Immunotherapy for Cutaneous Malignant Melanoma

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Contributor: Madison Ernst , Alessio Giubellino

Malignant melanoma (mM) is the leading cause of death among cutaneous malignancies. While its incidence is increasing, the most recent cancer statistics show a small but clear decrease in mortality rate. This trend reflects the introduction of novel and more effective therapeutic regimens, including the two cornerstones of melanoma therapy: immunotherapies and targeted therapies. Unlike chemotherapies or radiation, in which the therapy directly induces cancer cell death, immunotherapies stimulate the patient's immune system to control and eliminate the tumor. Advantages of immunotherapies over traditional cancer treatments include increased durability for long-term control or even cure and more precisely targeted anti-tumor activity that spares healthy tissues, many times with comparable or even reduced overall toxicity. The high immunogenicity and somatic mutation burden of melanoma likely contribute to the success of immunotherapy. Treatments combining immunotherapies with targeted therapies, which disable the carcinogenic products of mutated cancer cells, have further increased treatment efficacy and durability. Toxicity and resistance, however, remain critical challenges to the field. There are three types of immunotherapies currently approved by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma: (1) T-cell stimulating cytokines (i.e. interferon (IFN)-α2b and interleukin-2 (IL-2)); (2) T-cell exhaustion-mitigating immune checkpoint inhibitors (ICI); and (3) a dendritic cell (DC)-activating oncolytic virus (T-VEC). Still others, such as adoptive cell transfer (ACT), hold strong promise for the future.

metastatic melanoma | targeted therapy | immunotherapy | combined therapies | tumor relapse | tumor resistance

1. Early Immunotherapies

1.1. Interferon-α2b

Interferon (IFN)-α2b is a recombinant form of human IFN-α with antiviral and antitumor properties. It was the first immunotherapy approved for melanoma, first as an adjuvant treatment in 1996 and then as first-line therapy in 1998. By binding to IFN receptors 1 and 2, the drug triggers multiple dose- and time-dependent immunostimulatory effects, including upregulation of major histocompatibility complex 1 (MHC1) on tumor cells, enhanced activation of anti-tumor cytotoxic T lymphocytes (CTLs), depression of T regulatory cells (Tregs), enhanced dendritic cell (DC) response, and decreased intercellular adhesion molecule (ICAM) expression [1][2][3]. In 1996, high-dose (HD) IFN-α2b became the first adjuvant therapy, approved for use in stage IIB and III melanoma patients following surgical resection. Initial trials demonstrated significantly improved 5-year relapse-free survival (RFS) (37% vs 26%) [4][5].

HD IFN-α2b treatment is limited by high toxicity, with studies reporting dose reductions in 28-55% of patients and toxicity attrition rates of 10-26% (6). HD IFN-α2b remained the standard adjuvant therapy for high-risk melanoma until ipilimumab approval in 2015

Peginterferon-α2b (Peg-IFN), which has a longer half-life than IFN-α2b, was approved for adjuvant use in 2011 after demonstrating significant improvement in 7-year RFS compared to observation (39.1% vs 34.6%) but, like HD IFN-α2b, could not provide OS benefit [6][7].

Low dose (LD) IFN-α2b was approved as first-line therapy for stage II melanoma patients in 1998 based on a trial showing improved 5-year RFS (43% vs 51%) and a trend toward improved OS (24% vs 32%) compared to observation [8]. It does not have significant clinical benefit in mM [9].

Today, IFN-α is no longer a first-line agent for most patients; however, it may still have utility as an auxiliary immunostimulatory agent, enhancing the clinical benefits of other immunotherapies.

