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Review

Genetic immune escape in cancer: timing and implications for treatment

Francisco Martínez-Jiménez [1,2,*] and Diego Chowell [3,4,5,*]

Genetic immune escape (GIE) alterations pose a significant challenge in cancer by enabling tumors to evade immune detection. These alterations, which can vary significantly across cancer types, may often arise early in clonal evolution and contribute to malignant transformation. As tumors evolve, GIE alterations are positively selected, allowing immune-resistant clones to proliferate. In addition to genetic changes, the tumor microenvironment (TME) and non-genetic factors such as inflammation, smoking, and environmental exposures play crucial roles in promoting immune evasion. Understanding the timing and mechanisms of GIE, alongside microenvironmental influences, is crucial for improving early detection and developing more effective therapeutic interventions. This review highlights the implications of GIE in cancer development and immunotherapy resistance, and emphasizes the need for integrative approaches.

Highlights

The prevalence of genetic immune escape (GIE) alterations varies significantly across cancer types, and loss of HLA expression is the dominant mechanism of GIE.

GIE alterations often arise early in cancer development.

Environmental exposures, such as smoking and air pollution, play a significant role in promoting immune evasion by creating an immunosuppressive tumor microenvironment.

Some GIE alterations promote resistance to T cell immunotherapies in a very cancer type- and treatment-specific manner.

Detecting GIE alterations in premalignant or early-stage tumors can open new avenues for personalized therapies and immunoprevention strategies, thereby improving the chances of intercepting cancer before it escapes immune surveillance.

Immune evasion is a key hallmark of cancer development [1]. As tumors accumulate specific genetic alterations that generate neoantigens [2,3] they employ various mechanisms to escape immune surveillance, such as downregulating major histocompatibility complex (MHC) molecules or modifying antigen-presentation pathways, which impairs the recognition of neoepitopes by cytotoxic T cells [4]. These immune evasion strategies can be broadly categorized as tumor-intrinsic or tumor-extrinsic, depending on whether they originate from within the tumor or from external factors in the TME [5–7].

Tumor-extrinsic immune escape mechanisms work by creating and sustaining an immunosuppressive TME [8]. These mechanisms often involve the recruitment of immunosuppressive cell populations such as myeloid-derived suppressor cells (MDSCs) [9] and regulatory T cells (Tregs) [10]. In addition, malignant and stromal cells secrete various cytokines and growth factors, including TGF-β [11,12], IL-10 [13], and VEGF [14], which suppress the activation and function of immune cells, ultimately impairing the infiltration and effectiveness of cytotoxic T lymphocytes. Systemic mechanisms, such as chronic inflammation triggered by environmental exposures (e.g., smoking, obesity, or infection), can facilitate immune evasion by promoting an immunosuppressive niche. Chronic inflammation recruits immunosuppressive cells (e.g., Tregs) and promotes the secretion of protumorigenic cytokines, which together impair immune surveillance and hinder effective antitumor immune responses [15]. As a result, tumors may evade immune detection even in the absence of genetic immune escape alterations, highlighting the importance of considering both intrinsic and extrinsic immune evasion strategies in cancer progression. By contrast, tumor-intrinsic mechanisms involve cancer cell-specific alterations that impact on their ability to be recognized and eliminated by immune cells. These mechanisms encompass genetic and epigenetic [16–18] changes that directly modulate how cancer cells interact with the immune system. Notably, large-scale studies of cancer genomes [18–24], along with functional screenings [25,26], have identified a wide range of somatically acquired genetic alterations,

[1]Systems Oncology Program, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[2]Hartwig Medical Foundation, Amsterdam, The Netherlands
[3]The Marc and Jennifer Lipschultz Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[4]Department of Immunology and Immunotherapy, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[5]Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

collectively known as genetic immune escape (GIE) alterations, which enable tumor cells to evade immune detection.

Some recent studies suggest that GIE alterations may arise during the early stages of malignant transformation, even in premalignant lesions [27–29]. This poses challenges for early cancer detection and intervention. Identifying premalignant lesions that harbor GIE alterations may open a critical window for preventive treatment strategies, but this also presents a clinical dilemma – determining the appropriate time for intervention to prevent cancer progression without overtreatment. Personalized surveillance and preventive strategies could benefit patients with early GIE alterations. Nevertheless, better diagnostic tools are necessary to distinguish between high-risk lesions and those unlikely to progress into cancer.

