Natural Killer Cell Suppression in the Tumour Microenvironment: Mechanisms and Therapeutic Opportunities

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Abstract

Natural killer (NK) cells are a critical component of the innate immune system, responsible for detecting and eliminating virally infected and malignant cells. However, NK cell function is often suppressed in the tumour microenvironment (TME), allowing tumour cells to evade immune surveillance. This review examines the primary mechanisms by which the TME suppresses NK cell activity, including the impact of immunosuppressive molecules such as adenosine, hypoxia, lactate, prostaglandin E2 (PGE2), and transforming growth factor-beta (TGF-β). These molecules collectively inhibit NK cell metabolism, suppress cytokine production, and diminish cytotoxic activity, ultimately promoting tumour progression. Additionally, we discuss the role of other immunosuppressive cell populations, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2-like tumour-associated macrophages (TAMs), which further contribute to immune evasion. A deeper understanding of these suppressive pathways is essential for developing novel immunotherapeutic strategies aimed at restoring NK cell function in cancer. Future efforts should focus on disrupting these inhibitory signals through approaches such as metabolic reprogramming, immune checkpoint blockade, and combination therapies to reinvigorate NK cell-mediated tumour elimination.

Introduction

Natural Killer (NK) cells are a vital subset of the innate immune system, playing an essential role in the surveillance and defense against viral infections, pathogens, and even cancerous cells. These lymphocytes are distinguished by their ability to identify and eliminate transformed or infected cells without prior sensitization (Russick, Torset, et al. 2020). They exhibit potent cytotoxic capabilities through perforin and granzymes and secrete cytokines like interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α), which can modulate the activity of other immune cells (Russick, Joubert, et al. 2020; Riggan, Shah and O'Sullivan 2021).

During viral infections, NK cells function as early responders by directly killing infected cells and stimulating the adaptive immune response, thereby playing a critical role in controlling pathogen spread. In homeostasis, NK cells contribute to immune surveillance by maintaining tissue integrity and preventing malignancies through the identification of abnormal or stressed cells (Coënon et al. 2024). However, in the context of cancer, NK cells often encounter a hostile tumour microenvironment (TME) that can impair their function and hinder their ability to control cancer progression (Dean et al. 2024; Russick, Joubert, et al. 2020).

Tumour cells actively evade NK cell detection through mechanisms such as the expression of inhibitory ligands and the secretion of immunosuppressive factors, including transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), which dampens NK cell cytotoxicity (Dean et al. 2024). Additionally, NK cells within the TME exhibit phenotypic and functional changes, such as the upregulation of inhibitory receptors like NKG2A, which reduces their cytotoxic potential (Russick, Joubert, et al. 2020).

Recent research highlights the importance of NK cell-tumour interactions in shaping the immune landscape, with dysregulation of NK cell function contributing to tumour progression (Riggan, Shah and O'Sullivan 2021). Despite these challenges, strategies aimed at enhancing

NK cell activity, such as cytokine-based therapies, are being explored to overcome the suppressive effects of the TME and revive their anti-tumour function (Russick, Torset, et al. 2020; Riggan, Shah and O'Sullivan 2021). Understanding the complex role of NK cells in both homeostasis and disease is crucial for developing immunotherapies that can effectively harness their cytotoxic potential in the fight against cancer and other pathologies (Coënon et al. 2024; Russick, Joubert, et al. 2020). By focusing on the molecular mechanisms that regulate NK cell activity, researchers aim to develop more targeted and effective treatments for cancer patients.

Suppressive Factors in the TME and Their Role in NK Cell Dysfunction

The tumour microenvironment is a highly dynamic and immunosuppressive space that plays a pivotal role in promoting immune evasion, or the ability of cancer cells to avoid being identified and attacked by the immune system, and reducing the effectiveness of immune cells, particularly natural killer (NK) cells. NK cells, which are crucial for immune surveillance and anti-tumour immunity, undergo functional impairment or exhaustion when exposed to the various immunosuppressive factors present in the TME. These factors, including adenosine, hypoxia, lactate, prostaglandin E2 (PGE2), and TGF-β), work in concert to suppress NK cell activation, metabolism, and cytotoxicity, contributing to tumour progression.

