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Title

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Journal

Cytokine & Growth Factor Reviews, 76

ISSN

1359-6101

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Publication Date

2024-04-01

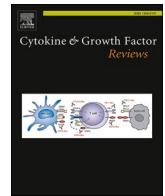
DOI

10.1016/j.cytogfr.2024.02.003

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Cytokines and soluble mediators as architects of tumor microenvironment reprogramming in cancer therapy

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ARTICLE INFO

Keywords:

Tumor microenvironment (TME)
Cytokines
Soluble mediators
TME reprogramming
Precision oncology
Immune modulation
Extracellular vesicles (EVs)
Therapeutic targeting

ABSTRACT

Navigating the intricate landscape of the tumor microenvironment (TME) unveils a pivotal arena for cancer therapeutics, where cytokines and soluble mediators emerge as double-edged swords in the fight against cancer. This review ventures beyond traditional perspectives, illuminating the nuanced interplay of these elements as both allies and adversaries in cancer dynamics. It critically evaluates the evolving paradigms of TME reprogramming, spotlighting innovative strategies that target the sophisticated network of cytokines and mediators. Special focus is placed on unveiling the therapeutic potential of novel cytokines and mediators, particularly their synergistic interactions with extracellular vesicles, which represent underexplored conduits for therapeutic targeting. Addressing a significant gap in current research, we explore the untapped potential of these biochemical players in orchestrating immune responses, tumor proliferation, and metastasis. The review advocates for a paradigm shift towards exploiting these dynamic interactions within the TME, aiming to transcend conventional treatments and pave the way for a new era of precision oncology. Through a critical synthesis of recent advancements, we highlight the imperative for innovative approaches that harness the full spectrum of cytokine and mediator activities, setting the stage for breakthrough therapies that offer heightened specificity, reduced toxicity, and improved patient outcomes.

1. Introduction

Traditionally, cancer has been viewed primarily as a disease of unchecked cellular proliferation, with treatments predominantly focused on eradicating rapidly dividing malignant cells [1]. This perspective, however, has evolved significantly with the recognition of the tumor microenvironment (TME) as a complex network of cellular and extracellular components crucial to cancer progression and metastasis [2,3]. The TME, consisting of immune cells, fibroblasts, extracellular matrix components, vasculature, and a variety of soluble factors, is now understood to play a pivotal role in tumor growth, tissue invasion, and therapeutic resistance [4,5].

This understanding bridges to the core elements of TME dynamics. At the heart of TME dynamics are cytokines and soluble mediators, which orchestrate intercellular communication and modulate the balance between tumor promotion and suppression [6,7]. These include cytokines like interleukins and interferons [8], as well as chemokines and growth factors [9], affecting both tumoral and non-tumoral cells within the TME [10]. Their roles are paradoxical, capable of both inhibiting and facilitating tumor growth by influencing immune responses, cellular proliferation, angiogenesis, and evasion of immune detection [3,11].

Acknowledging this complexity has led to a significant shift in therapeutic strategies. This evolving comprehension of the TME has prompted a paradigm shift in cancer therapy, moving beyond the

Abbreviations: CAFs, Cancer-associated fibroblasts; CCL2, Chemokine C-C motif ligand 2; CtDNA, circulating tumor DNA; CTLA-4, Cytotoxic T-lymphocyte antigen 4; CXCL8, C-X-C motif chemokine ligand 8; EGF, Epidermal growth factor; EMT, Epithelial-mesenchymal transition; FAP, Fibroblast activation protein; FGF, Fibroblast growth factor; FGFR, Fibroblast growth factor receptor; HIFs, Hypoxia-inducible factors; IFN- γ , Interferon gamma; IL-6, Interleukin 6; MABs, Monoclonal antibodies; MMPs, Matrix Metalloproteinases; NK cells, Natural killer cells; NSCLC, Non-small cell lung cancer; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PDGF, Platelet-derived growth factor; TAMs, Tumor-associated macrophages; TLR, Toll-like receptor; TGF- β , Transforming growth factor beta; TME, Tumor microenvironment; VEGF, Vascular endothelial growth factor.

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<https://doi.org/10.1016/j.cytogfr.2024.02.003>

Received 23 February 2024; Accepted 26 February 2024

Available online 28 February 2024

1359-6101/Published by Elsevier Ltd.

singular focus on cancer cells to targeting the TME’s supportive mechanisms [12,13]. Strategies aimed at reprogramming the TME seek to convert it from a tumor ally into an antagonistic setting that fosters immune-mediated tumor destruction and thwarts disease progression [13,14]. Such approaches offer promising avenues for overcoming therapeutic resistance and reducing relapse rates, marking a potential revolution in cancer treatment [15,16].

However, this progress is not without its challenges and debates. Despite consensus on the TME’s significance in cancer biology, controversies persist regarding the best strategies for its reprogramming. The variability in TME composition across different cancer types and even within individual tumors presents a challenge for developing universal therapeutic strategies [3]. Additionally, the dual roles of cytokines and soluble mediators in tumor progression and suppression complicate their targeting, as interventions may have unintended pro-tumorigenic effects [11].

The call for focused research is clear. There remains a critical need for research that elucidates the precise mechanisms by which the TME influences cancer progression and response to therapy. Identifying specific cytokine and mediator pathways most amenable to therapeutic intervention could vastly improve treatment outcomes. Additionally, the development of biomarkers for TME profiling could enable more personalized therapeutic approaches, allowing for interventions to be tailored to the unique TME characteristics of individual patients [16].