GIE alterations are also increasingly recognized as key contributors to immunotherapy resistance, especially in the context of T cell receptor (TCR)-engineered T cell (TCR-T) therapy. If GIE alterations occur early in cancer development, these immune escape mechanisms may be well established by the time the tumor is treated and may restrain the efficacy of cancer immunotherapies. Therefore, earlier detection of GIE alterations could guide the timing of immunotherapy and lead to more effective interventions. Targeting these escape mechanisms at earlier stages might prevent the tumor from developing the resistance that currently limits the success of immunotherapies.

In this review we explore the implications of GIE alterations in cancer, focusing on their prevalence, timing, and role in immunotherapy resistance. We may uncover new avenues for early detection, prevention, and more effective therapeutic interventions by elucidating how and when these immune escape mechanisms emerge.

Genetic immune escape across cancer types

A recent large-scale pan-cancer genomic study revealed that GIE alterations are a common feature across human cancers [23]. The study focused on somatic alterations affecting six GIE pathways previously linked to immune evasion. Remarkably, 25% of tumors exhibited alterations associated with immune escape, although the prevalence varied significantly across cancer types. For example, whereas glioblastoma showed almost no GIE alterations, >50% of cancers such as diffuse B cell lymphoma and non-small cell lung cancer (NSCLC) harbored these alterations. This variability suggests that some cancers face stronger evolutionary pressures from the immune system than others. Notably, tumors with a high tumor mutational burden (TMB), such as (ultra)hypermutated tumors, consistently demonstrated a higher prevalence of GIE alterations which cannot be explained solely by their increased mutational load [30].

This raises a key question: which mechanisms underlie immune evasion in the 75% of tumors that lack GIE alterations? It is possible that other GIE alterations, such as those reported in *CASP8* [31] or *PTEN* [32], were not considered in the study. This possibility is particularly relevant for low-TMB cancers, such as neuroendocrine tumors, which exhibit low rates of conventional GIE alterations. Recent publications suggest that these tumors may exploit alternative immune checkpoint axes beyond the PD-1/PD-L1 pathway [33], indicating that other GIE mechanisms may be at play. Nevertheless, it is important to recognize that functional screenings using orthogonal approaches have consistently identified the traditional GIE pathways as key players [25,26]. This makes it less likely that the absence of identified GIE alterations in low-TMB tumors can be fully explained by unrecognized or alternative GIE pathways.

Consequently, it is highly likely that additional factors, including non-genetic immune escape mechanisms and tumor-extrinsic influences, play a significant role in enabling cancers to evade

*Correspondence:
fmartinez@vhio.net (F. Martínez-Jiménez)
and diego.chowell@mssm.edu
(D. Chowell).

the immune system. The contributions of these mechanisms, as well as their interactions with GIE alterations, are discussed in further detail later.

Loss of heterozygosity (LOH) of HLA-I and HLA-II: it takes two to tango

The most prevalent pan-cancer mechanism of GIE is the LOH in the human leukocyte antigen (HLA) region that is detected in ~18–20% of tumors overall [22,23]. However, the frequency of HLA-I LOH varies significantly across cancer types. For example, HLA-I LOH occurs in 70% of pancreatic neuroendocrine tumors (PANETs) [23] and 40% of NSCLC cases [34], whereas cancers such as glioblastoma and lung neuroendocrine tumors exhibit much lower rates of HLA-I LOH.

Although the impact of HLA-I LOH on neoepitope diversity is clear for fully heterozygous HLA individuals, it remains uncertain whether HLA-I LOH is actively selected during tumor evolution or is merely a byproduct of the high genomic instability observed in advanced tumors, where >50% of the genome may experience LOH [23]. To address this crucial question, a study was conducted to determine whether the loss preferentially affects the allele with a higher combined neoepitope repertoire. The analysis revealed that focal and highly focal LOH events, characterized by losses of chromosomal regions significantly smaller than the entire chromosome arm, selectively targeted the allele presenting the highest number of neoepitopes [23,24]. Similarly, a recent study revealed that LOH of HLA-I significantly decreased the immunogenicity of recurrent driver variants in colorectal cancer [35]. Together, these findings suggest that LOH quantitatively diminishes overall tumor immunogenicity, but additional factors may be necessary to fully evade immune surveillance.

