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Immunoediting and tumor neoantigens that can impact the efficacy of immunotherapies

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Abstract

Immunoediting is by far the most serious challenge in the immunotherapies that are on the rise for Glioblastoma Multiforme (GBM). However, it is a double-edged sword because this process can be suppressive of the tumor too. Personalized medicine will succeed only if there are effective methods in place to address this challenge. A thorough understanding of the host immune system and the tumor cells heterogeneity and their mutual interactions is necessary. There is a lot of research being pursued in this direction. So far, the main aspect identified for developing immunotherapy for GBM is finding the balance between the immunoediting and the use of neoantigens for neoantigen-directed T-cell therapies.

Introduction

Immunosurveillance

The understanding of the role of immunoediting came into full swing after Brunet and Thomas defined a novel concept called immunosurveillance [1]. They proposed that the host immune cells, especially the T-cells, are responsible for hunting down the tumor cells and destroying them. An overview of this concept is presented in **Fig. 1**. They also conceived the concept of neoantigens produced by the tumor cells as the driving force for the T-cells for recognition [2]. There are many evidences accumulated in literature over the years to show the presence of immunosurveillance. Tumor infiltrating lymphocytes (TIL) are responsible for the attack and elimination of tumors [3]. An abundance of $CD8^+$ T cells in tumors is a marker for their prognosis such as in colon cancer [4,5], breast cancer [6], carcinomas [7], melanomas [8], and so on. Further, natural killer (NK) cells inside the tumor cells in high density have also shown that presence of immunosurveillance [9–11]. This can also be proved by the development of tumors in patients that have had renal or cardiac transplants that immunosuppression can promote cancerous cells like the lung cancer, liver cancer, breast cancer, skin cancer and so on [12]. This especially true if the donors have had a history of cancer because their organs might hoard the metastatic tumor cells that have survived the immune system of the host [13].

R.D. Schreiber, et al., have shone light on the theory of immunoediting through their research which showed that (1) immunosuppressed mice developed sarcomas more aggressively than the wild type mice because lack of normal immune responses to IFNγ; (2) immunosurveillance was part of the entire immune response to the tumor antigens - they observed that the immunocompetent mice did not develop tumors derived from syngeneic mice were implanted in them; (3) T-cell mediated immune responses, especially CD4 and CD8 T-cells, were in place to protect host from tumors followed by development of immunological memory of the tumor antigens. However, they also found that transfection of major histocompatibility complex (MHC) class I and transporter associated with antigen processing 1 (TAP) genes, which are responsible for antigen presentation proteins in tumor cells, was seen in the tumor helping them escape the immune system of the host. They summarized their research by concluding that "The immune response thus functions as an effective extrinsic tumor-suppressor system. However, this process also leads to the immunoselection of tumor cells that are more capable of surviving in an immunocompetent host, which explains the apparent paradox of tumor formation in immunologically intact individuals" [14].

Immunoediting

Over the years of further understanding of this concept, it has been found that the immunosurveillance is a only a part of a bigger umbrella process called immunoediting [15–17]. Immunoediting is a concept where the tumor undergoes modifications in the characteristic immunogenicity in the presence of active immune system of the host that may develop immune-resistant tumor cells. It is dynamic process that has a role in aggressive tumor progression. There are three phases of immunoediting – Elimination, Equilibrium, and Escape. The summary of this concept has been given in **Fig. 2** [18].

Elimination

This phase is sometimes used synonymously with immunosurveillance. Both innate and adaptive immune systems have a major role to play in this phase. There might be a role of the non-immunogenic factors too in the triggering of this process like the p53 mutations or down-regulation that promotes cancer [3]. Inflammatory cytokines from the tumor cells, macrophages, dendritic cells or the stromal cells activate the effector cells including the NK, NKT, γδ T cells and the IL-12 and IFN-γ. The tumor cell death induced by the innate immune cells release the tumor antigens (TA) that activate the adaptive immune system [19–21]. Further, maturation of dendritic cells occurs, and they arrive at the tumor draining lymph nodes (TDLNs) presenting the TA to the immune system more that repeats the process described to eliminate the tumor cells in all [22]. There are many immune cells other than these primary cells like the T_H17 activated by IL-17, IL-17F, IL-21, IL-22 and IL-23 receptor (IL-23R), Regulatory T cells (T_{reg}), $CD25^+$ (IL-2 receptor alpha chain), T-cell-attracting chemokine CCL5 (also called RANTES), monocyte chemotactic protein 1 (MCP-1), nuclear factor-κB ligand (RANKL), etc. that have a role in the process of elimination [23].