Adenosine

Adenosine is one of the primary immunosuppressive molecules in the TME, where it accumulates due to high metabolic activity and ATP breakdown in tumour cells. Excess adenosine binds A2A and A2B receptors on NK cells, directly inhibiting their activation and blunting subsequent NK cell responses (Chambers et al. 2018). Studies have shown that adenosine suppresses NK cell functions such as cytokine production, including IFNγ and cytotoxic activity against tumour cells (Chambers et al. 2018; Han et al. 2024). By promoting immune suppression through adenosine receptor signaling, tumour cells can evade NK cell-mediated immunity, which is essential for tumour clearance in the early stages of cancer.

Hypoxia

Hypoxia is a hallmark feature of the TME, caused by the rapid proliferation of tumour cells and insufficient vascularization. Tumour hypoxia profoundly affects NK cell metabolism and function. Under hypoxic conditions, NK cells exhibit metabolic reprogramming characterized by a shift from oxidative phosphorylation (OXPHOS) to glycolysis, which results in decreased mitochondrial function and energy production (Zhang et al. 2024; Arvindam et al. 2021). The hypoxia-inducible factors (HIFs) activated during low oxygen conditions further impair NK cell function by reducing the expression of activation markers and decreasing their ability to produce key cytokines like IFNγ (Zhang et al. 2024). Moreover, hypoxia has been implicated in the fragmentation of NK cell mitochondria, similar to observations in exhausted T cells in cancer and chronic viral infections, which further dampens NK cell activity (Zhang et al. 2024).

Lactate

Lactate, a byproduct of anaerobic metabolism from heightened glycolysis in tumour cells, is another metabolic byproduct that accumulates in the TME. Tumours with high glycolytic activity produce substantial amounts of lactate, which can suppress NK cell function. Lactate has been shown to negatively affect NK cell activation by reducing their cytokine production and cytotoxicity (Terrén et al. 2019; Riggan, Shah, and O'Sullivan 2021). Specifically, lactate inhibits

NK cell proliferation and alters their signaling pathways, which are critical for activating NK cells to kill tumour cells. The elevated lactate levels thus contribute to a suppressive environment where NK cells are unable to effectively mount an immune response against tumour cells.

Prostaglandin E2 (PGE2)

PGE2 is a lipid mediator elevated in the TME that plays a significant role in suppressing NK cell activity. Produced by tumour cells and immune cells within the TME, PGE2 binds to specific receptors on NK cells, leading to inhibition of NK cell activation and function (Holt et al. 2011; Park et al. 2018). PGE2 directly downregulates NK cell activation markers and impairs their cytotoxic functions by reducing the expression of activating receptors such as NKG2D, which are critical for recognizing and killing tumour cells. Furthermore, PGE2 also decreases NK cell production of cytokines, including IFNγ, and suppresses granzyme B release, which is crucial for tumour cell killing (Park et al. 2018). As a result, PGE2 contributes significantly to NK cell dysfunction and immune evasion in cancer.

Transforming Growth Factor Beta (TGFβ)

TGFβ is one of the most potent immunosuppressive cytokines found in the TME, playing a central role in NK cell dysfunction. TGFβ exerts multiple inhibitory effects on NK cell metabolism and activity. One of the key mechanisms by which TGFβ suppresses NK cells is through the inhibition of mTORC1 signaling, which is essential for NK cell activation and metabolic function. In response to cytokine stimulation, TGFβ reduces NK cell mitochondrial respiration, thereby impairing energy production through oxidative phosphorylation (OXPHOS) (Slattery et al. 2021; Slattery and Gardiner 2019). This metabolic shift is further compounded by a reduction in the expression of CD25, an activation marker for NK cells, and a failure to stimulate proper cytokine production, such as IFNγ (Slattery et al. 2021). Moreover, TGFβ directly influences mitochondrial structure, contributing to mitochondrial fragmentation observed in NK cells from patients with breast cancer (Slattery et al. 2021; Slattery and Gardiner 2019). Importantly, neutralising TGFβ with blocking antibodies restores several of the defective metabolic and functional features of NK cells from cancer patients, suggesting that TGFβ is a key driver of NK cell dysfunction in the TME (Slattery and Gardiner 2019).

