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Identifying Predictive Biomarkers for Immunotherapy: The Need for Minimally Invasive, Inexpensive, Broadly Applicable across Cancer Type, Pharmacodynamic Biomarkers

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Commentary

Cancer immunotherapy has gained significant interest and widespread clinical application over the past few decades [1]. The development of immune checkpoint inhibitor (ICI) antibodies that block inhibitory pathways (e.g., CTLA-4, PD-1/PD-L1) has introduced a groundbreaking new approach to cancer treatment, shifting the focus from targeting tumor cells to modulating the patient's immune response [2,3]. Reversing T-cell exhaustion enables T cells, NK cells, and dendritic cells to overcome immunosuppression and effectively attack tumor cells, thereby improving therapeutic outcomes across various cancers. Their promising therapeutic efficacy has further advanced this field [4].

Aside from checkpoint inhibitors, immunotherapeutic strategies include a wide range of approaches, such as naked antibodies (e.g., trastuzumab [5], cetuximab [6], rituximab [7], bevacizumab [8]) and their modifications, including bispecific antibodies (e.g., blinatumomab [9], teclistamab [10]), trispecific antibodies [11], antibody-drug conjugates (ADCs) (e.g., brentuximab vedotin [12], trastuzumab emtansine [13], sacituzumab govitecan-hziy [14]), engineered immune cells (CAR-T and CAR-NK cells) [15], vaccines (mRNA) [16], cytokines [17], oncolytic viruses, and more recently, small molecules, peptides, nanoparticles, gene therapy, and exosomes aimed at targeting the tumor microenvironment (TME) [18]. These advances have transformed oncology practice, establishing immunotherapy as a central pillar of modern cancer treatment alongside surgery, chemotherapy, and radiotherapy [18,19].

Although these therapies have improved outcomes for some patients and offer long-term clinical benefits, their widespread use in cancer immunotherapy remains limited by challenges, including highly variable response rates, immunotherapy resistance, and immune-related adverse events (irAEs). Several obstacles need to be addressed. Therapy response rates vary by type, ranging from 20% to 40% with ICI [4], 50-90% with CAR-T cells [20], and 73% with CAR-NK cells [21]. In addition, some patients (10%-30%) can experience hyper-progressive disease [22]. Some patients experience lasting clinical benefits, and in some cases, even a cure. However, most tumors do not respond. Common challenges include primary resistance (never responding to immunotherapy), secondary resistance (initial response followed by treatment failure), and progression after stopping therapy [23]. Biological regulatory mechanisms underlying resistance include tumor cell-intrinsic factors, such as defects in the antigen presentation machinery, genetic alterations in the IFN-γ signaling pathway, oncogenic signaling, and epigenetic reprogramming; as well as extrinsic factors related to the TME [4]. An important challenge is irAEs, where immunotherapy-related toxicity can harm normal host tissue [24]. These events can range from mild to severe and [25], even be fatal, involving almost every organ [26–28]. Toxicities associated with CAR-T cell therapy include cytokine release syndrome (CRS) and neurologic toxicity, such as immune effector cell-associated neurotoxicity syndrome (ICANS) [29,30].

Therefore, it is essential to identify biomarkers that predict response and resistance, as well as the risk of irAEs and toxicity. These biomarkers will be key for selecting patients likely to benefit from immunotherapy, identifying those at high risk of toxicity, and ultimately developing alternative treatment strategies.

Today, standard clinical practice uses biomarkers to select patients for immunotherapy based on specific clinical scenarios. An active anti-tumor immune response is a crucial prerequisite for predicting response to ICI therapy. The most common way to assess this response is by evaluating the presence of T cells in tumor tissue biopsies. High levels of pre-existing CD8+ T cells expressing PD-1, located at the invasive tumor margin of metastatic melanoma tissue before anti-PD-1 therapy, are associated with tumor regression [31]. Another approach involves identifying gene expression profiling (GEP) associated with immune cell activation via RNA sequencing and may represent a complementary approach to PD-L1 evaluation. Transcriptome analysis of biopsies from advanced melanoma treated with nivolumab (anti-PD-1) alone or in combination with ipilimumab (anti-CTLA-4) revealed that T cell infiltration and IFN-γ signaling signatures strongly correlate with clinical response to therapy [32].