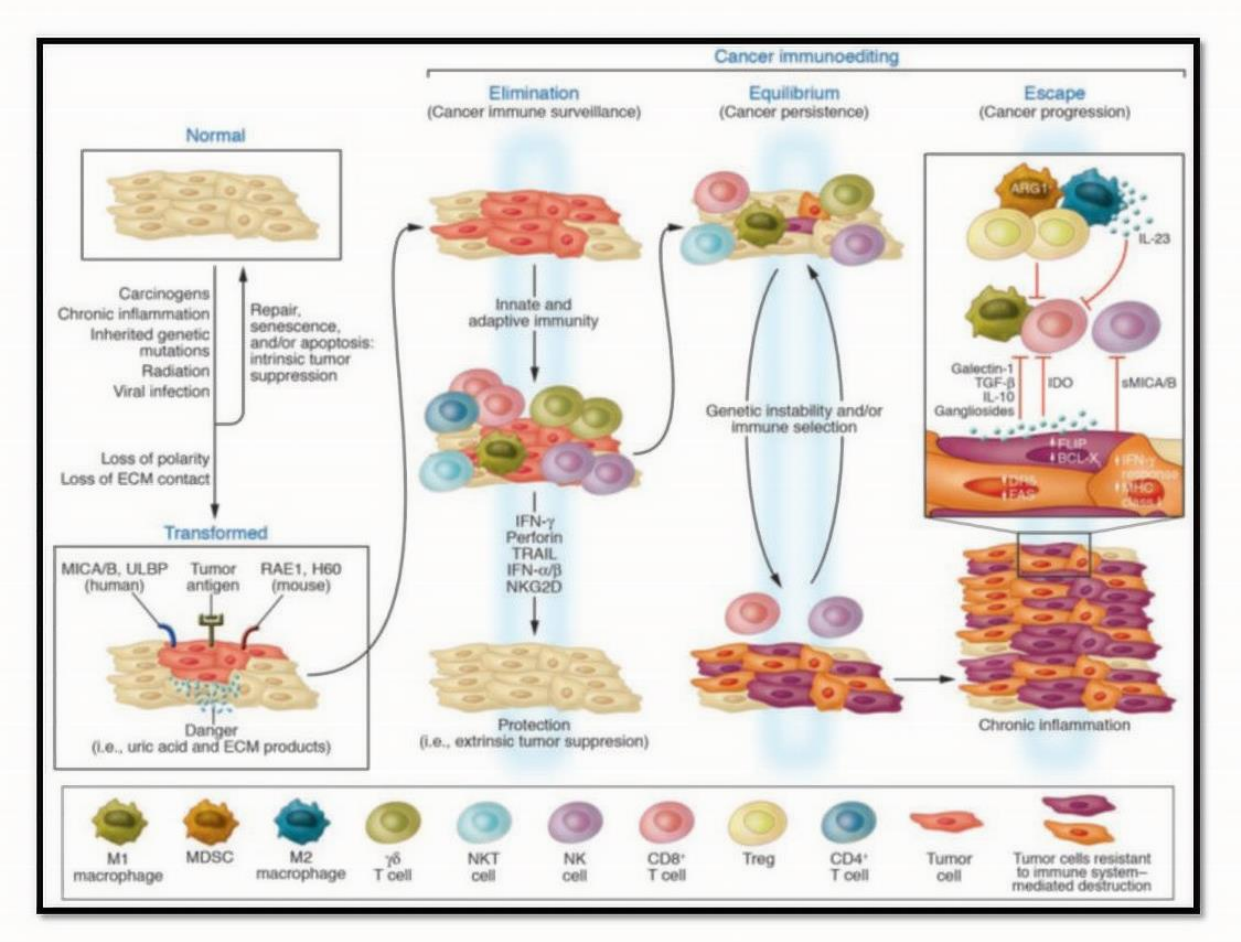

Fig. 1: The overall activity of the immune system in shaping the tumorigenicity

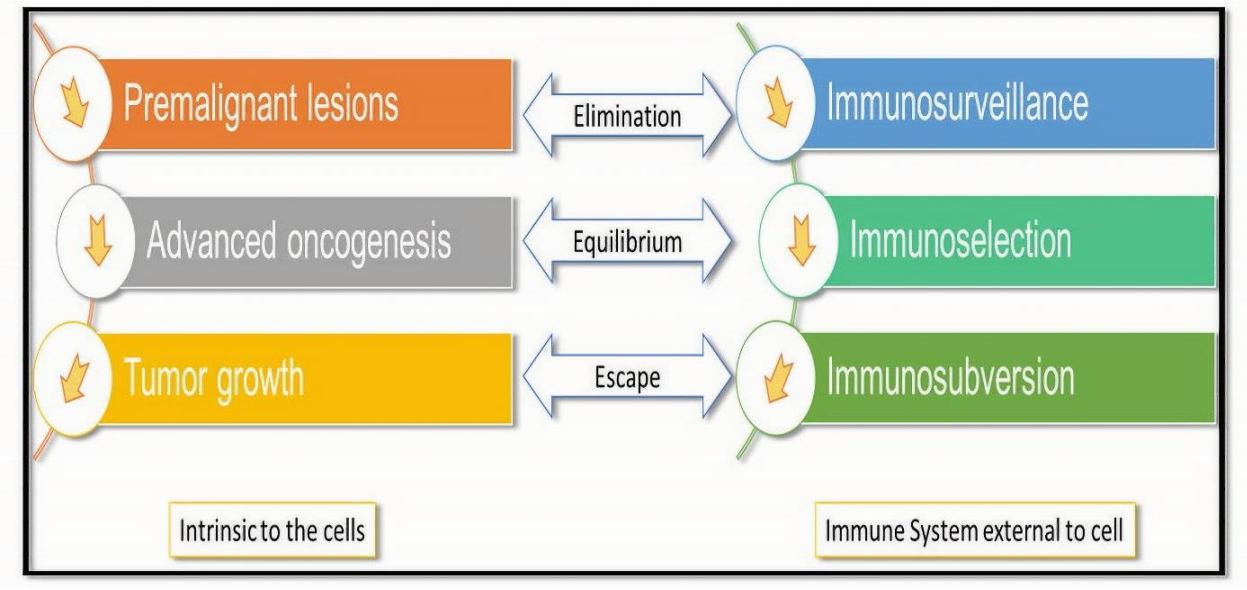

Fig. 2: The three phases of Immunoediting and the key players of the immune system involved

There are four phases to this process:

- **Phase I:** Tumor recognition and cell killing to a small extent occurs when the tumor grows to a discernible size of 2-3 mm that initiates pro-inflammatory responses from the innate immune system [24,25].
- **Phase II:** Dendritic cells mature and migrate and result in release of IFN-γ that will eventually show the cell killing by antiproliferative [26] and anti-angiogenic effects [27], and induces apoptosis [28]. Further, the necrotic tumor cells are ingested my immature dendritic cells.
- **Phase III:** IL-12 and IFN- γ produced by NK and macrophages in tumor cells lead to the activation of cytotoxicity mediators like the perforin, TNF-related apoptosis inducing ligand (TRAIL) and reactive oxygen [29,30]. This leads to the presentation of the tumor antigens on their surface to the naïve $CD4^+$ T cells and the production of the tumor antigen specific $CD4^+$ and $CD8^+$ T cells.
- **Phase IV:** Tumor killing by $CD4^+$ and $CD8^+$ T cells is the final step of elimination process by their recruitment at the tumor site producing more IFN- γ. The paradox here is that this is the phase where the tumor cells are educated that reduces their immunogenicity leading to the equilibrium phase of immunoediting [14].

Equilibrium

This is the next phase of immunoediting process. This phase is responsible for the development of the tumor cells that are resistant to the immune effector cells. There are several hypotheses that explain this phase. One such hypothesis is the absence of inflammatory signals of the immune system to the tumor antigens that activate the dendritic cells and macrophages of the innate immune cascade reactions [14,31–33]. This can lead to tolerance and immune selection of the tumor cells [25]. Another theory explains that the antigens presenting cells sometimes produce anti-inflammatory markers like IL-10 and transforming growth factor-β (TGF-β) that fails to elicit immune responses [34]. Yet another theory is the occurrence of random gene mutations promoting tumor [14]. It has also been suggested that the immunogenicity can alter based on the type of cytokines activated mechanism too that can be specific for the type of cancer. Further the immune selection also depends on the immunogenic capabilities of the original mode of tumorigenicity (like the chemical, or viral induction or spontaneous induction) or the original host of the tumor in case of transplantation [35–38] that has a role making the tumor cells more resilient to destruction. This phase is the longest phase of the immunoediting process spanning over years [15].