1.2 High Dose Interleukin-2

Interleukin-2 (IL-2) is a T-cell growth factor that leads to cytokine production and preferential expansion of CD8+ T-cells, NK cells, and Tregs. In 1998, HD intravenous (IV) administration of IL-2 became the first FDA-approved immunotherapy for the treatment of metastatic melanoma (mM) [10](11). Durable tumor responses have been well documented in a subset of mM patients, with 5-10% of patients achieving complete response and even more achieving increased disease stability [10][11][12]. A recent one is of IL-2-responsive mM patients who exclusively received HD IL-2 for systemic therapy confirms prolonged clinical and survival benefits [13]. As with IFN-α therapy, the use of HD IL-2 treatment is limited by the relatively high incidence of grade 3 and 4 toxicities, which requires the drug to be administered in an intensive inpatient setting [14]. The efficacy of treatment is further limited by the drug's activation of anti-inflammatory T-regs, which limit CD8+ activation and effector functions. Drugs targeting specific subunits of the IL-2 receptor, such as the recombinant IL-2 receptor βγ-biased agonist NKTR-214 (Bempegaldesleukin), have shown promise in the targeted expansion of anti-tumor T and NK cells with limited expansion of Tregs and dramatically reduced toxicity [15][16][17][18][19][20].

While rarely used as a single or first-line agent today, HD IL-2 remains a second- or third-line option that provides a possible survival benefit to patients who have failed treatment with first-line agents [21]. Many trials combining HD or low-dose IL-2 therapy with additional therapies are ongoing.

2. Immune Checkpoint Inhibitors

2.1. Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) inhibitors

CTLA4 is an immune-inhibitory molecule expressed on the surface of activated T-cells. Together with its immune-activating counterpart, CD28, CTLA4 creates a critical immune checkpoint that must be overcome to achieve a durable immune response [22]. CTLA4 is naturally upregulated in situations of chronic T-cell stimulation to prevent

uncontrolled immune reactions and inappropriate development of autoimmunity. In the TME, however, this system backfires: chronic presentation of tumor antigens to T-cells inhibits the immune system from mounting an anti-tumor immune response and contributes to the immune evasion that allows continued tumor growth [23][24][25][26].

Ipilimumab was approved as the first immune checkpoint inhibitor (ICI) in 2011, the same year that vemurafenib was approved to block BRAF-mediated growth signaling. Ipilimumab is an anti-CTL4 human IgG antibody. By preventing the interaction of CTLA4 and its ligands, the drug allows T-cells to bypass the inhibitory immune checkpoint and mount a response against tumor antigens. Phase III trials of previously-treated mM patients demonstrated improved OS compared to gp100, a melanoma antigen immunostimulant with limited anti-tumor effects (10.1 vs 6.4 months, $p = 0.0026$) [27]. A metanalysis of pooled data from nearly 2,000 mM patients treated with ipilimumab (both pre-treated and treatment-naïve) reported an increase in the 3-year OS rate to 22% (95% CI [20, 24%]), a dramatic increase from ~5% achieved by previous standard-of-care therapies [28]. Perhaps even more importantly, the OS survival curve plateaued after 3 years, maintaining the ~20% OS rate for the entirety of the 10+ year follow-up [28]. Thus, ipilimumab became both the first therapy to provide an OS benefit in advanced melanoma and the first to demonstrate that long-term durable mM disease control is possible with systemic therapy [29].

While responses to ipilimumab are durable, the response rates are low, ranging from 5-10%. Clinical trials have provided little insight into possible biomarkers of response. Attempts to improve response rates by adding ipilimumab to dacarbazine therapy were somewhat successful (15% vs 10%) and demonstrated a survival benefit over dacarbazine alone (OS 11.2 vs 9.1 months, $p<0.001$). However, these benefits came at the cost of high toxicity (rate of grade 3/ 4 AEs: 56.3% vs 27.5%, $p < 0.001$) [30]. Even as a monotherapy, ipilimumab is relatively toxic with immune-related toxicities occurring in 60-80% of patients, 10-26% of which are grade 3/4 reactions [31]. Perhaps unsurprisingly, severe AEs, which are often immune-related AEs (irAE), were found to be associated with improved ORRs [32]. Ipilimumab is still the only approved CTLA4 inhibitor for mM, though ipilimumab monotherapy is not a first-line therapy by ASCO guidelines [33].

