumor-specific antigens (TSA), which are exclusively expressed in malignant cells due to either viral oncogenes (shared TSAs) or somatic mutations (unique TSAs) (Dalet et al. 2011; Feng et al. 2008; Zilberberg et al. 2015). Specific immunotherapeutic and immunopreventive modalities exploit different types of tumor antigens to induce a specific T-cell response against malignant cells.

The identification of tumor antigens is a substantial achievement in the field of immunotherapy and immunoprevention (Chu et al. 2015). Two main approaches are used for identification of tumor antigens. The first one is direct or forward immunology, which depends on the isolation of tumor-directed T cells from patients, and finding cDNAs encoding the cytotoxic T lymphocyte epitopes from cDNA expression libraries (Traversari et al. 1992). The second method is indirect or reverse immunology, which exploits an algorithm-based approach to predict binding of a tumor antigen to MHC molecules (Hombrink et al. 2013). In this method, the predicted epitopes might not be naturally processed and presented by MHC molecules; therefore, validation is necessary (Popović et al. 2011). Tumor antigens identified by either forward or reverse immunology could be targeted for designing therapeutic and preventive cancer vaccines.

The selection of best antigens for intervention is the critical step to design an immune-based intervention. The selected tumor antigen must be immunogenic and ideally play an oncogenic role. The surface expression of the tumor antigen rather than internal expression also makes it more desirable (Engelhard et al. 2002; Kessler and Melief 2007; Khong et al. 2004). For example, oncoantigens are a type of tumor antigens playing a driving role in the growth of tumor cells in all stages. Therefore, the development of antigen loss variants and being affected by immunoediting is not a major concern for these antigens. Class I oncoantigens, which are the extracellular proteins of tumors, are particularly a great candidate for immune-based interventions, because they are a target for both humoral and cell-based immunity (Cavallo et al. 2007; Lollini et al. 2011; Rolih et al. 2017). Although

many tumor antigens have been found and used for designing therapeutic modalities, a number of them in particular those expressed in premalignant lesions are also appropriate for immunoprevention. Mucin 1 (MUC1), carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2), and some cancer-testis antigens (CTAs) are among the tumor antigens which are expressed in premalignant lesions (Farkas and Finn 2010; Ho et al. 1996; Ieni et al. 2015; Lollini et al. 2011). In the following paragraphs, characteristics of these tumor antigens as well as a new category known as retired antigens will be discussed.

Mucin 1

MUC1 is normally expressed in healthy tissues and supports the epithelium (Hanisch and Müller 2000). However, the overexpression of its aberrantly glycosylated form has been reported in a number of tumors including pancreatic, breast, and colon cancer (Al-Khayal et al. 2016; Chhieng et al. 2003; Kesari et al. 2015; McGuckin et al. 1995; Qu et al. 2004; Rakha et al. 2005). The overexpression of MUC1 has also been reported in high-risk colonic polyps and high-grade pancreatic intraepithelial neoplasms, which could be progressed to colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC), respectively. Therefore, MUC1 deserves as a potential target for immunoprevention of CRC and PDAC (Davis 2013; Maitra et al. 2003; Molaei et al. 2010).

Carcinoembryonic Antigen

CEA is normally expressed in various tissues including the gastrointestinal tract, and has different functions such as cell adhesion. It is a TAA and is overexpressed in many cancers including breast, lung, gastric, and colorectal cancer (Buie and Attard 2005; Hammarström 1999; Jothy et al. 1993). CEA secretes to the blood and its serum level is an important tumor marker for follow-up of patients with CRC (Buie and Attard 2005). CEA overexpression has also been reported in precancerous lesions of CRC, i.e., hereditary non-polyposis colorectal cancer (HNPCC), familial polyposis adenomatous, and adenomas (Ilantzis et al. 1997; Javan et al. 2019; Schiemann et al. 2005). In colonic polyps, intensity of tissue level of CEA associates with degree of dysplasia (Amanti et al. 1985; Au et al. 1986). Therefore, it is a potential target for prevention of CRC.