The assessment of PD-L1 expression in the TME using immunohistochemistry (IHC) is currently the most widely used clinical biomarker for evaluating pretreatment tumor tissue and predicting response to anti-PD-1/PD-L1 therapies [33], as PD-L1 expression was the first biomarker associated with anti-PD-1 therapy response [34]. However, PD-L1 evaluation by IHC has several limitations, including dynamic and heterogeneous expression, uncertain positivity threshold and scoring reproducibility, and differences in predictive significance between tumor and immune cell expression.

The advent of next-generation sequencing (NGS) revealed wide variation in the number of somatic mutations within a given tumor type and across tumors [35,36]. The tumor mutational burden (TMB) is associated with greater benefit from ICI therapy, with high TMB associated with higher response rates. However, NGS may be somewhat challenging to perform in the clinic [37].

Recently, quantifying multiple protein markers using multiplex immunohistochemistry/immunofluorescence (mIHC/IF) has become a promising method for identifying predictive tissue-based biomarkers of response to immunotherapies [38]. mIHC/IF enables the simultaneous visualization of multiple protein markers *in situ* on the same tissue section and allows for single-cell-resolution assessment of the spatial relationships between different cell types, including their locations within TME compartments [39]. Furthermore, mIHC/IF has been shown to be associated with improved performance over PD-L1 IHC, TMB, or GEP alone in predicting response to anti–PD-1/PD-L1 treatment [33].

Regarding engineered T and NK cells, extensive research has been conducted to develop biomarkers that predict immune responses to CAR-T and CAR-NK cell infusions, including susceptibility to toxicity, therapeutic effectiveness, and long-term remission [40,41]. Recently, a combination of multiparameter flow cytometry and circulating cytokine levels has been used to identify predictive biomarkers of response to CAR-T cell therapy in pan-hematologic cancers [42,43]. A significantly reduced risk of toxicity is associated with CAR-NK cells compared with CAR-T cells [44,45].

An ideal biomarker should possess specificity, predictive accuracy, reproducibility, clinical accessibility, and mechanistic informativeness. Tumor biomarkers can face context-dependent limitations, including tissue availability and quality, timing of sample collection (e.g., longitudinal biospecimens), resolution, specificity, sensitivity, and effectiveness across different cancer types (universal use/application), as well as the complexity and cost of the technology. Currently, there are no established predictive biomarkers for evaluating very early on-treatment response or resistance (pharmacodynamic). Non-invasive methods like imaging technologies and liquid biopsies would be highly valuable for routine use by patients and healthcare providers.

Over the past decade, research on circulating non-coding RNAs (ncRNAs) as blood biomarkers has grown rapidly. Because of their high abundance and stability, circulating ncRNAs hold promise as a non-invasive liquid biopsy for providing insights into tumor biology and the effects of treatments such as targeted therapies and immunotherapies [46]. In our previous publication, we found that elevated serum levels of miR-19a-3p were associated with a favorable prognosis in patients with metastatic HER2+ breast cancer treated with trastuzumab [47]. We sought to understand the underlying mechanism and the origin of miR-19a-3p. In our recent publication [48], we discovered that the high levels of miR-19a-3p in the blood of patients with metastatic HER2+ breast cancer may result from a combination of effective NK cell-mediated Antibody-Dependent Cellular Cytotoxicity (ADCC) and activation of CD4+ Th1 cells, both associated with a favorable prognosis [49,50]. Specifically, trastuzumab-induced NK cell-mediated ADCC *in vitro* triggered the release of miR-19a-3p from HER2+ tumor cells, which naturally express high levels of miR-19a-3p, during apoptosis and cell death. When trastuzumab engages CD16, it prompts NK cells to secrete IFN-γ [51], and T cell–recruiting chemokines (IL-8, RANTES, MIP-1α, MIP-1β, MCP-1, MDC) [52], crucial for CD4+ Th1 cell differentiation and promoting anti-tumor immune responses [53]. We also observed that polarized CD4+ Th1 cells expressed and secreted higher levels of miR-19a-3p than CD4+ Th2 cells, and