2.2. Programmed cell death protein 1 (PD-1) and PD-1 ligand (PD-L1) inhibitors

Like CTLA4, PD-1 is an inhibitory immune checkpoint receptor expressed by activated T cells. When PD-1 binds its receptors, PD-L1 and PD-L2, signaling through the SHP1/2 pathway downregulates the transcription factors necessary for T-cell effector functions, growth, and survival [34]. In healthy tissues, PD-L1 is broadly expressed and upregulated in response to proinflammatory cytokines [35]. Melanoma tumor and TME cells upregulate PD-L1 in response to tumor-infiltrating lymphocytes (TIL), suggesting that PD-L1 expression is used as a mechanism of immune evasion by the cancerous cells [36][37][38].

In 2014, two anti-PD-1 monoclonal antibodies, Pembrolizumab and nivolumab, were approved for treatment-resistant mM after demonstrating superiority over ipilimumab. Early trials of pembrolizumab monotherapy demonstrated improved 6- and 12-month PFS and RR (6-month PFS: pembrolizumab=47% vs ipilimumab=26%; 12-month PFS: P=74-68% vs I=58%; RR= P=33%, I=12%) [39][40]. Two and five-year follow-up studies and real-world findings of pembrolizumab monotherapy confirm its superior OS and durable antitumor immune activity for

both treatment naïve and pre-treated mM patients [41][42][43][44][45]. Similarly, the CheckMate 067 trial first demonstrated that nivolumab monotherapy confers a significantly greater PFS compared to ipilimumab in treatment-naïve mM patients (nivolumab: 6.9 months 95%[4.3, 9.5]; ipilimumab: 2.9 months 95%[2.8, 3.4] [46]. Follow-up data from 2019 then demonstrated superior 5-year OS rates (nivolumab = 44%, ipilimumab = 26%) [47]. Nivolumab has proven to be effective in a range of melanoma tumor subtypes, including both treatment-naïve and pre-treated tumors with either WT or mutant BRAF status [48][49].

The two PD-1 inhibitors differ by epitope binding location and target affinity strength but are equally effective as monotherapies by OS (pembrolizumab = 22.6 mo, nivolumab = 23.9 mo, $p = 0.91$) and time to next-line therapy or death (pembrolizumab = 15.7 mo, nivolumab = 10.8 mo, $p = 0.16$) [50][51]. Both are also relatively well-tolerated with lower rates of grade 3/4 toxicity (14% with pembrolizumab and 4% with nivolumab) than chemotherapy, ipilimumab, and most targeted therapies [52][50]. AEs during nivolumab therapy are associated with improved ORRs [50].

Both PD-1 inhibitors are also effective in the adjuvant setting. A five-year one on adjuvant pembrolizumab demonstrated significant increased RFS, decreased risk of distant metastasis or death (HR 0.60 95%[0.49,0.73]), and sustained treatment effect compared to placebo [51][53]. Interestingly, adjuvant pembrolizumab also proved efficacious in patients with PD-L1-negative and undetermined tumors [39][53]. In pre-treated stage IV melanoma patients with no evidence of residual disease, adjuvant nivolumab alone or in combination with ipilimumab proved similarly effective in increasing RFS compared to placebo [54]. These drugs are the current first-line adjuvant therapy for resected WT melanoma. Patients with resected BRAF-mutant melanomas may choose between pembrolizumab, nivolumab, or dabrafenib-trametinib combination therapy as first-line adjuvant therapy [33].