Human Epidermal Growth Factor Receptor 2

HER2 is an oncogenic growth factor receptor which fosters proliferation, survival, and invasiveness of tumor cells (Spangenberg et al. 2006; Timms et al. 2002; Zhan et al. 2006). Approximately 30% of breast cancers demonstrate HER2 overexpression (Slamon et al. 1987). Interestingly, roughly 50% of samples of carcinoma in situ, i.e., the early phase of breast malignancy, show HER2 overexpression (Park et al. 2006). These investigations can imply that in many cases in situ carcinoma of the breast does not progress to invasive breast cancer. In addition, HER2 status is preserved during progression of carcinoma in situ to invasive breast cancer, making it a potential target for immunoprevention (Carlsson et al. 2004). Similarly, both malignant and premalignant lesions of gastric cancer have shown HER2 overexpression (Fusco et al. 2013; Rossi et al. 2009). Therefore, it is rational to assess the efficacy of HER2 targeted immunoprevention for breast and gastric cancer.

Cancer-Testis Antigens

CTAs are TSAs normally expressed in trophoblasts during the fetal period and in testicular tissues in adulthood (Lim et al. 2012). They are immunogenic targets not affected by negative selection of the immune system, because they are concealed from the immune system by the blood-testis barrier and lack of HLA-I (Lim et al. 2012; Westbrook et al. 2004). Immunogenicity along with their oncogenic function makes them great targets for not only immunotherapy but also immunoprevention (Atanackovic et al. 2010; Greve et al. 2015; Nardiello et al. 2011; Por et al. 2010). CTAs including MAGE-A, NY-ESO-1, GAGE, CT7, CT10, CT45, and SSX are expressed in several premalignant lesions. They are expressed in the samples of BRCA positive carcinoma in situ of the breast, whereas they are not expressed in normal breast tissues of healthy individuals who carry BRCA mutations and undergo prophylactic mastectomy (Adams et al. 2011). The expression of CTAs has also been reported in other premalignant lesions including precursors of gastroesophageal cancer, SCC of the head and neck, and MM (Chen et al. 2014; Cho et al. 2003; Jungbluth et al. 2005; Piotti et al. 2013; Taylor et al. 2005). The expression of CTAs by premalignant lesions underlines their potential for cancer immunoprevention through targeted interventions such as vaccines.

Retired Antigens

Retired antigens are a new category of tumor antigens that recently gained attention for prevention of breast cancer. Retired antigens are self-antigens not expressed in the normal tissues of mature or aged people, while they are expressed in malignant cells of the breast and ovaries; therefore, their targeting does not induce self-damage in these populations. (Shoemaker and Forsthuber 2017). Alpha-lactalbumin is a type of retired antigen which was targeted for breast cancer prevention in a mouse model and led to decreased development of tumors (Jaini et al. 2010). The

extracellular domain of anti-Müllerian hormone receptor II (AMHR2-ED) is another tested retired antigen overexpressed in epithelial ovarian carcinoma but not in the normal ovaries after menopause. Targeting this antigen through vaccination in female mice deserved as a preventive and therapeutic approach to epithelial ovarian carcinoma (Mazumder et al. 2017). Retired antigens are potential targets for immunoprevention and should be evaluated in clinical studies for prevention of breast and ovarian cancer.

Cancer Immunoprevention in Clinical Settings

The promising results from preclinical studies targeting tumor antigens support clinical testing of immunoprevention for non-virally-induced tumors. Cancer immunoprevention has been tested in clinical trials for a number of cancers including multiple myeloma, colorectal, breast, skin, and oral squamous cell cancer. In this section, the clinical trials on cancer immunoprevention and the rationale behind the studies will be discussed. Table 1 also presents keynotes of these clinical trials.