that restimulation with anti-CD3/CD28 further increased both. Interestingly, CD4+ Th1 cells that acquired a central memory T (T_{CM}) phenotype (CD45RO+CCR7+CD62L+), during long-term *in vitro* cell culture, also expressed and secreted high levels of miR-19a-3p. Since miR-19a-3p regulates PTEN and BCL2L11, genes integral to sustaining proliferation, cytokine secretion in T helper cells, and resistance to apoptosis in T cells [54–56], higher miR-19a-3p expression levels can enhance the expansion, survival, and functions of CD4+ Th1 cells. Finally, we found that patients with metastatic HER2+breast cancer, good prognosis, and high serum miR-19a-3p levels had a higher proportion of CD4+IL-2+T cells relative to CD4+IL-4+T cells, an increased percentage of $CD56^{Bright}$ NK cells, and a trend toward a higher ratio of CD4+IFN-γ+/CD4+IL-4+T cells in their peripheral blood compared to those with poor prognosis and low serum miR-19a-3p levels.

We concluded that high levels of miR-19a-3p, associated with a favorable prognosis in patients with metastatic HER2+breast cancer treated with trastuzumab, may be due to the effective activation of key anti-tumor immune response mechanisms. Specifically, an effective ADCC activates NK cells, which not only kill tumor cells but also promote anti-tumor immune responses by secreting IFN-γ and immune cell-recruiting chemokines to the TME (IL-8, MIP-1α, MIP-1β, MCP-1, and RANTES). IFN-γ promotes the activation, maturation, and antigen presentation by DCs [57], and the differentiation of naïve CD4+T cells into CD4+Th1 effector cells [58]. IFN-γ from CD4+Th1 cells further activate DCs to secrete IL-12 and enhances cross-presentation of tumor-associated antigens [57,59]. In turn, IL-12, combined with IFN-γ, promotes CD4+Th1 cell polarization, increases the cytotoxic activity and IFN-γ production in NK cells, and induces the generation and activation of cytotoxic CD8+T lymphocytes (CTLs) [51,60–63]. Finally, IL-2 from CD4+Th1 cells, together with IFN-γ, enhances the proliferation and cytotoxic activity of CD8+ CTLs and NK cells, thereby supporting tumor cell killing [64,65]. In summary, high miR-19a-3p levels may reflect an active anti-tumor immune response in the TME ("hot" TME).

On the other hand, ineffective NK cell-mediated ADCC not only results in reduced tumor cell killing but also decreases the production of IFN-γ and chemokines by NK cells, leading to a diminished ability to trigger an effective CD4+Th1-mediated anti-tumor immune response. This could explain the poor prognosis of patients with low serum miR-19a-3p levels. Notably, an immunosuppressive TME, characterized by IL-10, TGF-β, PD-L1, MDSCs, and CD4+ Treg cells, can render NK cells dysfunctional, thereby hindering effective NK cell-mediated ADCC [66], and cytokine and chemokine secretion. Low levels of miR-19a-3p may reflect an immunosuppressed TME, or "cold" TME (**Figure 1**).