2. The cytokine network in the TME

The cytokine network is fundamental to the pathology of cancer and the immune response to tumors, orchestrating a complex interplay of signals within the TME [17,18]. These proteins, initially classified as immune mediators, have emerged as pivotal regulators of both tumor

progression and suppression [19]. Within the intricate landscape of the TME, a diverse array of cytokines operates, encompassing both pro-inflammatory and anti-inflammatory types. These cytokines play dual roles that can either promote or inhibit cancer development, highlighting the complexity of their functions in the TME [20–24].

Delving into the specific roles of these cytokines reveals that pro-inflammatory cytokines like IL-1 β , IL-6, and IL-23 often drive tumor-promoting inflammatory responses. At the same time, TNF- α and TGF- β are implicated in critical processes for metastasis, such as epithelial-mesenchymal transition (EMT) [25–27]. On the other side of the spectrum, interferons, particularly IFN- γ , are recognized for their cancer-suppressive properties by enhancing immune surveillance [28–30]. Yet, the complexity deepens with the acknowledgment that the sustained presence of IFN- γ might paradoxically aid tumor immune evasion by fostering the selection of resistant variants [31,32].

The debate around cytokines in the TME underscores a broader discourse on their therapeutic targeting. Controversies and Consensus: The TME’s cytokine network embodies a contentious field, especially concerning their dual functionalities-simultaneously promoting and suppressing tumors. This duality, exemplified by the conflicting roles of IL-10, underscores the therapeutic challenge of modulating cytokine activity without unintended consequences [23,24].

Looking ahead, the path to therapeutic innovation is fraught with uncharted territories. Gaps for Future Research: A significant research gap lies in deciphering how variations in cytokine concentrations, their temporal dynamics, and the diversity of receptor expressions impact the TME [33,34]. The interwoven nature of cytokine interactions further complicates the landscape, making it challenging to predict therapeutic outcomes accurately [11,35]. Future investigations are thus called to shed light on these dynamic interplays, aiming to refine strategies for TME reprogramming toward tumor suppression [36,37].