Optimal utilization of ICIs is hindered by several major challenges, including resistance and poor predictability of patient response. Approximately 30% of melanoma patients have an innate resistance to PD-1 inhibitors and 25% of responders acquire resistance during treatment [55][56][57]. CTLA4 inhibitors face a similar challenge [27]. Mechanisms of resistance likely include specific tumor cell genetics (loss-of-function mutations in *JAK1/2* [58]), differing expression levels of tumor cell surface proteins (for example, MHC I expression [59], alternate ICIs [60], and epigenetic T-cell changes limiting effector function and memory [61]). Efforts to increase durability by combining ICIs with auxiliary agents such as PEG-IFN [62] or hydroxychloroquine [63] have had mixed results, with none providing a clear clinical benefit. Unfortunately, increased toxicity often outweighs any benefit to durability or RR that auxiliary agents provide.

A few studies have identified markers associated with more successful clinical outcomes. For example, independent biomarkers associated with favorable OS of mM patients treated with pembrolizumab include high relative eosinophil count (>1.5%), high relative lymphocyte count (>17.5%), and absence of non-soft tissue or lung metastasis. Patients meeting none of these criteria have a poor prognosis with pembrolizumab [64]. Others have identified that the occurrence of immune-mediated AEs may be associated with better ORR, OS, and PFS with nivolumab and ipilimumab monotherapies but not with pembrolizumab [65]. Another—albeit much smaller ($n = 40$)—it was also found that PD-L1 expression on circulating tumor cells may also be a predictive biomarker for PD-1 inhibitor response, suggesting that liquid biopsy may provide clinically relevant information during treatment

selection [66]. However, subgroup analyses have demonstrated the PD-1 blockade still provides clinical benefits in PD-1 negative tumors [46]. Conflicting evidence on the subject makes using tumor PD-L1 expression as a predictive marker for PD-L1 inhibitor response or overall prognosis for mM controversial [67][68].

2.3. Combination ICI Therapy

Combining CTLA4 and PD-1 blockade is more effective than either class in monotherapy [69][70], yet carries a significantly higher risk of severe toxicity. As monotherapies, nivolumab and ipilimumab have grade 3/4 AE rates of 16-27% and 27%, respectively. When used together, this rate increases to 55-71% [46][54]. Reducing toxicity while maintaining the clinical benefit of combination therapy may be possible with alternative dosing strategies. Regimens of standard-dose pembrolizumab (200 mg) with either 150mg or 50 mg reduced-dose ipilimumab show a meaningful reduction in toxicity (grade 3-5 toxicity rate <26%) without a significant reduction in ORR (PEM200+IPI50: ORR, 55%, and CR, 16%; PEM200+IPI100: ORR, 61%, and CR, 25%). In fact, 12-month PFS and OS rates are actually higher with these regimens (12-mo PFS: 65% for PEM200+IPI50; 82% for PEM200+IPI100; OS: >90% for both) compared to standard dosage and previous alternative dosages (12-mo PFS: 46-53% with standard dosing, 47% and 68% with alternative dosing; 12-mo OS: 73-89%) [71][72][73][74][75]. Larger trials are still necessary.

2.4. Novel immune checkpoint inhibitors

The second generation of PD1 and CTLA4 ICIs are emerging. These new agents include anti-PD1 antibody HX008 [75], anti-PDL1 monoclonal antibody LP002 (NCT04756934), anti-CTLA4 antibody ONC-392 [76]. Lymphocyte activation gene 3 (LAG3) is another T-cell inhibitory checkpoint receptor, the upregulation of which may be a resistance mechanism to PD1 inhibition therapy [77]. Another promising ICI target is TIM-3 (T-cell immunoglobulin and mucin domain 3). TIM-3 blockade restores anti-tumor functions in *ex vivo* of previously exhausted NK and effector T-cells [78] and enhances cancer vaccine-induced antitumor responses in murine melanoma models [79]. A bispecific anti-PD-1 and TIM-3 antibody (RO7121661/RG7769) demonstrated superior anti-tumor TIL activity, IFN-γ secretion, and tumor growth control compared to the monospecific PD-1 antibody in mouse models [80]. The agent has recently entered phase I human trials (NCT03708328).