In addition to its direct effects on NK cell metabolism, TGFβ also participates in autocrine signaling within NK cells. NK cells produce TGFβ themselves, further exacerbating their functional decline through autocrine signaling loops. This self-sustaining cycle of TGFβ production and signaling is especially evident in patients with metastatic breast cancer, where NK cells both produce and respond to TGFβ, contributing to their metabolic dysfunction and exhaustion (Slattery et al. 2021). Furthermore, GARP, a molecule involved in the activation of latent TGFβ, is overexpressed on NK cells in cancer patients, further supporting the role of TGFβ in NK cell exhaustion. Blocking GARP restores NK cell function and metabolism, providing a potential therapeutic target for reversing NK cell exhaustion in cancer (Slattery et al. 2021).

The suppressive TME employs multiple mechanisms to suppress NK cell activity, resulting in immune evasion and tumour progression. Factors such as adenosine, hypoxia, lactate, PGE2, and TGFβ all play significant roles in impairing NK cell function by altering their metabolism, signaling pathways, and cytokine production. Adenosine inhibits NK cell activation, while hypoxia and lactate reprogram NK cell metabolism to a less effective state. PGE2 downregulates critical activation receptors and cytokine production, and TGFβ directly inhibits

NK cell metabolism and function through multiple pathways, including autocrine signaling. Understanding these mechanisms offers potential therapeutic opportunities, including targeting these suppressive factors to restore NK cell function and enhance cancer immunotherapy. By neutralising these inhibitory signals, it may be possible to reinvigorate NK cells, thereby improving their ability to combat tumour growth and progression.

Immune Cell Types Driving Tumour Progression

The TME is a complex ecosystem where various cell types interact to influence tumour growth and progression. Among these, certain immune cells play a crucial role in suppressing anti-tumour responses, thereby promoting cancer development. This section will focus on three key immunosuppressive cell types: regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2-like tumour-associated macrophages (TAMs).

Regulatory T cells (Tregs) are a subset of CD4+ T cells that play a critical role in maintaining immune homeostasis. In the context of cancer, however, Tregs can significantly hinder anti-tumour immunity. Tregs utilise multiple suppressive mechanisms within the TME, including inhibition of effector T cell function, secretion of inhibitory cytokines, and metabolic disruption (Scott et al. 2021). These cells also create barriers to immune cell infiltration into tumours by modulating the extracellular matrix and affecting blood vessel formation (Scott et al. 2021). The presence of Tregs with an activated phenotype in tumours is often associated with poor prognosis in various cancer types (Togashi, Shitara and Nishikawa 2019).

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells that become activated under pathological conditions, including cancer. MDSCs have potent capacities to support tumour growth by inhibiting anti-tumour immune responses and inducing other immunosuppressive cells (Wang et al. 2020). These cells employ various mechanisms to promote tumour progression, such as the production of reactive oxygen species, nitric oxide and arginase-1, which collectively suppress T cell functions (Wang et al. 2020). MDSCs also contribute to pre-metastatic niche formation, facilitating tumour spread (Wang et al. 2020).

M2-like tumour-associated macrophages (TAMs) represent another crucial immunosuppressive cell type within the TME. These cells predominantly exhibit an anti-inflammatory phenotype and promote tumour progression through various mechanisms. M2-like TAMs secrete growth factors and cytokines that enhance angiogenesis, facilitate metastasis and inhibit T and natural killer (NK) cell functions (Gao, Liang and Wang 2022). They also express surface markers and produce factors that contribute to an immunosuppressive environment, such as TGF-β, IL-10 and prostaglandin E2 (Gao, Liang and Wang 2022; Carannante, Wiklund and Önfelt 2023).

The interplay between these immunosuppressive cell types creates a complex network that effectively shields tumour cells from immune attack. For instance, MDSCs can induce the expansion of Tregs, while Tregs can promote the differentiation of monocytes into M2-like TAMs (Wang et al. 2020; Togashi, Shitara and Nishikawa 2019). This collaborative suppression of anti-tumour immunity significantly contributes to tumour growth, metastasis, and resistance to various cancer therapies (Carannante, Wiklund and Önfelt 2023; Gabrilovich 2017).