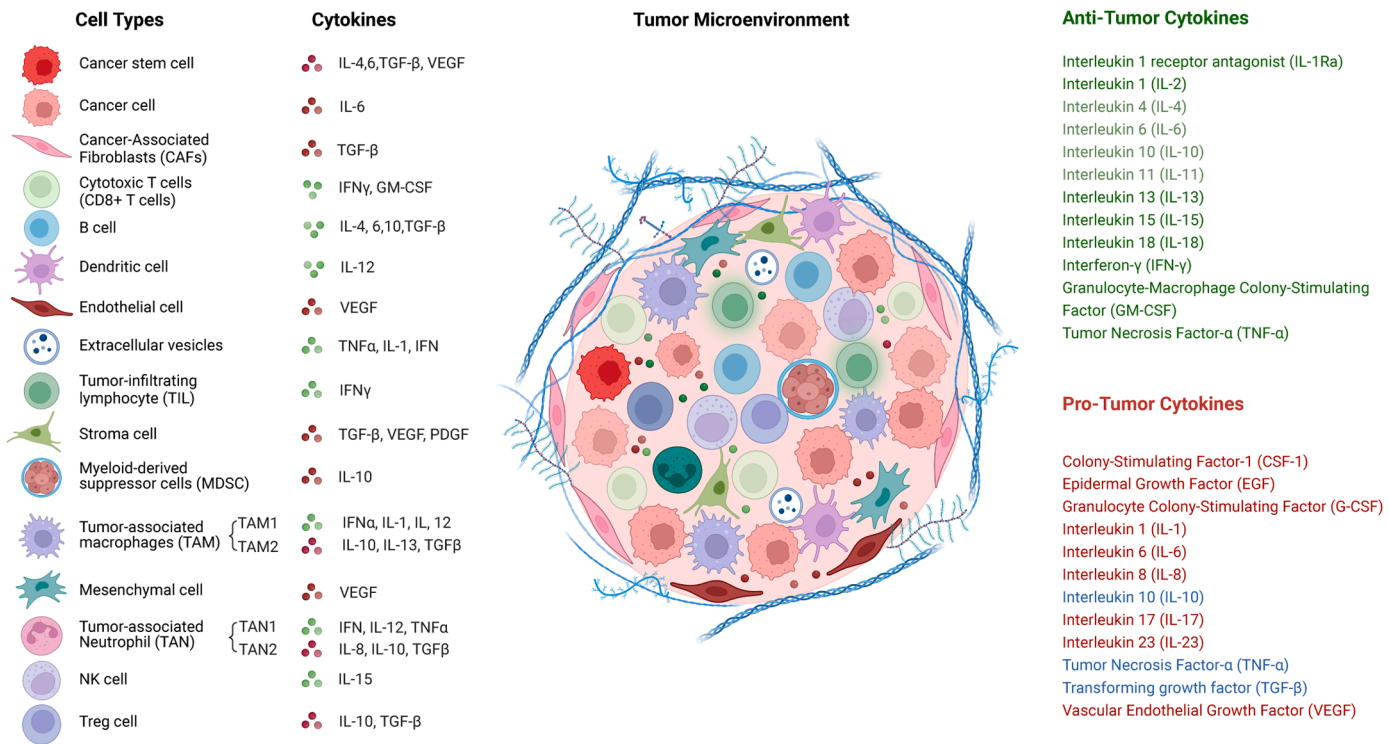


Fig. 1. The Cytokine Network in the TME. This figure offers an in-depth view of the cell types within the TME and the cytokines they produce, which collectively drive the cancer process. On the left, key cell types, including cancer stem cells [38], T cells, and immune cells, are matched with the cytokines they secrete, highlighting the origins of these significant signaling entities. The central visual emphasizes the TME’s cellular complexity and the cytokine milieu that underpins intricate cell-to-cell communication. On the right, cytokines are grouped by their impact on cancer dynamics: green for those commonly suppressing tumor growth or enhancing immune activity, red for those generally promoting cancer progression and immune evasion, and blue for those with context-dependent roles. This depiction emphasizes the critical, multifaceted roles of cytokines in the TME, spotlighting their potential as therapeutic targets in strategies to reprogram the TME for cancer control.

To complement our discussion on the intricate cytokine network within the TME, Fig. 1 below maps out the diverse cell types, outlines the cytokines they secrete and illustrates the complex interactions that can either hinder or facilitate tumor development.

Addressing these gaps requires a nuanced approach that considers the heterogeneity of the TME across different cancer types and within individual tumors. The development of targeted therapies may benefit from a more comprehensive understanding of cytokine networks, potentially leveraging systems biology and computational modeling to predict the impact of therapeutic interventions on TME dynamics [39, 40].

In summary, the journey through the cytokine network within the TME has illuminated both progress and persistent hurdles in harnessing this knowledge for cancer treatment. As we venture forward, addressing the controversies and filling the research gaps highlighted here may unlock new therapeutic avenues. These efforts aim to exploit the TME's intricacies, offering hope for more precise and effective cancer interventions, thereby enhancing patient outcomes in the ongoing battle against cancer.

3. Soluble mediators and their influence on the TME

Soluble mediators play a critical role in the TME, significantly impacting cancer progression and response to therapy. Growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) are central to this discussion, driving angiogenesis and tumor cell proliferation. Elevated VEGF levels correlate with poor cancer prognoses, underscoring the therapeutic potential of targeting these pathways. VEGF inhibitors like bevacizumab have shown significant benefits in managing disease progression, especially in colorectal and non-small cell lung cancers (NSCLC) [41–45].

Transitioning from growth factors to chemokines, Chemokine (C-C motif) ligand 2 (CCL2) and C-X-C motif chemokine ligand 8 (CXCL8) exemplify the dual roles soluble mediators occupy within the TME. While acting as chemoattractants to potentially aid tumor suppression,

they also play a part in creating an immunosuppressive environment, highlighting the complexity of their therapeutic targeting. This duality is pivotal in ongoing research into chemokine receptor inhibitors, aimed at enhancing the efficacy of immunotherapies [46–48].

Moreover, the transformation of fibroblasts into cancer-associated fibroblasts (CAFs) by tumor-derived factors presents another layer of complexity within the TME. These CAFs create a supportive niche for tumor growth and resistance, pinpointing a crucial area for therapeutic intervention. Preclinical efforts to disrupt the signaling pathways involved in this transformation hold promising therapeutic potential [49–52].

Additionally, matrix metalloproteinases (MMPs) contribute to the TME's dynamics by remodeling the extracellular matrix, thus facilitating tumor invasion and metastasis. The nuanced roles of MMPs in cancer, as demonstrated by clinical trials investigating MMP inhibitors, underscore the importance of targeted approaches to minimize potential physiological disruptions [53–55]. To provide a clearer perspective on these interactions, the following table summarizes the key soluble mediators, their sources within the TME, their roles in cancer progression, and current approaches to therapeutic targeting.

In exploring the multifaceted roles of soluble mediators, consensus on their significance in cancer biology is met with controversies regarding the best approaches to their therapeutic targeting. The dynamic interactions and feedback loops that characterize the TME's complexity remain partially understood, marking a significant gap in current research. Further studies are needed to unravel these mechanisms fully, particularly to enhance the precision of cancer therapies tailored to individual tumor profiles [56,57].

In summary, the investigation into soluble mediators within the TME opens avenues for significant therapeutic advancements. By dissecting their complex roles and interactions, new targets for disrupting cancer's pathological communications emerge, setting the stage for more effective and personalized approaches to cancer treatment [58–61]. This ongoing exploration promises to refine our understanding and treatment of cancer, aligning closely with the evolving paradigms of precision oncology.

Table 1
Sources, roles, and therapeutic targeting of the key soluble mediators in the TME.