3. Oncolytic virus therapy

Cancer cells achieve a neoplastic phenotype by genetic and epigenetic mutations. These mutations, however, impair signaling pathways (*RAS, WNT, PTEN, RB1, TP53*) that are essential for the intra-cellular antiviral response [81]. Recent advances in genetic modification, such as CRISPR, have allowed researchers to create anti-neoplastic viruses that exploit the vulnerability of mutated cells to viral infection while sparing healthy cells [82].

Talimogene laherparepvec (T-VEC), an oncolytic human herpes simplex virus 1(HSV-1), is the first and only oncolytic virus (OV) approved for metastatic and unresectable melanoma. When T-VEC is injected directly into the tumor site, it promotes the secretion of granulocyte-macrophage colony-stimulating factor (GM CSF) to activate

DCs and increase tumor antigen presentation to T-cells. In the phase 3 OPTiM trial, 64% of directly injected and 34% of uninjected non-visceral lesions decreased in size by >50%. Complete resolution of lesions occurred in 47% of injected lesions, 22% of non-injected non-visceral lesions, and 9% of non-injected visceral lesions. When compared to recombinant GM-CSF administration, T-VEC demonstrated higher durable RR (16% vs 2.1%, p = 0.001), ORR (26% vs 5.7%), and OS (23.3 months, p = 0.051). Severe toxicity rates were only 2% [83]. Laboratory evidence shows that T-VEC has increased efficacy in melanomas with INFγ-JAK-STAT pathway mutations [84]. Since dysregulation of INFγ is a common mechanism of resistance to ICI therapy, ongoing trials are investigating T-VEC as a salvage or combination therapy (NCT04330430, NCT04068181).

Systemic administration of OV therapy is also being explored. However, maintaining viral titers capable of generating an anti-tumor response after systemic administration has proved challenging to systemic OV monotherapy [85][86]. Trials are also investigating their role as sensitizing agents or within combination immunotherapies. Systemic OVs may still have a role as priming agents or within combination therapy (NCT04152863).

4. The Future of Melanoma Immunotherapy

Over the past 8 years, immunotherapy has revolutionized the treatment of mM, offering patients more treatment options with higher efficacy and less toxicity. Two-year overall survival rates have risen dramatically from ~10% to ~60% [47]. Further into the identification of melanoma neoantigens and their immunogenic potentials is essential for the advancement of the field. The ability to create individualized therapies specific to each patient's tumor and immune landscape has the potential to revolutionize melanoma therapy. However, significant advances in rapid tumor-cell sequencing and vaccine production must first be achieved. In the shorter term, combination therapy and melanoma vaccines show promise for improving the efficacy, response rates, and durability of current first-line immunotherapies.

4.1 Sequencing and combining therapies

Using combined therapies to treat mM may be the easiest way to achieve longer-lasting disease control, overcome innate resistance, evade adaptive resistance to immunotherapy, and optimize clinical response. There is significant interest in finding the best combinations of the two most effective approved therapy classes—targeted and ICI therapy (NCT02631447, NCT03235245, NCT02902029, NCT02224781). Such may also address the two major roadblocks in the deployment of these therapies: rapid resistance development and modest response rates.

4.2 Neoadjuvant therapy

Neoadjuvant therapy is typically used to reduce tumor burden and allow for less extensive surgeries. Before immunotherapy, neoadjuvant systemic therapy was not standard-of-care for mM treatment, likely because the risks of delaying surgery outweighed the limited benefits these therapies could provide. However, preclinical data suggest that this may not be true for immunotherapy [87], especially for therapies targeting T-cell function and

proliferation. Theoretically, initiating immunotherapy while the major tumor mass is still present may induce a stronger anti-tumor T-cell response. Indeed, a small feasibility one confirmed these results, demonstrating that patients receiving neoadjuvant and then adjuvant treatment had significantly more expansion of tumor-resident T-cell clones than patients who received the same treatment courses exclusively as adjuvant [88]. Neoadjuvant immunotherapy also seems to outperform adjuvant therapy in comparative studies with event-free survival benefit [89]. However, the sample size was small and the toxicity profile of the neoadjuvant arm was disappointing. Larger trials are currently underway to investigate neoadjuvant regimens that preserve efficacy while limiting toxicity (NCT02977052) with promising initial results [90].