Colorectal Cancer

The most-known clinical trial of testing a preventive vaccine for non-virally-induced cancers is an early clinical trial for patients with advanced colorectal adenomatous polyps. Adenomatous polyps are precursors of CRC and approximately 25% of people ≥ 50 years old have colorectal adenomatous polyps (Corley et al. 2013). Although polypectomy can reduce the risk of CRC development, which usually takes around ten years, (Shinya and Wolff 1979; Winawer et al. 2000), vaccines with a safe profile and long-term efficacy could be an alternative.

Given the high incidence rate of CRC and the feasibility to detect colonic polyps by screening, various preventive approaches such as immunoprevention have been designed and tested for CRC. In an early clinical trial, researchers tested a vaccine targeting MUC1, which is upregulated on polyps and indicates an increased risk of malignancy (Molaei et al. 2010). A TLR3 agonist was also added as an adjuvant to the vaccine, and treatment was tested in 39 patients with history of advanced colorectal adenomatous polyps, i.e., polyps with villous features, high-grade dysplasia, or size ≥ 1 cm. The vaccine was well-tolerated without significant high-grade adverse effects, and 43% of patients developed anti-MUC1 IgG after vaccination which shows the immunogenicity of the vaccine. Interestingly, the non-responder participants had high levels of MDSCs in their peripheral blood. This evidence indicates the immunosuppressive phenotype of premalignant lesions. Therefore, cancer immunoprevention can also benefit from the strategies attenuating the immunosuppressive phenotype (Kimura et al. 2013). This study led to designing the next clinical trials for immunoprevention of CRC. An ongoing phase-II clinical trial to assess efficacy of the MUC1 peptide vaccine compared with placebo is underway to prevent recurrence in 110 patients with newly diagnosed advanced adenomas (NCT02134925). Altogether, the MUC1 vaccine for prevention of CRC showed immunogenicity and safety in the first clinical trial and advanced clinical trials are warranted to evaluate its clinical efficacy.

There are also other conditions that increase the risk of CRC. Lynch syndrome (LS) or HNPCC, which causes different neoplasia including colorectal cancer, is an autosomal dominant syndrome initiated due to a mutation in DNA mismatch repair (MMR) system (Laghi and Malesci 2012). Somatic hypermutation in microsatellite instability occurs due to defective DNA MMR and leads to the accumulation of frameshift (FS) mutations which contribute to malignancy by replication errors (Aaltonen et al. 1994). If mutations take place in coding regions, neo-antigens are developed. They are unique TSAs, which powerfully induce a specific immune response. These FS-derived neo-antigens have predictable sequences and could be useful for designing multivalent preventive vaccines (Saeterdal et al. 2001).

One of the tumor antigens targeted for prevention and treatment of CRC is CEA. It has previously been targeted through DC- and mRNA-based vaccines for the treatment of metastatic CRC and has shown immunogenicity (Lesterhuis et al. 2006, 2010). However, due to the compromised immune system in metastatic status and/or after receiving several lines of treatment, the vaccine has not been tested in advanced clinical trials. Instead, a phase-II clinical trial was designed to assess the DC vaccine loaded with CEA/FS-derived neo-antigens to prevent progression of LS to CRC and treat cases with LS who already developed CRC (NCT01885702). If the early clinical trial shows promising results, advanced clinical trials can determine the efficacy of this vaccine.

Breast Cancer

Ductal carcinoma in situ (DCIS) is the early phase of breast cancer, restricted to the ducts of the breast. In recent years, its diagnosis rate has increased due to emerging screening modalities such as mammography. Therefore, attention has been paid to the application of interventions for treatment of the lesion and prevention of its progression to invasive breast cancer (Ernster et al. 2002). The standard interventions include either mastectomy or lumpectomy combined with radiation or endocrine therapy, which depends on expression of estrogen or progesterone receptors (Fisher et al. 2001; Hird et al. 2006; Silverstein and Lagios 2007).