Interestingly, non-focal LOH events affecting entire chromosomal arms did not show the same impact on neoepitope diversity, suggesting that HLA may not be the primary target in these broader genomic events [23]. This finding is particularly significant for some cancer types, such as chromophobe renal cell carcinoma and PANETs, where non-focal HLA-I LOH is similarly pervasive (75% and 70%, respectively, in the analysis). Notably, there is no evidence suggesting that these events are selected based on HLA-specific neoepitope properties. This raises several important questions: what is the primary target of these highly recurrent LOH events? Could these events instead be driven by other selective forces? One possibility is that tumor-suppressor gene loss – rather than immune evasion – drives LOH, and HLA-I loci are affected as part of a broader chromosomal loss [36]. These non-focal LOH of HLA events often occur in tumors with high rates of recurrent patterns of chromosome losses (RPCLs), suggesting that replicative stress [37] or aneuploidy [38] could be driving chromosomal instability and large-scale LOH, where HLA-I loss is an indirect consequence. Further functional studies will be necessary to investigate these mechanisms and unravel the driving forces behind these recurrent LOH events.

Recent analysis also reports that HLA-I LOH is often accompanied by HLA-II LOH, and only a minority of lung tumors show gene- or locus-specific LOH [24]. This highlights that immune evasion may involve both HLA-I and HLA-II loci, and not only the disruption of cytotoxic T cell responses via HLA-I loss. HLA-II LOH plays an equally crucial role by impairing antigen presentation to helper T cells, which is essential for coordinating a broader immune response that includes macrophages, cytotoxic T cells, and B cells. A key finding is that HLA-II LOH selectively targets HLA alleles that are capable of presenting a broader range of neopeptides, thereby allowing tumors to avoid immune detection by reducing the diversity of neoepitopes presented to T cells. These results align with the growing body of evidence highlighting the importance of HLA-II in cancer evolution and antitumor immunity [39–41]. These findings also raise important new questions: to what extent are HLA-II genes expressed in cancer cells, and to what extent do HLA-II LOH events function as a mechanism of immune evasion in cancer?

Beyond GIE: non-genetic and environmental influences on immune escape

Although GIE alterations are crucial to understanding immune evasion, several non-genetic and environmental factors also play a significant role in shaping the tumor–immune interface. These influences work in concert with GIE alterations or, in some cases, operate independently to promote immune evasion.

Transcriptional repression of antigen presentation

In addition to genetic mechanisms, tumors can evade immune detection through transcriptional repression of antigen-presentation pathways. For example, HLA genes can be downregulated via epigenetic modifications or other transcriptional regulators. Unlike genetic mutations, transcriptional repression is reversible, which allows tumors to dynamically adjust antigen presentation during different stages of their evolution. This dynamic process poses challenges for therapies aimed at restoring antigen presentation because tumors may transiently evade immune detection by shutting down these [42–44]. In addition, it has been shown that disruption of HLA-I expression through alternative splicing and allele-specific transcriptional repression significantly contributes to immune evasion in lung and breast cancers, emphasizing the broad role of non-genetic mechanisms in orchestrating tumor immune escape [18].

The TME and immune suppression

The TME is a highly immunosuppressive niche that directly impacts on the ability of immune cells to recognize and attack tumor cells. Non-genetic factors within the TME, such as the recruitment of immunosuppressive cells, create a local environment that impairs cytotoxic immune responses. Moreover, secretion of cytokines such as TGF-β, IL-10, and VEGF further promotes immune suppression by inhibiting T cell infiltration and activity. This immune-suppressive environment often acts synergistically with GIE alterations, allowing tumors to evade immune detection even more effectively [11,12].