Soluble Mediator	Source Cells	Role in TME	Target Cells	Effect on Cancer Progression	Effect on Immune Response	Therapeutic Targeting
VEGF	Cancer cells, Stromal cells	Promotes angiogenesis	Endothelial cells	Promotes angiogenesis, tumor growth, metastasis	May impair immune cell maturation	VEGF inhibitors (e.g., bevacizumab)
TGF-β	Tumor cells, Tregs, Macrophages	Induces EMT, enhances metastasis	Various cells in TME	Induces EMT, enhances metastasis	Suppresses cytotoxic immune cells, promotes Treg development	TGF-β inhibitors [e.g., Galunisertib (LY2157299), Fresolimumab (GC1008), LY3200882 and LY3022855, etc.]
PDGF	Cancer cells, Stromal cells, Immune cells	Stimulates stromal and fibroblast growth	Fibroblasts, Pericytes	Stimulates stromal proliferation, supports tumor stroma, Tumor stroma development	Limited direct immune modulation	PDGF receptor antagonists
CCL2	Tumor cells, Macrophages	Recruits immune cells to TME	Monocytes, T cells	Recruits immunosuppressive cells to TME	Attracts monocytes and T cells, can be immunosuppressive	CCR2 inhibitors
CXCL8	Cancer cells, Macrophages, Endothelial cells	Chemoattractant for neutrophils	Neutrophils, T cells	Supports tumor proliferation and survival, Inflammation, tumor growth	Recruits neutrophils, can support an immune-suppressive microenvironment	CXCR1/2 inhibitors
IL-6	Tumor cells, Macrophages	Promotes tumor progression	Various cells in TME	Facilitates tumor growth and drug resistance	Promotes inflammation, can suppress, or enhance immunity	IL6 inhibitors include mAbs to IL6 (siltuximab) or IL6 receptor (tocilizumab).
EGF	Cancer cells, Stromal cells	Promotes cell proliferation	Cancer cells	Enhances tumor cell growth and migration	Limited direct immune modulation	EGFR inhibitors (e.g., cetuximab)
FGF	Cancer cells, Stromal cells	Promotes tumor development	Multiple cell types	Contributes to angiogenesis and cell survival	Can promote tissue repair, effect on immune response is context-dependent	FGFR inhibitors (e.g., ponatinib, nintedanib, and dovitinib, etc.)
MMPs	Cancer cells, CAFs, TAMs, etc.	Degradation of extracellular matrix	Multiple cell types	Tumor invasion, induces metastasis	Dual effects: promote immunity, or contribute to immune evasion	MMP inhibitors (e.g., marimastat)

4. The interplay between cytokines, soluble mediators, and cellular components

The TME's orchestration involves a complex network in which cytokines and soluble mediators play essential roles in cellular communication and regulation. These components not only dictate the TME's architecture and functionality but also influence the dynamics of cancer progression and immune response, making them pivotal in the nuanced interplay of tumor biology and host defense mechanisms [59,62].

4.1. Interaction with cellular components of the TME

Within the TME, cytokines and soluble mediators serve as critical communicators, facilitating interactions that significantly influence cellular behavior. Cancer cells, for instance, utilize growth factors like EGF to promote their proliferation through autocrine mechanisms or affect stromal and immune cells via paracrine actions to create a supportive environment. This complex exchange underscores the TME's capacity to adapt and respond to cancerous growth [5, 63, 64]. Conversely, cytokines such as IL-12 can stimulate immune responses against the tumor, highlighting the dual nature of these mediators in cancer biology [65]. Similarly, TGF- β 's role in promoting an immunosuppressive milieu exemplifies the intricate balance between promoting and suppressing tumor progression within the TME [66,67].

The process of fibroblast transformation into CAFs under cytokine influence, particularly TGF- β , further illustrates the dynamic interplay between cellular components within the TME. These CAFs contribute to a pro-tumorigenic state, facilitating tumor growth and survival, while endothelial cells' response to angiogenic stimuli like VEGF supports the metabolic demands of growing tumors, emphasizing the collaborative nature of cellular components in tumor advancement [43, 50, 68, 69].

To visually encapsulate the complex interactions between cellular

components, cytokines, soluble mediators, and the resultant therapeutic interventions within the TME, the schematic representation detailed in Fig. 2 below provides a comprehensive overview.

4.2. Signaling cascades and feedback loops

The TME is characterized by intricate signaling cascades and feedback loops, essential for modulating tumor growth and the immune response. For instance, VEGF-induced angiogenesis is a prime example of a signaling cascade that facilitates tumor growth and influences adjacent cells' behavior, showcasing the complex interplay of signals within the TME [42,70]. Feedback mechanisms maintain a dynamic balance, with positive feedback loops enhancing tumor-promoting signals and negative feedback loops aiming to dampen these effects. This delicate balance is crucial for the TME's adaptability and poses a significant challenge for therapeutic intervention [9,59].

The dual functionality of cytokines and soluble mediators acting as tumor promoters and suppressors presents controversies in therapeutic targeting. Despite these challenges, there is consensus on the importance of these mediators in shaping the TME, with targeted interventions like VEGF inhibitors recognized for their potential to disrupt pathological signaling pathways [3, 41, 58, 70–72].

However, our understanding of the TME's signaling networks and feedback mechanisms is far from complete. Identifying and elucidating these complex interactions remains a critical area for research, highlighting the need for innovative strategies to reprogram the TME effectively. Advancements in this area could lead to the development of treatments that are finely tuned to the specific characteristics of individual tumors, offering a more personalized approach to cancer therapy [2, 22, 61, 73]. This exploration into the TME's signaling intricacies not only promises to enhance therapeutic efficacy but also paves the way for a new era in precision medicine, where the unique molecular and