Escape: This phase is where the mutated immune selective cells escape the immune system of the host leading tumor progression. There may be a few ways this happens. The first one may be the alterations developed in the signal transduction molecules of the effector cells. The primary signal transduction cells involved are the T-cell receptors such as TCR–CD3 complex (specifically the CD3-ζ chain) found on the TILs that are responsible for the expression of TA, T_{helper}-1 polarization, upregulation of the IL-10 and TGF-β and downregulation of IFN-γ that elicit the immune responses [39]. A loss of this complex in the tumor cells causes the evasion of the host immune system. This kind of evasion is seen in many cancers like the pancreatic cancer, renal cancer, and several melanomas [40–43]. Further, it has been known that TCR-ζ is involved in the apoptosis by activating the caspase 3, and downregulation of anti-apoptotic factors like the Bcl-xL and Bcl-2. Thus, the loss of TCR-ζ can make the T lymphocytes in the tumor vulnerable to apoptosis by increasing the FasL expression on tumor cells [44–47]. This mechanism operates in a vicious cycle. The other way is the emergence of the tumor-derived soluble factors (TDSF) like vascular endothelial growth factor (VEGF), IL-10, TGF-β, prostaglandin E2, soluble phosphatidylserine, soluble Fas, soluble FasL and soluble MHC class I chain-related A (MICA) [48,49,58,50–57] that promote evasion of the immune system of the host by the tumor cells. Moreover, the overall the presentation of the TA may just not be sufficiently enough to activate the immune system efficiently to combat the tumors [59].

Neoantigens and their impact on the immunotherapies

In the light of these novel understanding of the tumor immunoediting and its interactions with the host immune system, there are a new class of therapeutic agents developed called the neoantigen-directed T-cell based immunotherapy. Neoantigens are the antigens on the tumor cells that are specifically

identified by neoantigen-specific T-cell receptors (TCRs). They have known to play an important role in T-cell mediated anti-tumor immunity. There is evidence in the research conducted proving this fact by showing the presence of T-cell recognized anti-tumor activity against neoantigens, the immune check point blockade being affected by the neoantigens, the rise of the adoptive T-cell based therapies and vaccines developed based on neoantigens [60–63]. While neoantigens are specific tumor cells, there are other tumor antigens called the tumor-associated antigens (TAAs) and cancer-germline antigens (CGAs) that are expressed both on healthy as well as well as the tumor cells [64–66]. These two targets of the have shown more tolerance, less affinity (because of their low level of expression), less specific targetability, more chances of autoimmune responses in non-target tissues and thus failure of the therapies based on them in comparison to the ones based on neoantigens [67,68]. Hence, the greatest advantage of neoantigens is that they are identified as true antigens by the immune system that eliminates all the above drawbacks of targeting the TAAs and CGAs [60].

Jiang et al. have very clearly explained the growth of the neoantigens as targets for cancer immunotherapy as shown in **Fig. 3** [69].

There have been several researchers who attempted to show the existence of antitumor immunity after a second challenge by the tumor. All of them have succeeded in proving that the immune system was capable of recognizing and eliminating the tumor cells after the second exposure by malignant cells [70–72]. These findings led to further work in the field to understand that T-cells were involved in the recognition of these tumors and that they were highly specific to the neoantigens [73–75]. They began applying neoantigen reactive T-cells as a part of therapy to achieve maximum regression in melanomas [76,77]. They also found that these therapies were active at high levels in the tumors as well as the blood for a very long time [78]. To maximize the advantages of the neoantigen therapies, several novel techniques are being put into practice to develop personalized medicine/vaccines for cancer treatment like the next-generation sequencing (NGS) technology [79–86]. The most recent developments in this direction are the checkpoint inhibitors like the CTLA-4 and PD-1 inhibitors on the T-cells [87–91] that work by allowing enhanced functioning of the immune responses using these immune checkpoints [92–96]. Like the two sides of a coin, these developments can also be not very effective in the achieving the goals [97] showing that there is still a long road to be explored along [97] and translate them to the clinical settings [98]. The same is true with the developing of vaccines for cancers using the immune checkpoint inhibitors which are on the rise and are actively crossing the pre-clinical barriers in melanomas [99–101], carcinomas [102,103], sarcomas [104,105]. Vaccines are also developed for mutation specific antitumor responses. Some of these vaccines have gone to the Phase I clinical trials like the dendritic cell vaccine for melanoma in 2015 [106]; the synthetic long peptide vaccine in conjunction with PD-1 inhibitor for melanomas in 2017 [107]; personalized RNA mutanome vaccine for melanoma combined with PD-1 inhibitor to achieve complete regression of the tumor [108]. Further, glioblastomas are explored now with multi-epitope vaccines [109,110] in the Phase I clinical trials. Some of the current clinical trials that are based on neoantigen based vaccines for cancer are listed in **Table 1** [69].