4.3 Adoptive cell transfer with tumor-infiltrating lymphocytes

In melanoma, the presence of tumor-infiltrating lymphocytes (TILs) is associated with more favorable OS, RFS, and DSS/MSS [91]. Adoptive cell transfer (ACT) of TILs is the process of expanding autologous lymphocytes *in vitro,* usually aided by IL-2, IL-7, IL-15, and/or IL-21, followed by re-infusion to the patient [92]. This strategy circumvents many limitations of other immunotherapies. For example, *in vitro* TIL culture allows for the selective expansion of lymphocytes with the strongest effector function and the highest tumor-antigen affinity. Using autologous cells from resected tumor specimens avoids issues of rejection and allows each treatment to be uniquely targeted to the patient's specific tumor antigens [93]. Since expansion and activation occur without the suppressive effects of the TME, higher numbers of activated lymphocytes (>10^{11} TILs) can be achieved. This also allows for pretreatment manipulation of the patient's immune system to optimize the efficacy of ACT or other planned immunotherapies without compromising the anti-tumor response. Greater response rates have been achieved when lymphodepletion proceeds and IV IL-2 follows ACT, both of which promote T-cell homeostatic cytokine production [94][95][96].

Since TIL-ACT regimens are not yet standardized, the degree of treatment efficacy reported in clinical trials has varied. Disease progression and overall survival after ACT-TIL are dependent on the expansion of neoepitope-specific CD8+ T-cells [97]. ORRs typically range from 28% - 45% [92]. Five-year follow-up found notable durability and suggests curative potential. Of the 22% CRs, all but one remained disease-free after 3 years, resulting in 100% 3-year and 95% 5-year survival rates [98]. It is especially exciting that these results occurred in challenging mM cases, in which patients had a median of 3 metastatic sites and had all failed first-line treatments, including 20% who had failed ICI therapy.

Overall, patients who receive TIL-ACT after failing ICI treatment have lower ORRs (56% vs 24%) and OS (28.5 vs 11.6 months) than ICI-naïve patients [99]. The same is true for patients with BRAF V600E/K mutations who failed prior targeted therapy (ORR: 21% vs 60% if naïve; OS 9.3 vs 50.7 months) [99]. This is likely because the poor immunogenicity and complex resistance mechanisms that allow tumors to evade ICIs also limit the efficacy of TIL-ACT [92]. However, an ongoing one of TIL-ACT in treatment-resistant mM has demonstrated an 80% disease control rate. Considering the higher toxicity rates and similar response rates of other second-line treatments, such as nivolumab or ipilimumab, TIL-ACT may be the best option for some patients resistant to alternative treatments [100][101].

Limitations to ACT-TIL are similar to those of other immunotherapies. As discussed above, resistance remains a central issue. Similarly, target identification, predictability of immunogenicity, and anti-tumor specificity (sparing healthy tissues) are essential for ACT-TIL success, but solutions remain in the early stages of development. Protocols for TIL expansion, antigen identification, pre-treatment immunodepletion, and post-infusion TIL maintenance (for example, IL-2 dosing) must be optimized for time, cost, efficacy, and safety in order to make this therapy feasible on a larger scale.