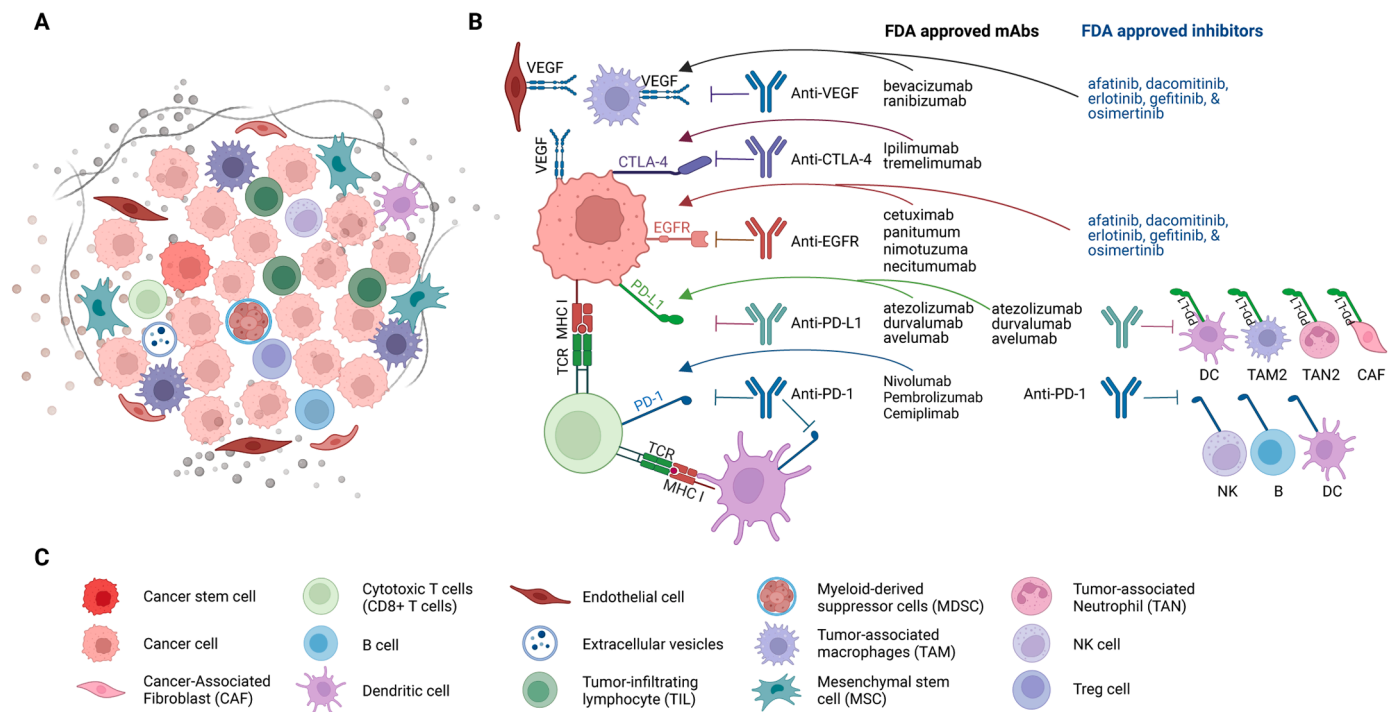


Fig. 2. Therapeutic Targets and Interventions in the TME. A. Illustration of the TME highlighting the diversity of cell types, including cancer cells, immune cells, and stromal cells, and their interactions within this complex ecosystem. B. Diagram of targeted therapies within the TME, showing FDA-approved monoclonal antibodies (mAbs) and inhibitors against specific cytokines and receptors. These therapies are designed to disrupt the supportive cancer cell network and enhance anti-tumor immune responses. The diagram includes agents targeting VEGF, CTLA-4, EGFR, PD-L1, and PD-1, illustrating the multifaceted approach to modulating the TME for therapeutic benefit. C. Key to the cell types and associated cytokines depicted in the TME illustration, providing a reference for the source and target of these soluble mediators and their implications in both tumor progression and the immune response. The graphic representation aligns with the current and emerging strategies for precision medicine in oncology, reflecting the intricate balance and potential targets within the TME that are leveraged for cancer therapy.

cellular contexts of tumors guide treatment strategies.

5. Therapeutic reprogramming of the TME

The strategic disruption of the TME is a critical front in the ongoing battle against cancer [74], targeting the ecosystem that nurtures tumor growth and undermines immune responses [2, 39, 75–77]. This approach represents a paradigm shift in oncology, focusing not just on the tumor cells but on their interactive environment as well.

5.1. Strategies for cytokine and mediator signaling

Innovative therapeutic strategies have been developed to manipulate cytokine and mediator signaling within the TME, aiming to enhance anti-tumor immunity or counteract tumor-promoting inflammation. For instance, the administration of IL-2 has shown promising results in boosting the activity of natural killer (NK) cells and T cells in metastatic cancers, showcasing the potential of cytokine-based therapies [78,79]. Additionally, the use of inhibitors targeting cytokines like IL-6 or TGF- β highlights the approach of neutralizing the immunosuppressive factors within the TME [80]. The success of angiogenesis inhibitors, such as bevacizumab, which directly target the VEGF pathway, further exemplifies the clinical benefits of disrupting key mediators in tumor vascularization and growth [70,81].

5.2. Efficacy of current therapies

Checkpoint inhibitors, including pembrolizumab and nivolumab, have marked a significant advancement in cancer treatment, particularly for melanoma, by inhibiting the PD-1 pathway to re-engage T-cell activity against tumors [82–84]. These therapies, especially when combined with other treatment modalities, have significantly improved patient outcomes, underscoring the therapeutic potential of targeting the TME [85–87]. Moreover, the use of biomarkers to predict therapeutic responses and monitor effectiveness, such as gene signatures and circulating tumor DNA (ctDNA), is enhancing the precision and adaptability of TME-targeted therapies [88–90].