Yet another avenue based on neoantigens that is explored now is the adoptive T-cell transfer therapies (ACT) that are tumor neoantigen specific but are manufactured *in vitro* [62]. These are beneficial in the way that do not have immunosuppressive effects from tumor microenvironment (TME). On the other hand, they also have a disadvantage that it quickly becomes dysfunctional too. They are a very effective in developing personalized therapies for various cancers [111–117]. Needless to say, the ACT also are translated to the clinical trials such as the adoptive transfer ERBB2 interacting protein (ERBB2IP) mutation–reactive $CD4^+$ tumor infiltrating lymphocytes (TILs) in 2014 for metastatic epithelial cancer, breast cancer [(SLC3A2, KIAA0368, CADPS2, and CTSB)-reactive TILs and colorectal cancer (mutant KRAS G12D reactive $CD8^+$ TILs) [118–121]. These have shown to achieve reasonable tumor regression. Further, the vaccine and ACT therapies are used in combination with each other and with other conventional therapies or immunotherapies that are already in place for stronger immune responses against tumors [122–131].

Conclusion

In conclusion, we can say that immunoediting is posing a serious challenge to immune therapies for cancer. However, it is a double-edged sword that not only develops immune-resistant tumor variants but also can be used to our advantage for developing

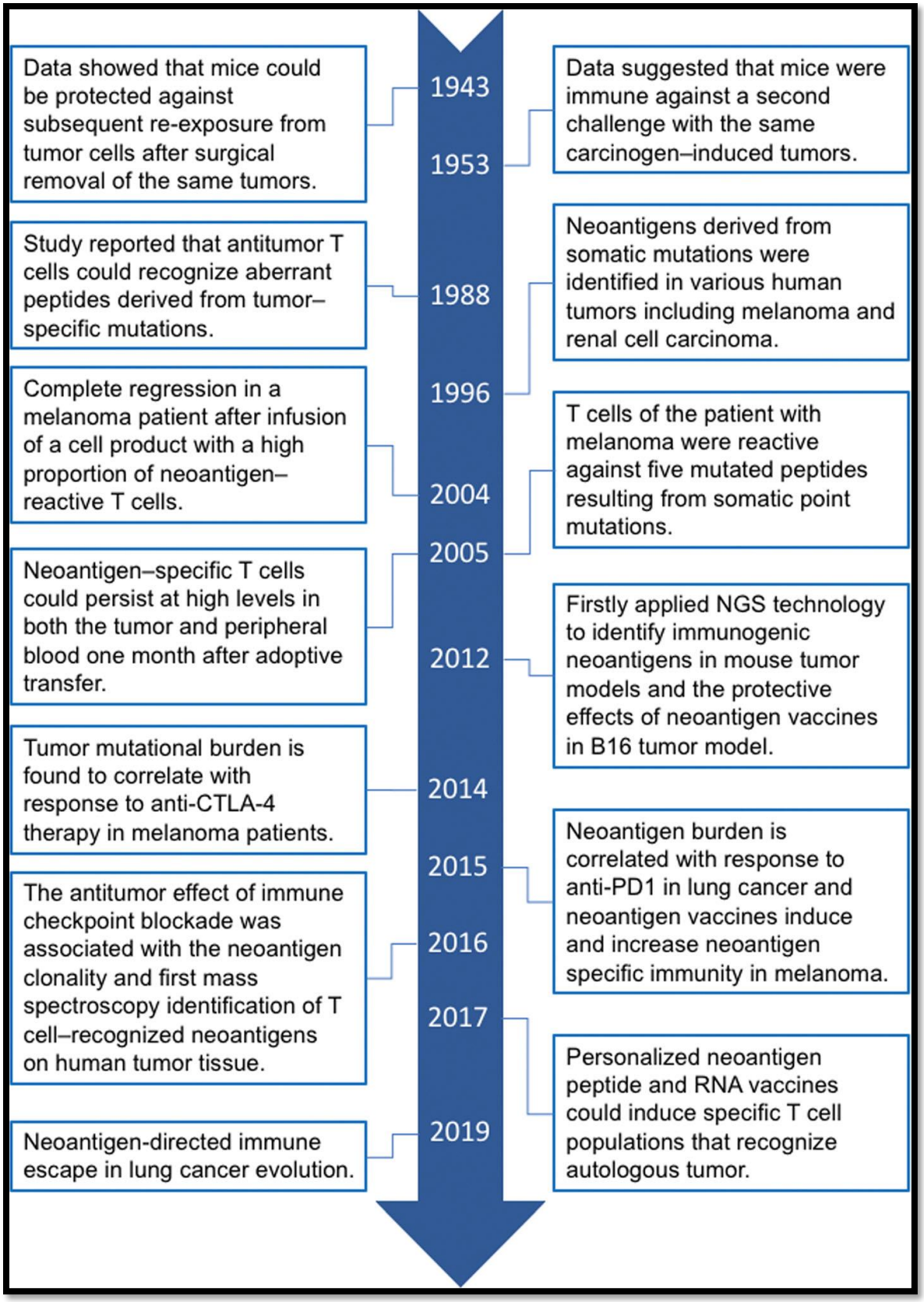

Fig. 3: History of the tumor neoantigens as immunotherapy targets

Table 1: List of current clinical trials for neoantigen based vaccines

Interventions	NCT number	Phase	Enrollment status	Cancer types	Combinations
Neoantigen vaccine	NCT03558945	I	Recruiting	Pancreatic tumor	None
Neoantigen vaccine	NCT03359239	I	Recruiting	Urothelial/bladder cancer	Atezolizumab
Neoantigen vaccine	NCT03645148	I	Recruiting	Pancreatic cancer	GM-CSF
Peptide vaccine	NCT03558945	II	Not yet recruiting	TNBC	Nab-paclitaxel, Durvalumab