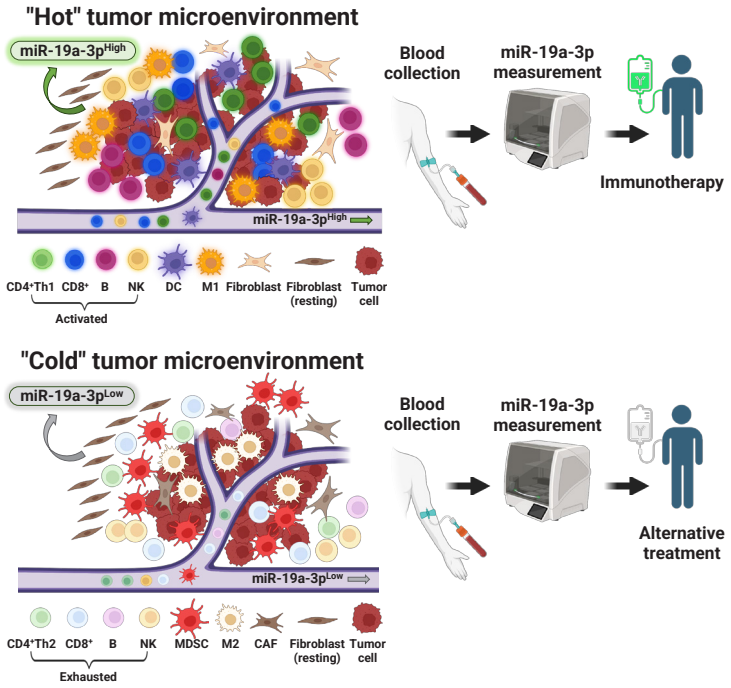

Figure 1. The potential utility of miR-19a-3p as a blood tumor biomarker. The levels of miR-19a-3p are associated with the activation status of the anti-tumor immune responses in the TME ("hot" versus "cold"). They can be measured in the blood of cancer patients treated with immunotherapy by RT-qPCR methods or Droplet Digital PCR (ddPCR). Longitudinal sampling can be performed to monitor the status of the anti-tumor immune responses in the TME.

Our findings could potentially be applied to studying the activation of ADCC and CD4+ Th1-mediated immune responses triggered by other ADCC-inducing antibodies across various cancer types, such as anti-EGFR cetuximab in metastatic colon cancer, head and neck cancer (HNSCC), triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), the anti-CD20 rituximab in chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL). The potential applications of our findings may also extend to evaluating the effectiveness of blood levels of miR-19a-3p in assessing CAR-T cell activation and identifying patients who may respond to CAR cell therapy. CAR CD4+ T cells with Th1 polarization provide essential help with therapeutic responses, improving persistence and cytokine production like IFN-γ [67,68]. Furthermore, in CAR-T and CAR-NK cells, CAR engagement with specific targets can induce higher levels of IFN-γ than in native T and NK cells [69].

As we mentioned earlier, an active anti-tumor immune response is crucial for predicting response to ICI therapy. Therefore, a biomarker that can assess a pre-existing immune cell-mediated anti-tumor response would be valuable for identifying patients who are likely to benefit from ICI therapy. In this context, recognizing an active and effective CD4+ Th1 cell-mediated response is essential for treatment decisions. In fact, CD4+ Th1-mediated functions are important for effective anti-tumor responses, as they support the proliferation and cytotoxic activity of CD8+ CTLs and NK cells. The levels of CD4+ Th1 cells infiltrating the TME are associated with favorable clinical outcomes [70], and pre-existing CD4+ Th1 responses are associated with better clinical outcomes in patients treated with ICIs [71–74]. Our funding could be used to evaluate the presence of an active CD4+ Th1 cell-mediated response and to monitor its levels over time in longitudinal biospecimens (at baseline and on-treatment) in cancer patients treated with ICI.

We propose miR-19a-3p as a potential blood biomarker for effective NK cell-mediated ADCC and CD4+ Th1 cell effector functions in patients with metastatic HER2+ breast cancer treated with trastuzumab, and prediction of their clinical outcomes. Specifically, blood levels of miR-19a-3p could help identify patients with activated anti-tumor immune responses who might benefit from this therapy. We believe that the advantage of blood miR-19a-3p as a minimally invasive biomarker is its ability to serve as a valuable pharmacodynamic indicator, providing early evidence of ongoing anti-tumor immune activity or resistance, thereby aiding treatment decision-making. Additionally, as a blood biomarker, it allows for continuous, "real-time" sampling to monitor the activation status of tumor immunity (longitudinal biospecimens), such as ADCC and Th1-mediated responses. The use of miR-19a-3p as a blood tumor biomarker could potentially be a complementary tool alongside other clinical tools, such as diagnostic imaging and pathology assessments. Since our retrospective studies were conducted in a relatively small patient cohort, these findings need to be confirmed in a prospective study with a larger patient cohort.

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