Chronic inflammation and environmental exposures

Chronic inflammation, driven by environmental risk factors such as smoking, air pollution, and obesity, fosters a protumorigenic environment through immune suppression. These factors trigger inflammatory responses that recruit immunosuppressive cells and release cytokines such as TGF-β, IL-10, and VEGF which support tumor progression by inhibiting immune cell activation. In addition, chronic inflammation may promote the selection of somatic driver alterations, including GIE events, thus conferring a selective advantage to tumor cells in inflamed environments. This highlights how environmental factors can synergize with GIE alterations to drive tumor progression [8,24,45–47]. For instance, smoking not only increases mutational burden but also reshapes the immune landscape by modulating HLA-II expression in alveolar macrophages and epithelial cells [24]. Although early upregulation of HLA-II may enhance immune surveillance through improved antigen presentation, chronic antigen exposure can lead to T cell exhaustion and exert selective pressure on tumor cells to downregulate HLA molecules, ultimately promoting immune escape.

Immune-privileged sites

Some organs, such as the brain, testes, and liver, are considered to be immune-privileged sites owing to their naturally immunosuppressive environments. Tumors arising in these locations can exploit the intrinsic immunoregulatory features of these tissues to evade immune surveillance. In these cases, the tumors do not necessarily rely on GIE alterations and instead take advantage of the local immune landscape to grow undetected. This is particularly evident in cancers such as glioblastoma and hepatocellular carcinoma where the immunosuppressive microenvironment is a significant barrier to effective immune response [48,49].

Timing of GIE

Large-scale genomic analyses of unpaired primary and metastatic cohorts reveal that GIE rates are largely consistent between primary and metastatic tumors across most cancer types [23]. Exceptions include prostate and thyroid adenocarcinomas, which exhibit higher GIE rates in metastatic settings, likely owing to extensive genomic remodeling at advanced stages [23]. These findings, corroborated by studies in lung squamous cell carcinoma (LUSC) and other cancers [18–20,23,29], support the view that GIE events are primarily selected during early tumor development.

Although GIE alterations can arise early in tumorigenesis (Figure 1), their impact may be significantly amplified by non-mutagenic, tumor-promoting factors. These external influences can reshape the fitness landscape of tissues, thereby allowing oncogenic cells with subclonal GIE alterations to gain a selective advantage over other clones. For instance, LUSC patients exhibit higher rates of subclonal LOH of HLA-I compared to clonal LOH [34], suggesting that selection for GIE may occur in response to selective pressures in specific tumor regions.

Notably, the absence of GIE alterations appears to impose a strong selective pressure on tumors. Long-term survivors of pancreatic cancer present an intriguing pattern where immune pressure edits tumors by eliminating more immunogenic clones, leaving behind those with fewer high-quality neoantigens [50]. This process of immunoediting demonstrates how tumors evolve under sustained immune pressure, and could potentially explain why some tumors select for GIE alterations to evade detection by the immune system entirely.

Recent interest in understanding the interplay between somatic mutations and positive selection has led to a surge in DNA sequencing of healthy and premalignant tissues [51,52]. These studies, as well as many others currently underway, have significantly advanced our understanding of malignant transformation [46,47]. Contrary to previous beliefs, cancer driver mutations are not exclusive to cancerous tissues but are also commonly found in healthy tissues. These mutations exhibit distinct tissue-specific patterns that are often associated with microclonal expansions [53,54]. Despite these advances, it is still unclear how frequently GIE alterations occur in healthy tissues