Peptide vaccine	NCT03929029	I	Recruiting	Melanoma	Nivolumab, ipilimumab
Peptide vaccine	NCT03715985	I	Recruiting	Solid tumors	None
Peptide vaccine	NCT01970358	I	Active, not recruiting	Melanoma	None
Peptide vaccine	NCT03639714	I/II	Recruiting	Solid tumors	Nivolumab, ipilimumab
Peptide vaccine	NCT03956056	I	Not yet recruiting	Pancreatic cancer	Adjuvant chemotherapy
Peptide vaccine	NCT02287428	I	Active, not recruiting	Glioblastoma	Radiation therapy
Peptide vaccine	NCT02950766	I	Recruiting	Kidney cancer	Ipilimumab
Peptide vaccine	NCT03219450	I	Not yet recruiting	Lymphocytic leukemia	Cyclophosphamide
Peptide vaccine	NCT03422094	I	Recruiting	Glioblastoma	Nivolumab, ipilimumab
DC vaccine	NCT03871205	I	Not yet recruiting	Lung cancer	None
DC vaccine	NCT02956551	I	Recruiting	NSCLC	None
DC vaccine	NCT03674073	I	Recruiting	Hepatocellular carcinoma	Microwave ablation
DC vaccine	NCT03300843	II	Recruiting	Solid tumors	None
RNA vaccine	NCT03908671	Not Applicable	Not yet recruiting	Esophageal cancer, NSCLC	None
RNA vaccine	NCT03480152	I/II	Recruiting	Solid tumors	None
RNA vaccine	NCT03468244	Not Applicable	Recruiting	Solid tumors	None
DNA vaccine	NCT03532217	I	Recruiting	Prostate cancer	Nivolumab, Ipilimumab
DNA vaccine	NCT03122106	I	Recruiting	Pancreatic cancer	Adjuvant chemotherapy
DNA vaccine	NCT03199040	I	Recruiting	TNBC	Durvalumab

novel therapies based on the neoantigens produced during the immunoediting. This is the age of rapidly developing neoantigen based therapies and vaccines and their combinations thereof. These novel strategies of immune therapy that make use of the checkpoint inhibitors must be explored more aggressively while considering the possibility of developing resistance. A thorough understanding and organized extensive research in this area will light up a bright future in the field of personalized immunotherapy.

Conflict of interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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