Understanding the roles and interactions of these immunosuppressive cell types in the TME is crucial for developing effective cancer therapies. Targeting these cells, either alone or in combination with other immunotherapies, represents a promising approach to overcome the immunosuppressive TME and enhance anti-tumour effects (Scott et al. 2021; Wang et al. 2020;

Gao, Liang and Wang 2022). As research in this field progresses, new strategies to modulate these cell populations may lead to more effective cancer treatments and improved patient outcomes.

The Role of The Cancer Genome Atlas in Developing Immunotherapies

The Cancer Genome Atlas (TCGA) is a landmark cancer genomics program initiated in 2006 as a collaborative effort between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) to comprehensively map the molecular alterations in various cancer types (Barker and Lee 2022). Initially designed as a pilot project to study three types of cancer, TCGA rapidly expanded and eventually characterized 33 different types, including rare cancers, by integrating multi-omics data such as whole-genome and whole-exome sequencing, RNA sequencing, epigenetic modifications, and proteomic analyses (Barker and Lee 2022). The project generated an unprecedented 2.5 petabytes of publicly available data, establishing a critical resource for understanding cancer biology, identifying novel driver mutations, and classifying tumours into molecular subtypes to inform precision medicine approaches (B. Sun and Chen 2023). One of TCGA's major strengths is its high data quality, standardized protocols, and accessibility, enabling large-scale studies that refine cancer diagnosis and treatment strategies (Barker and Lee 2022). Furthermore, TCGA data have been instrumental in developing deep-learning models that predict patient survival and optimize treatment selection based on transcriptomic and clinical profiles (B. Sun and Chen 2023). However, TCGA also has notable limitations. Since it primarily relies on bulk sequencing, it does not capture single-cell heterogeneity or the complexity of the TME, which can influence cancer progression and therapy response (Barker and Lee 2022). Additionally, while TCGA has provided extensive genomic data, challenges remain in translating these insights into clinical applications due to the complexity of cancer biology, computational constraints, and the need for improved data standardization across different studies (B. Sun and Chen 2023). Despite these challenges, TCGA remains a cornerstone of cancer genomics research, continuously shaping advancements in precision oncology and personalized medicine.

TCGA studies have significantly helped understand the role of natural killer (NK) cell-related gene signatures in cancer prognosis. In glioma, for example, NK cell-related gene signatures derived from TCGA data have shown strong correlations with patient survival outcomes. The risk score (RS) associated with NK cell genes was shown to predict survival, with higher RS correlating with worse survival outcomes. Additionally, TCGA data highlighted the involvement of immune-related genes in immune cell infiltration, cell adhesion pathways, and neutrophil-mediated immunity, which were enriched in high-risk patients. These results suggest that a robust NK cell-related signature can be used to predict a patient's prognosis and guide therapeutic decisions, including the use of immunotherapy (Hwang et al. 2020). Further, TCGA data illustrated that high-risk patients had higher PD1/PDL1 expression, reinforcing the idea that immune checkpoint modulation could play a significant role in improving outcomes for those with higher risk scores (Li et al. 2022). Therefore, by analyzing TCGA datasets, it becomes clear that NK cell-related gene signatures are not only valuable for prognostic predictions but also for developing more tailored, immune-focused therapies in the future.