Table 1 Key notes of clinical trials evaluating cancer immunoprevention

Premalignant lesion	Immune-based intervention	Type of study	Results	References
HPV16$^+$, high-grade vulvar intraepithelial neoplasia	HPV16 E6/E7 synthetic long-peptide vaccine	Early clinical trial	60% clinical responses and relief of symptoms at 3 months. 25% complete regression of the lesions. 20% no detectable HPV16. 79% clinical responses and 47% complete response at 12 months, which was maintained at 24 months of follow-up	Kenter et al. (2009)
HPV16$^+$ high-grade cervical squamous intraepithelial lesion	HPV16 E6/E7 synthetic overlapping long-peptide vaccine	Early randomized controlled trial	HPV16-specific T-cell immunity	de Vos van Steenwijk et al. (2012)
HPV16$^+$ low-grade cervical squamous intraepithelial lesion	HPV16 E6/E7 synthetic overlapping long-peptide vaccine	Early controlled trial	HPV16-specific T-cell immunity lasting for at least 1 year	de Vos van Steenwijk et al. (2014)
CIN grade 2/3 associated with HPV16 or 18	DNA vaccine targeting HPV16 and 18, E6 and E7 proteins	Early randomized, double-blind, controlled trial	Histopathological regression of CIN in 49·5% of the vaccine arm vs 30·6% of the placebo arm	Trimble et al. (2015)
Advanced adenoma of the colon	MUC1 peptide vaccine	Early clinical trial	Specific immune response and long-lived memory in 43% of participants. non-responder participants had more myeloid derived suppressor cells	Kimura et al. (2013)
Newly diagnosed adenomatous polyps of colon	MUC1 peptide-poly-ICLC adjuvant vaccine	Early randomized double-blind, controlled trial	Ongoing, to prevent the recurrence of adenomatous polyps and development of colorectal cancer	NCT02134925
Lynch syndrome or colorectal cancer with MSI	DC vaccine loaded with CEA/frameshift derived neo-antigen	Early clinical trial	Ongoing, to treat or prevent cancer in different arms of the study	NCT01885702
HER2$^+$ DCIS of the breast	DC1 vaccine pulsed with HER2/neu peptides	Early clinical trial	Peptide specific IFN-γ-secreting CD4$^+$ and CD8$^+$ T cells, decreased HER2/neu expression in surgical tumor specimens of 7/11 patients	Czerniecki et al. (2007)
HER2$^+$ DCIS of the breast	DC1 vaccine pulsed with HER2/neu peptides	Early clinical trial	Anti-HER2/neu peptide responses were observed up to 52-month postimmunization	Koski et al. (2012)
HER2$^+$ DCIS of the breast	DC vaccine pulsed with HER2/neu peptides	Early clinical trial	Complete regression in 5/27, eradication of HER2/neu expression in 11/27, better results in estrogen receptor negative patients	Sharma et al. 2012
HER2$^+$ DCIS of the breast	Autologous DC1 vaccine pulsed with HER2 peptides	Early clinical trial	Complete tumor regression in 25% of patients and 38% complete tumor regression in estrogen receptor negative patients	Fracol et al. (2013)

Table 1 (continued)