5.3. Challenges in selectively targeting the TME

Despite notable advances, targeting the TME presents numerous challenges, including the redundancy of signaling pathways and the variability of the TME across different patients, complicating the development of universally effective treatments [70,91]. The potential for off-target effects and resistance necessitates careful consideration and ongoing adjustment of therapeutic strategies [92,93]. The exploration of multi-targeted approaches, integrating immunotherapy with specific cytokine or growth factor modulation, is promising but requires further research to fully realize its potential in patient-specific cancer treatment [49, 94–96].

The journey towards the therapeutic reprogramming of the TME is fraught with complexities but remains a cornerstone of innovation in cancer treatment. It requires a comprehensive understanding of the TME's intricate biology, thoughtful integration of clinical trials, and the development of precise biomarkers for tailoring therapies to individual patient needs [36, 37, 61, 90, 97]. The journey towards the therapeutic reprogramming of the TME is fraught with complexities but remains a cornerstone of innovation in cancer treatment. It requires a comprehensive understanding of the TME's intricate biology, thoughtful integration of clinical trials, and the development of precise biomarkers for tailoring therapies to individual patient needs.

6. Unexplored frontiers in TME reprogramming

Exploration of the TME is at the forefront of oncological research, presenting untapped opportunities for therapeutic innovation that

promise to redefine cancer treatment strategies [98]. This domain, characterized by its complexity and diversity, harbors potential targets whose manipulation could lead to breakthrough therapies. To better understand the future potential of TME reprogramming, Fig. 3 below delineates a range of emerging cytokines and mediators, along with novel molecular players, offering a glimpse into the next frontier of therapeutic targets and their multifaceted roles within the TME.

6.1. Novel methodologies uncovering the TME

The exploration of the TME has been greatly enhanced by novel technological methodologies such as multispectral imaging and machine learning algorithms [99]. These innovative approaches allow for the detailed visualization and analysis of cellular and molecular interactions within the TME, providing insights into the heterogeneity and dynamic nature of the cancerous landscape [100]. Advanced bioinformatics tools complement these techniques by synthesizing vast datasets to uncover patterns and relationships previously obscured [101]. These methodologies are not only broadening our scientific understanding but also opening new possibilities for identifying therapeutic targets that can lead to more effective and individualized treatment strategies [102].

6.2. The role of predictive modeling

Predictive modeling has become a cornerstone in the battle against cancer, with systems biology and artificial intelligence leading the charge in forecasting the behavior of the TME and the likely responses to various therapies [103,104]. By incorporating complex biological data, including genomics, proteomics, and metabolomics, these models can simulate the intricate workings of the TME, predicting how it might evolve under different treatment scenarios [105,106]. This level of prediction is invaluable for the design of personalized treatment plans, allowing clinicians to tailor therapies to the unique genetic and environmental contexts of each patient's tumor, thereby enhancing the likelihood of therapeutic success and reducing the chances of adverse effects [107,108].

6.3. Insights from single-cell analysis and spatial profiling

Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have revolutionized our understanding of the TME by providing a high-resolution view of cellular heterogeneity and the spatial distribution of different cell types [109]. These cutting-edge techniques can track the expression patterns of individual cells over time, revealing how specific cytokines and other factors contribute to the dynamic interplay between cancer and immune cells [60]. By pinpointing the precise location and timing of cytokine activity, researchers can identify new opportunities for intervening in the TME [110]. Such detailed mapping is crucial for developing strategies that can modulate the immune response at optimal times and locations to combat cancer more effectively [111].

6.4. Extracellular vesicles: a new frontier

Recent research into extracellular vesicles, especially exosomes, has opened a new chapter in understanding cellular crosstalk within the TME. These tiny vesicles serve as messengers, shuttling proteins, RNA, DNA, and lipids between cells. By ferrying oncogenic factors and immunomodulatory signals, they influence a range of TME dynamics, including cancer progression, metastasis, and the evasion of immune surveillance. The cargo of these vesicles reflects the physiological state of their cells of origin, making them invaluable for biomarker discovery [112]. Moreover, their ability to traverse biological barriers presents an exciting avenue for the delivery of targeted therapies. Harnessing exosomes for drug delivery could offer a sophisticated approach to target cancer cells while minimizing systemic toxicity selectively. As such, exosomes are at the forefront of novel strategies for non-invasive