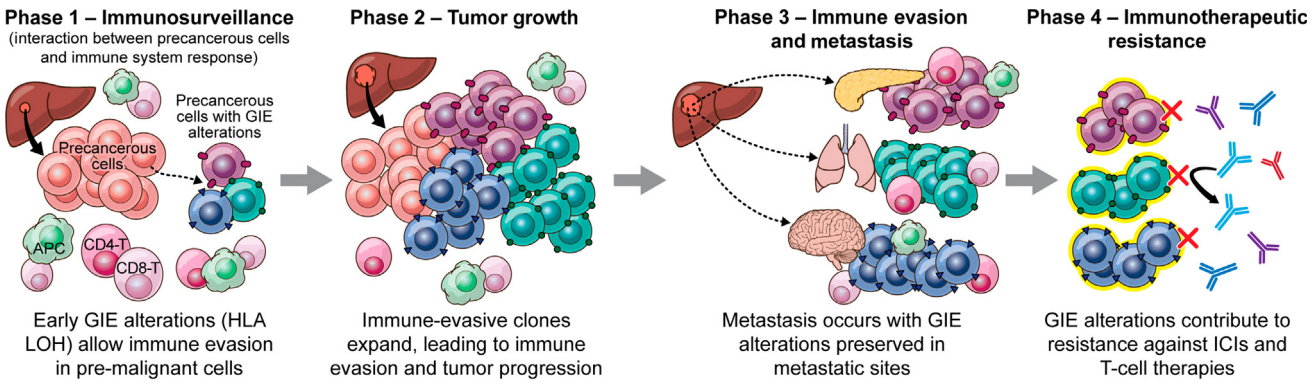

Figure 1. Timing of genetic immune escape (GIE). The dynamic process of tumor evolution from the early accumulation of mutations to advanced stages is characterized by immune evasion and metastasis. During the early phase of tumor development, immune surveillance plays a key role in detecting and eliminating abnormal cells. However, the accumulation of mutations, including early GIE alterations, enables immune evasion even in premalignant cells. As tumors grow, GIE alterations allow the tumor to bypass immune defenses, thereby facilitating progression and leading to eventual resistance to immunotherapies. The colored cells represent various factors contributing to immune evasion, metastasis, and treatment resistance, highlighting the complexity of tumor evolution and the challenges in developing effective therapies. Abbreviations: APC, antigen-presenting cell; ICI, immune checkpoint inhibitor; LOH, loss of heterozygosity; MHC, major histocompatibility complex.

and what their potential consequences might be. Could GIE be a key factor that drives malignant transformation (Figure 1)? Could it serve as the missing link between the presence of cancer driver mutations and the actual progression to cancer? What level of clonality is required for GIE events to confer a selective advantage to clones carrying these alterations?

New single-molecule sequencing technologies, combined with single-cell analysis of healthy tissue, have the potential to shed light on these crucial questions. By allowing the precise identification and tracking of GIE alterations at the level of individual cells, these approaches could help us to determine the timing of these alterations and their specific roles in the early stages of tumor initiation. This deeper understanding of when and how GIE events occur could also significantly impact on efforts to detect premalignant lesions with a higher risk of progressing to malignant tumors [55]. If GIE alterations are found to be early markers of malignant transformation, they could serve as valuable targets for early intervention, thus improving our ability to identify high-risk lesions before they evolve into fully developed cancer. This knowledge could ultimately lead to new diagnostic tools that enhance early detection and cancer prevention strategies.

Understanding the timing of GIE acquisition has important implications for metastasis (Figure 1). Metastasis-initiating cells face significant hurdles, from detachment from the primary tumor to migration through the bloodstream, but they appear to have inherent immune escape capabilities [56]. These cells also leverage non-genetic immune evasion mechanisms [56], allowing them to evade detection during transit and establish themselves in immune-excluded niches such as liver, bone, and brain that are common metastatic sites [57]. Longitudinal studies using matched primary and metastatic biopsies, together with multi-omic profiling of circulating tumor cells (CTCs), will be essential to fully uncover the immune evasion strategies employed during metastasis.

The impact of GIE alterations on immunotherapy efficacy

GIE alterations have been associated with the response to immune checkpoint inhibitors (ICIs) [58]. For example, loss of β2 microglobulin (*B2M*) has been linked to ICI resistance in melanoma and other cancers [59–61] (Figure 2A). However, in tumors with mismatch repair deficiency (MMRd) that lack *B2M*, some cases still respond to ICIs [62], although the mechanisms behind this remain unclear (Figure 2B). Other GIE alterations, such as disruptions of the IFN-γ pathway [63] and *CD58* [64], have also been associated with resistance to ICIs. However, their clinical significance remains to be fully elucidated. Despite these findings, *B2M*, *IFNG*, and *CD58* genetic alterations account for only a small fraction of ICI resistance in melanoma and are almost negligible in other cancer types [23]. This indicates that these alterations alone cannot explain the high rates of acquired and intrinsic immunotherapy resistance observed in these cancers.