Premalignant lesion	Immune-based intervention	Type of study	Results	References
$HER2^+$ DCIS and invasive cancer of the breast	DC1 vaccine pulsed with HER2/neu peptides through different routes of administration including intralesional, intranodal or both	Early clinical trial	28.6% complete response in DCIS vs. 8.3% in invasive breast cancer, no significant difference in immune response rates by different routes of vaccination	Lowenfeld et al. (2017)
$HER2^+$ DCIS of the breast	DC1 vaccine pulsed with HER2/neu peptides through different routes of administration including intralesional, intranodal or both	Early randomized clinical trial	Ongoing	NCT02061332
$HER2^+$ DCIS of the breast	DC1 vaccine with Trastuzumab and pertuzumab	Early clinical trial	Ongoing	NCT02336984
$HER2^+$ DCIS of the breast	Nelipepimut-S (E75) plus GM-CSF peptide vaccine	Early randomized clinical trial	Ongoing	NCT02636582
$HER2^+$ DCIS of the breast	Neoadjuvant multi-epitope HER2 peptide vaccine	Early clinical trial	Ongoing	NCT03793829
DCIS of the breast after lumpectomy	Radiation therapy with or without trastuzumab	Phase III randomized clinical trial	Ongoing	NCT00769379
Smoldering multiple myeloma	PVX-410, multipeptide vaccine, with or without lenalidomide	Early clinical trial	7/12 stable disease in vaccine group and 5/12 clinical response in combination group	Nooka et al. (2018)
Smoldering multiple myeloma	PVX-410 vaccine combined with citarinostat or citarinostat and lenalidomide	Early clinical trial	Ongoing, to prevent progression to multiple myeloma	NCT02886065
High risk smoldering multiple myeloma	Peptide vaccine against PD-L1	Early clinical trial	Ongoing, to prevent or delay progression to symptomatic myeloma	NCT03850522
Oral proliferative verrucous leukoplakia	Nivolumab, PD-1 blocker	Early clinical trial	Ongoing, to prevent oral proliferative verrucous leukoplakia and reduce the risk of Squamous cell carcinoma	NCT03692325
Actinic keratosis	Imiquimod 3.75% or 2.5% cream (TLR7 agonist)	Phase III randomized double-blind controlled trial	Imiquimod 3.75%: in two 2 weeks cycles treatment 40.5% complete clearance and in two 3 weeks cycles treatment 47.9% complete clearance Imiquimod 2.5%: in two 2 weeks cycles treatment 33.3% complete clearance and in two 3 weeks cycles treatment 43.2% complete clearance	Hanke et al. (2011)
Actinic keratosis	Imiquimod 3.75 or 2.5% cream (TLR7 agonist) or placebo	Phase III randomized double-blind controlled trial	35.6, 30.6, and 6.3% complete clearance rates for imiquimod 3.75, 2.5% cream and placebo, respectively (both $p < .001$ vs vehicle)	Swanson et al. (2014)

CIN cervical intraepithelial neoplasia, *MSI* microsatellite instability, *CEA* carcinoembryonic antigen, *DCIS* ductal carcinoma in situ, *GM-CSF* granulocyte–macrophage colony-stimulating factor

Some patients also undergo preventive contralateral mastectomy, since they are at an increased risk of contralateral breast malignancy (Gao et al. 2003). The interventions are necessary to decrease the risk of developing invasive breast cancer, and improved interventions are also required, since these patients have a risk of recurrence despite application of standard interventions (Solin et al. 2015; Wärnberg et al. 2014; Wong et al. 2014).

As mentioned earlier, HER2 overexpression occurs in DCIS more often than invasive breast cancer (Park et al. 2006). Therefore, HER2 targeted vaccines could be suitable interventions for the prevention of DCIS progression. To assess this notion, several preclinical studies were undertaken on mice models. For example, vaccination with whole tumor cells upregulating HER2 successfully led to inhibition of tumor development in the mouse model of Balb-neuT (Nanni et al. 2001). In another study, a HER2 DNA vaccine showed efficacy in 3 months but not 6-month-old mice indicating importance of the earlier intervention (Pupa et al. 2001). The next preclinical study targeted multiple antigens including HER2, IGFBP2, and IGFIR, prevalent antigens in invasive breast cancer, and showed multi-peptide vaccines have superior efficacy for the prevention of breast cancer (Disis et al. 2013). All of these preclinical studies were undertaken to begin a new era of breast cancer prevention.

Immunoprevention of breast cancer has been assessed in clinical trials as well. In the first early clinical trial, 13 patients with $HER2^+$ DCIS received a DC1 vaccine using type-1-polarized DCs which are able to induce a long-lasting tumor-specific Th1 responses (Mailliard et al. 2004). The DCs were loaded with HER2 peptides from both HLA class I and II and administered to patients before excisional surgery. Notably, the HER2-directed $CD8^+$ T cells of many participants had high levels of CTLA-4 prior to the intervention. However, the expression level was decreased after the vaccine administration. The vaccine led to enhanced humoral and cellular immunity, decreased expression of HER2, and clinical response. The clinical response, i.e., measureable decrease in residual DCIS was observed in 6/11 patients (Czerniecki et al. 2007).