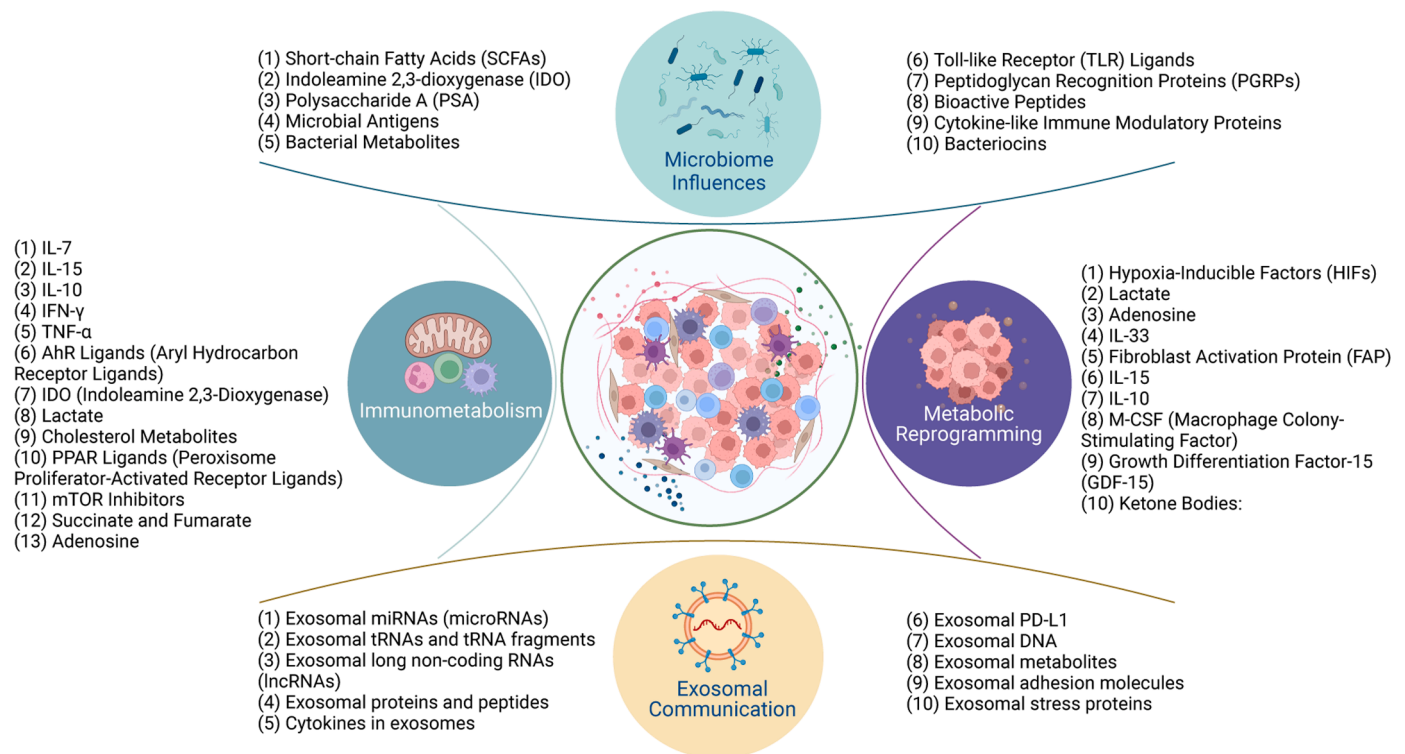


Fig. 3. Charting the Course of TME Reprogramming with Emerging Mediators. This figure provides a roadmap to the future of TME reprogramming, centering on the TME's complexity and the interplay of cancer, immune, and stromal cells. It spotlights four critical research domains that are unlocking new therapeutic avenues: Microbiome Influences: In the top-left, we explore the microbiome's influence on the TME, with factors like TLR Ligands and Bacterial Metabolites suggesting a significant impact on the TME's behavior. Immunometabolism: The bottom-left focuses on the intersection of metabolism and immune function within the TME, with agents like HIFs and Adenosine demonstrating how metabolic processes can shape immune responses. Metabolic Reprogramming: The bottom-right reveals factors such as Lactate and FAP that are pivotal in the metabolic shifts accompanying tumor growth and survival. Exosomal Communication: The top-right illustrates how exosomes, carrying components like miRNAs and PD-L1, are crucial in the TME's communication network, impacting tumor dynamics. The mediators listed in each quadrant shed light on the multifaceted biochemical dialogues within the TME, emphasizing their relevance in developing innovative cancer therapies.

diagnostics and precision medicine, paving the way for the next generation of cancer therapeutics that exploit the body's natural communication systems [113–115].

6.5. High-throughput and synthetic biology approaches

Emerging techniques in high-throughput screening and synthetic biology are expanding our arsenal against cancer. High-throughput methods enable the rapid identification of compounds that can modulate the TME, while synthetic biology offers innovative approaches to engineer biological systems for precise therapeutic delivery directly to the tumor site [116].

As we venture into these unexplored territories, the debate over the optimal use and potential of specific TME mediators continues. The consensus on the utility of novel methodologies in targeting the TME's intricacies is growing, yet significant research gaps remain. These include a complete understanding of the TME's signaling networks and the therapeutic potential of extracellular vesicles. Bridging these gaps requires a concerted effort to delve deeper into the TME's biology, aiming to integrate the latest technological advancements into effective cancer therapies [117].

In summary, the journey into the TME's uncharted territories is filled with both challenges and opportunities. By critically evaluating emerging research and addressing the current gaps, we can pave the way for innovative therapeutic strategies that effectively disrupt the TME's support for cancer, enhancing treatment outcomes and ushering in a new era of precision oncology [12,54].

7. Clinical implications

Reprogramming the TME stands at the forefront of a paradigm shift in cancer therapy, marked by its potential to translate cutting-edge research into effective clinical applications. Yet, this journey is fraught with multifaceted challenges that span economic, logistical, and ethical realms. Fig. 4 illustrates the critical stages in transforming TME reprogramming strategies from innovative research concepts into practical treatments within clinical settings, delineating the path through preclinical testing, clinical trials, regulatory review, and finally to market approval and healthcare integration.