Regarding LOH of HLA-I, the most common GIE alteration, the evidence of its impact on responses to anti-PD-1/PD-L1 therapies is mixed [22,65]. Although some studies suggest an association, others do not find a significant link (Figure 2C,D). This might be because HLA LOH represents a partial mechanism of immune evasion, where tumor cells still retain some antigen-presentation capacity. As a result, the tumor may still elicit an immune response upon immunotherapy. These findings suggest that, although GIE alterations can help tumors to sustain immune evasion, this 'immune-escaped equilibrium' can still be disrupted by ICI treatment (Figure 2). This highlights the importance of identifying cancer- and subtype-specific mechanisms of resistance to immunotherapy, which may not necessarily overlap with the mechanisms of immune evasion occurring during tumor progression (Figure 2E).

T cell-targeted immunotherapies, such as T cell transfer therapies and neoantigen vaccines, function by directing T cells to recognize and attack specific tumor-associated antigens [66–68].

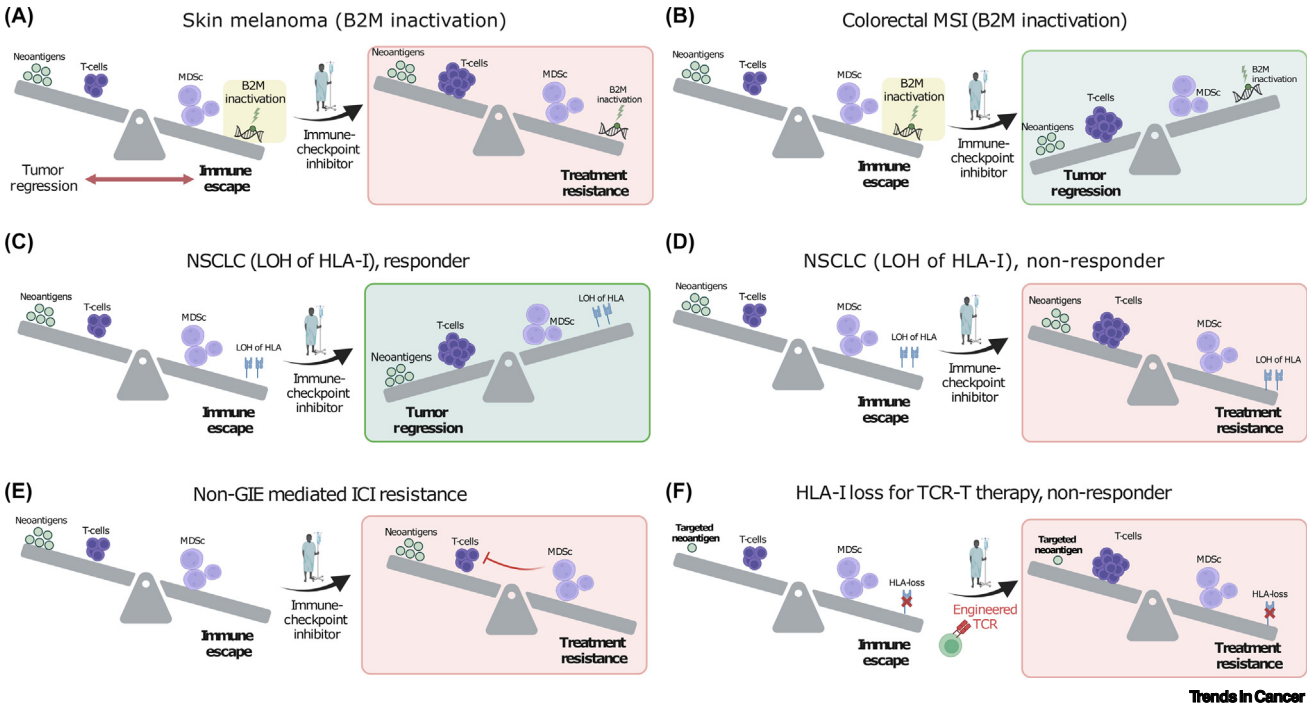

Figure 2. Mechanisms of immune escape and their impact on responses to T cell immunotherapy across different cancer types. (A) In skin melanoma and (B) colorectal cancers with microsatellite instability (MSI), *B2M* inactivation leads to immune escape, but treatment with immune checkpoint inhibitors (ICIs) can have very different outcomes. Tumor-associated immune cells, such as myeloid-derived suppressor cells (MDSCs), further promote resistance. In non-small cell lung cancer (NSCLC) with HLA-I loss of heterozygosity (LOH), the tumor may (C) respond or (D) become resistant to ICI. (E) Tumors may display resistance to ICIs without a known GIE event, presumably through MDSC-mediated suppression**.** (F) Tumors in patients treated with T cell receptor (TCR)-engineered T cell therapy (TCR-T) therapies often display loss of the specific HLA-I alleles that present the targeted neoantigen. The role of MDSCs and neoantigen presentation is highlighted in all cases, showing how these mechanisms interact to influence treatment responses.

These therapies either target patient-specific neoantigens (private neoantigens) or use off-the-shelf products directed at recurrent neoantigen–HLA-I pairs (public neoantigens). Both approaches have shown significant promise in treating solid tumors, either as monotherapies or in combination with ICIs [69–73]. For example, the mRNA-4157 cancer vaccine, combined with pembrolizumab, has demonstrated clinical efficacy in the adjuvant treatment of melanoma [74]. Another milestone was the FDA approval of the first TCR-T therapy for synovial sarcoma [75], and several other therapies are advancing through clinical stages [71].