A similar early clinical trial recruited 27 patients with $HER2^+$ DCIS to receive the DC vaccine before surgery. Less than 20% of patients showed complete regression of the lesions, while this rate was higher in estrogen receptor-negative (ER–) patients (40%) (Sharma et al. 2012). Similarly, in the next clinical trial including 38 patients, 25% of all patients and 38% of ER–patients experienced complete regression (Fracol et al. 2013). It seems that the vaccine is more effective in ER–patients, and these results highlight importance of ER expression in efficacy of the preventive vaccine. Currently, a combination of the DC1 vaccine with two monoclonal antibodies against HER2, trastuzumab, and pertuzumab, is being evaluated in an ongoing clinical trial for $HER2^+$ DCIS (NCT02336984). Moreover, peptide vaccines including E75 and multi-epitope HER2 peptide vaccines are being tested for treatment of $HER2^+$ DCIS in other ongoing clinical trials (NCT02636582, NCT03793829). Further clinical trials are provided in Table 1. Overall, immunoprevention of $HER2^+$ DCIS is possible through vaccines. However, there is a need for identification and inclusion of subgroups of patients who most benefit from the intervention.

Multiple Myeloma

Multiple myeloma, which is the malignant expansion of clonal plasma cells, is the consequence of a stepwise progression of AMGs such as smoldering MM (SMM) (Kyle et al. 2007; Landgren et al. 2009). A detectable M protein > 30 g/L and clonal expansion of plasma cells > 10% in the bone marrow indicate SMM. SMM is asymptomatic, because it is restricted into the bone marrow and despite MM does not have extramedullary growth causing end-organ damages. The risk of SMM progression into MM is 10% per year within the first five years. The rate is decreased to 3 and 1% per year in the second five years and the next ten years, respectively (Kyle et al. 2007). Although monitoring of asymptomatic monoclonal gammopathies is necessary, there is no definite preventive approach to inhibit their progression to MM (Khouri et al. 2019).

To design immune-based interventions for prevention of SMM progression, multiple epitopes including X-box–binding protein 1 (XBP1)-unspliced, XBP1-spliced, syndecan-1 (CD138), and CS1 (CD2 subset 1, CRACC, SLAMF7, CD319) were identified in MM. The peptides were able to induce cytotoxic T-cell responses in both MM and SMM (Bae et al. 2012, 2015). Recently, PVX-410, a multi-peptide vaccine consisting of the four abovementioned peptides, alone and in combination with lenalidomide was tested in an early clinical trial recruiting 22 individuals with a moderate- to high-risk SMM. The modalities were well-tolerated and immunogenic, measured by tetramer-positive and IFN-γ positive $CD8^+$ cells. In the group of vaccine alone, seven out of 12 patients had stable disease and in the combination group, five out of 12 patients showed clinical response (Nooka et al. 2018). It is worth mentioning lenalidomide, a derivative of thalidomide, has been approved for treatment of myelodysplastic syndrome and MM by the US Food and Drug Administration (FDA) (Kotla et al. 2009). Its combination with dexamethasone also showed efficacy for prevention of high-risk SMM progression and improved overall survival in a previous phase-III clinical trial (Mateos et al. 2013). Aside from its direct anti-tumor activity, lenalidomide has also immunomodulatory effects including improved activity

of T cells and NK cells (Corral et al. 1999; Davies et al. 2001). Lenalidomide has some adverse effects such as development of second primary malignancy including invasive hematologic malignancies as well as invasive and non-invasive solid tumors (Jones et al. 2016). This can restrict its usage in early stages of oncogenesis but for usage in AMG which is an already established asymptomatic malignancy, its benefits outweigh the risks.