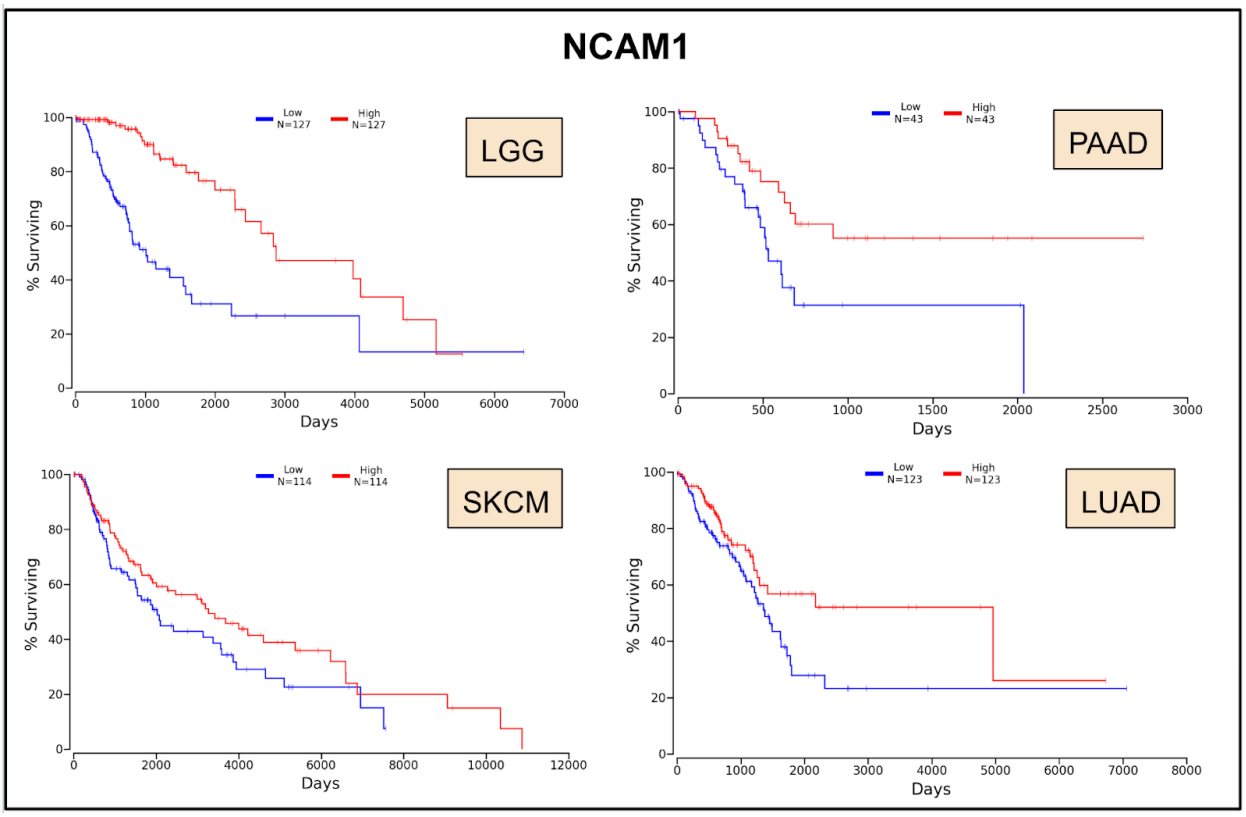

Figure 1. Kaplan-Meier Survival Curves for NCAM1 Expression in Multiple Cancer Types. Kaplan-Meier survival analysis comparing patients with high (red line) versus low (blue line) expression of NCAM1 (Neural Cell Adhesion Molecule 1) across four TCGA cancer types: LGG (Lower Grade Glioma), PAAD (Pancreatic Adenocarcinoma), SKCM (Skin Cutaneous Melanoma), and LUAD (Lung Adenocarcinoma). NCAM1 is used as an identifying marker for NK cells. Patients were stratified based on NCAM1 expression levels. The y-axis represents the percentage of surviving patients over time (x-axis, in days). Higher NCAM1 expression is associated with improved overall survival in several tumour types, suggesting a potential role in enhancing immune responses, particularly involving NK (Natural Killer) cell-mediated tumour clearance. Sample sizes (N) are shown for each expression group within each plot.

Ways to Use TCGA for Future Therapies

TCGA is an invaluable resource in cancer research, especially in predicting responses to immunotherapy. By leveraging TCGA data, researchers can identify key genetic signatures and immune-related pathways that influence a patient's response to various therapeutic approaches, including immune checkpoint inhibitors (such as PD-1 and PD-L1) and other immune-based therapies. For example, TCGA datasets enable the robust identification of tumour-specific features, such as microsatellite instability (MSI) and tumour mutational burden (TMB), which have been established as predictive biomarkers for the effectiveness of immunotherapy (Chen et al. 2022). Studies utilising TCGA data have shown that patients with high TMB are more likely to respond to immune checkpoint inhibitors, as their tumours present a greater number of neoantigens that can trigger an immune response. Additionally, TCGA's transcriptomic data have been used to assess immune cell infiltration patterns within tumours, including the