4.4 ACT with T-CARs

Another approach to ACT utilizes autologous T-cells modified *ex vivo* with cell-surface chimeric antigen receptors (CAR-T cells). The extracellular component of the CAR is a variable region of a synthetic antibody. It is attached to a T-cell signaling moiety and co-stimulatory domains, which allows MHC-independent T-cell activation [102]. CAR-T cells can thus target tumors cells that have downregulated MHCs as an immune-escape mechanism [103]. Success with CAR-T ACT for the treatment of hematologic malignancies sparked the investigation into the therapy for solid malignancies. However, success in mM clinical trials has been limited

4.5 Melanoma Vaccines

The five major categories of melanoma vaccines currently in development include (1) melanoma cell-targeted vaccines, (2) dendritic cell (DC) vaccines, (3) peptide-based vaccines, (4) vector-based vaccines, and (5) mRNA or DNA vaccines. Unlike preventative immunizations, cancer vaccines are therapeutic, activating the patient's immune system to incite an anti-tumor response against a known cancer or to prevent disease recurrence in the adjuvant setting.

Whole-cell vaccines use modified melanoma cells to simultaneously expose the immune system to many potential melanoma antigens, circumventing the need to identify the most immunogenic antigens for each tumor [104]. DC vaccines are used to directly inject activated or modified DCs into the tumor site to increase anti-tumor T-cell activation. Peptide vaccines supply tumor-specific or tumor-associated antigen (i.e. gp100, MART-1/MelanA, tyrosinase) fragments that can be presented by professional APCs to induce effector T-cell activation. Vector vaccines use recombinant viral vectors to deliver tumor antigen transgenes directly to APCs. Within the APCs, the transgenes are expressed to produce high concentrations of tumor antigens that can be presented on both MHCI and MHCII for enhanced T-cell activation. The simultaneous expression of viral proteins by the delivered vectors boosts the immunogenicity of the vaccine [105]. Therapeutic mRNA vaccines have garnered significant excitement after the advancements and efficacy demonstrated in the COVID-19 pandemic response. While still in the early stages, mRNA vaccines may have the potential to induce the targeted expression of nearly any protein. Using an mRNA approach avoids safety concerns associated with DNA and viral vector vaccines. Therapeutic mechanisms under investigation include enhancing the expression of tumor-specific antigens in DCs, mRNA-mediated delivery of specific anti-tumor or anti-ICI antibodies, and programming cancer cells to express suicidal intracellular proteins [106][107][108].

4.6 Toll-like receptor agonists

Toll-like receptor (TLR) activation and the resulting pro-inflammatory cytokine release is a critical step in the induction of both the innate and adaptive immune response [109]. As poor immunogenicity continues to limit the efficacy of melanoma immunotherapies in some patients, TLRs are a logical ancillary agent that provides pro-inflammatory modulation of the tumor microenvironment

4.7 Predictive markers and personalized medicine

Predicting response rates, toxicity, and durability present a major challenge to current mM immunotherapies. The melanoma and immune oncology one communities are investing significant resources to identify predictive biomarkers [110] that would allow treatments to be better optimized for each patient's therapeutic goals. Identification of tumor neoantigens and predictability of immunogenicity poses another issue. There are over 16,200 distinct class I HLA alleles, each with distinct peptide-binding preferences. Predicting which epitopes will likely be presented by each patient's APCs is key to the future of immunotherapies such as ACT, OVs, and melanoma vaccines as this interaction ultimately determines the immunogenicity of a given neoantigen. Some recent progress has been made: The HLAthena model can predict endogenous HLA-binding peptides with >75% accuracy [111]. The Tumor Neoantigen Selection Alliance (TESLA) developed a bioinformatic-informed model of tumor epitope immunogenicity capable of filtering out 98% of non-immunogenic peptides with a precision of over 0.70 [112]. However, no tool currently exists that can accurately predict if a specific neoantigen-HLA combination will be recognized by an individual's TCRs. More informed models will require a larger and more diverse data set. The accessibility and affordability of next-generation molecular and functional diagnostics may one day allow each patient to receive personalized immunotherapy, optimized specifically to their tumor and goals.

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