A recent clinical trial was also designed to assess the combination of PVX-410 and citarinostat (CC-96241) with or without lenalidomide to inhibit SMM progression (NCT02886065). Citarinostat is a selective histone deacetylase six inhibitor which has recently been assessed in combination with paclitaxel for blocking growth of solid tumor cells, and showed no increased risk of adverse effects (Gordon et al. 2018). Overall, immunoprevention could be an effective approach to inhibit progression of AMG; however, the potential side effects might be considered especially in earlier stages.

Oral SCC

Oral proliferative verrucous leukoplakia (OPVL) is a white lesion in the oral cavity with approximately 70% risk of progression to oral SCC, which has a significant mortality rate (Romeo et al. 2014; Silverman and Gorsky 1997). There are several therapeutic options for OPVL including CO_2 and diode laser, surgery, radiation therapy, cryotherapy, topical chemotherapy, and photodynamic therapy. However, none of potential treatments have successfully eradicated the lesion, and the recurrence rate remained high (Bagan et al. 2003; Bombeccari et al. 2018; Capella et al. 2017; Hansen et al. 1985; Yeh 2003; Zakrzewska et al. 1996). Therefore, a novel approach or combination therapy is required to prevent its progression to oral SCC.

As mentioned earlier, it has been observed that there is an association between PD-L1 expression in oral premalignant lesions and their risk of malignant transformation (Dave et al. 2020; Yagyuu et al. 2017). Besides, a preclinical study on prevention of SCC by PD-1 blockade in a mouse model showed promising results (Wang et al. 2017). Therefore, nivolumab, an anti-PD-1 antibody blocking the PD-1/PD-L1 pathway, is now being evaluated in an early clinical trial on 33 patients with OPVL (NCT03692325). Although PD-1 blockade might be promising for prevention of oral SCC, patients must be seriously monitored for development of irAEs.

Skin SCC

Actinic keratosis (AK) is the premalignant lesion of skin SCC (Krouse et al. 2009). AK is a common disease presenting in approximately 6.5% of the general population in the United States. Its incidence increases with age and higher sun exposure (Bickers et al. 2006). Thanks to preventive strategies, SCC is potential to be inhibited by eradication of AK. Various approaches including ablation, topical creams, and photodynamic therapy have been approved by the FDA for treatment of AK in different parts of the body (Del Rosso et al. 2014). Therefore, treatment of AK by various approved interventions is substantial to prevent skin SCC.

Imiquimod is one of the topical creams approved and clinically established for clearance of AK. It causes secretion of cytokines and induction of innate and adaptive immune responses as it is a TLR7 agonist (Hemmi et al. 2002; Miller et al. 1999). Several advanced clinical trials tested imiquimod and revealed its efficacy. In an advanced clinical trial, imiquimod 3.75% cream was tested once daily for two 2 week or two 3 week cycles with a 2 week no-treatment period between cycles, which led to 40.5 and 47.9% complete clearance of AK at one-year follow-up, respectively. Imiquimod 2.5% cream was also evaluated in the same manner and resulted in 33.3 and 43.2% complete clearance of AK, respectively (Hanke et al. 2011). In another advanced phase-III randomized controlled trial, imiquimod 3.75% cream, imiquimod 2.5% cream, and placebo were tested once daily for two 2 week cycles, with a 2 week no-treatment period between cycles for 479 patients. The intervention resulted in significant complete clearance of AK by imiquimod 3.75% cream, and imiquimod 2.5% cream, compared to placebo (35.6, 30.6, and 6.3%, respectively) (Swanson et al. 2014).