presence of cytotoxic T cells and natural killer cells, which are associated with better responses to immunotherapy (Wu et al. 2022). Computational methods, such as CIBERSORT and xCell, have been applied to TCGA RNA-seq data to estimate the proportion of different immune cell types in tumour samples, providing insights into the tumour immune microenvironment (S. Sun et al. 2021). These findings have been validated in clinical trials where higher immune infiltration, particularly the presence of CD8+ T cells, has correlated with improved outcomes in patients receiving PD-1 and PD-L1 inhibitors (Sun et al. 2021; Craven, Gökmen-Polar and Badve 2021). By leveraging these TCGA-derived biomarkers, researchers can stratify patients based on their likelihood of responding to immunotherapy, ultimately guiding more effective and personalized treatment strategies (Kang et al. 2023). These markers are crucial in stratifying patients for personalized treatment, ensuring that only those most likely to benefit from immunotherapy receive it, while minimizing potential side effects for others (Hwang et al. 2020).

Furthermore, TCGA allows the study of specific immune-related gene signatures that could guide therapy development. The presence of tumour-associated antigens or immune checkpoint gene expression patterns in tumour samples can predict whether immunotherapies will be effective. By integrating TCGA-derived data with clinical outcomes, researchers can refine therapeutic strategies, ultimately leading to the development of more targeted and efficient treatments (Li et al. 2022). For example, the correlation between risk scores (RS) and immune checkpoints (such as PD-1 and PDL1) in TCGA datasets has helped predict patient prognosis and response to immunotherapies in various cancer types, including glioma (Hwang et al. 2020).

Discussion and Future Directions

The TME is a dynamic and complex ecosystem where the interactions between various immune cell types and tumour cells shapes cancer progression and response to therapy. This study highlights the critical roles of immunosuppressive cells, including regulatory T cells, MDSCs, and M2-like TAMs, in creating an immunosuppressive environment that facilitates tumour growth and metastasis. These cells utilise various mechanisms to suppress anti-tumour immune responses, thereby contributing significantly to the challenges encountered in cancer immunotherapy.

Understanding the mechanisms by which Tregs, MDSCs, and M2-like TAMs operate within the TME is crucial for developing targeted therapies. For instance, therapies aimed at depleting or inhibiting the activity of these immunosuppressive cell types may enhance the effectiveness of existing cancer treatments, including immune checkpoint inhibitors. For example, CSF1R inhibitors, such as pexidartinib, have been investigated for their ability to reduce M2-like TAM populations, thereby alleviating immunosuppression within the TME. Similarly, mogamulizumab, a CCR4 antagonist, can selectively deplete Tregs to enhance anti-tumour immune responses. Additionally, MDSC-targeting strategies, such as entinostat, a histone deacetylase inhibitor, have shown promise in reprogramming these cells to restore immune activation. Recent studies using data from TCGA indicate that NK cell-related gene signatures can serve as prognostic biomarkers, which allow doctors to predict patient response to the treatment, guiding the selection of immunotherapy strategies tailored to individual patients. By integrating genomic data with clinical outcomes, researchers can refine therapeutic approaches and optimize treatment plans.

Future research should aim to uncover the complex interactions between different immunosuppressive cell types within the TME. Investigating the interactions among Tregs,

MDSCs, and M2-like TAMs may reveal new therapeutic targets and pathways for intervention. Furthermore, leveraging advances in single-cell sequencing technologies could provide deeper insights into the heterogeneity of the TME, allowing for a clearer understanding of how these cells contribute to immune evasion and tumour progression.

Additionally, as the field of precision medicine evolves, there is a growing necessity to identify novel biomarkers that predict patient responses to immunotherapies. The identification of tumour-specific mutations, tumour mutational burden (TMB), and microsatellite instability (MSI) as predictive factors in TCGA studies emphasizes the importance of personalized approaches in cancer treatment. Future studies should aim to validate these findings in diverse patient populations and investigate the extent to which these biomarkers can be integrated into clinical practice.

Ultimately, our growing insight into how suppressive cell types orchestrate immune evasion lays a powerful foundation for next-generation cancer therapies. Moving forward, turning these scientific discoveries into medicines that stop harmful cells in the tumour environment is critical. By combining TME-targeted interventions with existing immunotherapies, we can not only amplify anti-tumour immunity but also overcome resistance in hard-to-treat cancers, paving the way for more durable remissions and improving patient survival.

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