T cell therapies targeting TP53 and KRAS neoantigens have shown that tumors can undergo LOH of HLA, where the allele presenting the targeted neoantigen is lost [76–78]. A recent Phase 1 clinical trial also identified LOH occurring either before or during treatment, highlighting the need to screen and monitor GIE events throughout therapy [73]. This is particularly important for cancers with high subclonal LOH rates, such as NSCLC [24,34], where the treatment may create a strong evolutionary bottleneck for subclones exhibiting LOH of HLA-I (Figure 2F). To overcome resistance in these cases, T cell therapies targeting neoantigens presented by different HLA alleles from both maternal and paternal origins could be effective because complete HLA loss is rare and could activate innate immunity [79]. Therefore, GIE screening before and during targeted T cell therapy is crucial. In this context, genomic profiling of circulating tumor DNA (ctDNA) is emerging as a valuable tool to monitor tumor genomes and detect emerging GIE alterations [80], helping to guide treatment decisions and reducing the risk of ineffective therapies.

Concluding remarks

GIE alterations pose a significant challenge in cancer immunology because they play a crucial role in tumor immune evasion and resistance to immunotherapies (see Outstanding questions). The diversity of these alterations across cancer types highlights the necessity for a more thorough understanding of the mechanisms behind immune escape. Current evidence indicates that GIE alterations can emerge early during tumorigenesis, and potentially act as crucial drivers of malignant transformation. Detecting GIE at earlier stages could unlock new opportunities for preventive strategies and personalized therapies that are specifically tailored to the unique genetic profile of each tumor. In addition, the TME and non-genetic mechanisms of immune evasion must not be overlooked. Environmental factors such as smoking and pollution may accelerate the development of immune escape mechanisms by creating an immunosuppressive niche. As a result, an integrated approach that considers both genetic and non-genetic factors is essential for a more comprehensive understanding of tumor evolution and resistance to therapy.

Outstanding questions

What is the precise timing of GIE alterations during tumor evolution, and how early do they arise?

Can early detection of GIE alterations prevent malignant transformation and improve cancer outcomes?

How do non-genetic mechanisms interact with GIE alterations to shape immune evasion, and can these pathways be cotargeted to overcome immunotherapy resistance?

How does the TME influence the selection and maintenance of GIE alterations, and could modifying this environment reduce immune escape?

How do GIE alterations contribute to metastatic potential, and could targeting these alterations in metastasis-initiating cells reduce metastatic spread?

Declaration of interests

D.C. is coinventor on a patent (US11230599/EP4226944A3) filed by Memorial Sloan Kettering Cancer Center (MSKCC) for using tumor mutational burden to predict immunotherapy response, licensed to Personal Genome Diagnostics (PGDx). D.C. is coinventor on a patent (US20240282410A1) filed jointly by Cleveland Clinic and MSKCC for a multimodal machine learning model to predict immunotherapy response, licensed to Tempus.

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