Although imiquimod 5% was approved for AK in 2004, the long-term regimen, i.e., twice a week for 16 weeks or two 4 week cycles, made some patients not to be compliant with the treatment. Moreover, daily application of imiquimod 5% was not tolerable for some patients (Del Rosso 2005; Swanson et al. 2014). Therefore, based on the results of the abovementioned clinical trials, imiquimod 3.75 and 2.5% cream applied once daily for two 2 week cycles with a 2 week no-treatment period between cycles were also approved in 2010 and 2011, respectively, for the treatment of AK in the face and balding scalp (FDA 2010, 2011).

Importantly, clearance of both clinical and not detectable subclinical AK is one of the advantages of topical creams (Del Rosso et al. 2014). In a clinical study, imiquimod 5% was administered to 15 patients with a history of long exposure to sunlight but without evidence of AK in histopathologic assessment. The intervention led to appearance of early AK in three patients with skin inflammation and then complete clearance of AK after eight weeks of treatment (Kopera and Kerl 2014). The study highlights the role of imiquimod for the prevention of SCC not only in case of AK presentation but also before any clinical manifestation of AK.

In addition to imiquimod, thymic stromal lymphopoietin, a cytokine that exerts immune response against cancer,

combined with 5-fluorouracil was tested for regression of AK in mice and showed expression of NKG2D as well as a $CD4^+$ T cell-dependent response leading to 87% clearance of AK lesions (Cunningham et al. 2017). This intervention is also potential to be tested in future clinical studies.

Challenges and Future Directions

Cancer immunoprevention has been examined for virally-induced tumors, i.e., HPV-associated cervical and vulvar cancer, and showed promising results. The premalignant lesions of these cancers are readily detectable and oncogenic peptides of HPV can be targeted without causing significant toxic effects for normal cells. However, identification of potential targets for cancer immunoprevention of non-virally-induced tumors is more challenging.

The immunoprevention of non-virally-induced tumors is accompanied by several hurdles. Initially, detection of premalignant lesions and understanding the stepwise progression of lesions are necessary for cancer immunoprevention. It is more practical for cancers such as breast and colorectal cancer with known predisposing genetic mutations, detectable premalignant lesions, and established screening methods (Loomans-Kropp and Umar 2019). Since detection of premalignant lesions is a vital step for cancer prevention, in addition to routine modalities such as, imaging, immunohistochemistry, and genetic assessments; novel techniques such as immune biomarkers and epigenetic alterations could also be applied to the field (Beane et al. 2017; Cheng 2015; Jeanmart et al. 2003; Lowe et al. 2014; Massion et al. 2009; Selamat et al. 2011).

The next hurdle of cancer immunoprevention is designation of target population. The development of criteria to determine individuals at high-risk of malignant progression especially for inadequately investigated cancers is warranted. The criteria should contain clinical information, risk factors, imaging data, genetic, epigenetic, immunohistochemistry, and immune profile. Moreover, the target population should have premalignant or early malignant lesions with low rate of spontaneous regression (Loomans-Kropp and Umar 2019; Uleberg et al. 2014). Overall, specification of subgroups of patients who most benefit from cancer immunoprevention are required.

It is worth mentioning that one of the major concerns for designing preventive modalities is their probable side effects. Due to the fact that target population in primary prevention is often healthy individuals, interventions are not allowed to cause serious adverse effects. In addition, less aggressive approaches are more acceptable by healthy people and even patients with early stages of malignancy. Therefore, a risk–benefit assessment should be considered for designing preventive modalities (Dunn and Kramer 2016).

As reviewed in this paper, various approaches including surgical excision, radiation therapy, chemoprevention, and photodynamic therapy could be applied to inhibit progression of premalignant lesions. However, considering the risk of recurrence and recent investigations that outlined immune dysregulation in premalignant lesions, application of cancer immunoprevention is necessary. Immune-based interventions with a relatively safe profile, systemic effects rather than local effects, and long-term protection due to immunological memory could be a beacon of hope for cancer prevention. Although preclinical studies in mice models and early clinical trials have supported strength of immune-based interventions to inhibit cancer progression, cancer immunoprevention is at the beginning of its way and needs to be tested in advanced randomized clinical trials prior to turning into an established practice.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

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