7.1. Economic and logistical challenges

The clinical adoption of TME reprogramming strategies is encumbered by substantial economic barriers, including the significant costs associated with their development, validation, and market introduction [36]. Logistical hurdles further complicate this landscape, as the need for specialized infrastructure can limit patient access, especially in under-resourced settings [117]. The complexity of producing and distributing personalized therapies, such as CAR T-cell treatments, adds another layer of difficulty, impacting healthcare budgets and patient accessibility on a global scale [118,119].

7.2. Ethical considerations

As the field progresses, ethical considerations come to the forefront. The risks associated with TME-targeted therapies, including potential unintended effects on the immune system and the risk of developing

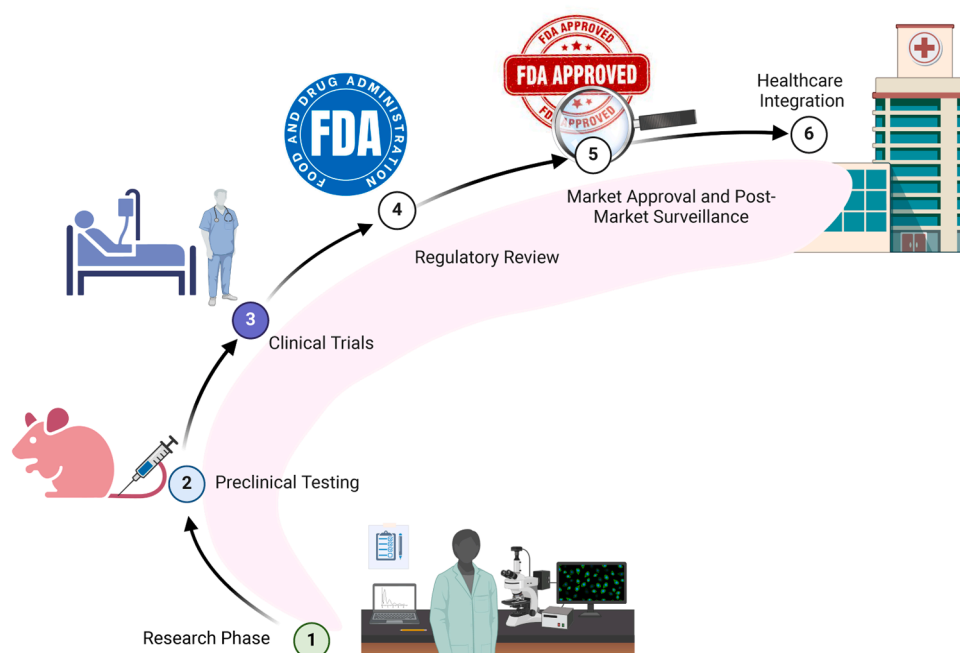


Fig. 4. Navigating TME Reprogramming from Research to Clinical Application. This figure illustrates the sequential stages in the development of cancer therapies targeting the TME. Beginning with the research phase (1), it progresses through preclinical testing (2), extensive clinical trials (3), and regulatory review (4), culminating in FDA approval (5). The final stage depicts the integration of new therapies into healthcare systems (6), emphasizing the ongoing surveillance post-market approval to ensure the safety and efficacy of the treatments.

resistant cancer variants, necessitate a careful evaluation of their therapeutic benefits [120–122]. Moreover, the shift towards personalized medicine raises important questions about resource allocation and the equitable distribution of these advanced treatments, emphasizing the need to ensure broad access across diverse patient populations [123, 124].

7.3. Clinical integration and personalized medicine

The successful integration of TME reprogramming into clinical practice relies on rigorous clinical trials to establish the safety and efficacy of these innovative strategies [125]. These studies are critical for understanding how the modulation of cytokine and mediator signaling can be effectively combined with existing treatments to improve patient outcomes and overcome resistance mechanisms [126].

The variability of the TME across different cancers underscores the importance of a personalized approach to therapy. Leveraging biomarkers for therapy selection promises to refine treatment efficacy and reduce adverse effects, with advancements in genomic and proteomic technologies paving the way for customized treatment plans [127,128].

8. Conclusion and future directions

This review delineates the pivotal influence of cytokines and soluble mediators within the TME, demonstrating how they can both advance and hinder cancer development. We highlight the paradigm shift towards personalized medicine through TME reprogramming, advocating for the use of biomarkers to customize treatment plans. The success of this endeavor hinges on the scientific community's united efforts to refine cancer therapies that are both precise and minimally invasive. By delving into the complexities of TME and harnessing innovative methods, we are on the cusp of a transformative era in oncology, one that promises better outcomes for those affected by cancer. We must continue our collaborative research efforts to fully exploit the potential of TME reprogramming, marking a notable leap in the quest to conquer cancer.

Looking ahead, the prospect of TME reprogramming is illuminated by the potential of innovative therapeutic approaches, including the development of bi-specific and multi-specific agent's adept at navigating intricate cytokine networks. Novel drug delivery modalities, such as nanoparticles, are poised to target the TME with increased precision while reducing collateral effects. Furthermore, the integration of computational tools and artificial intelligence promises to refine treatment protocols and enhance response predictions, propelling precision oncology into the future.

To summarize, the endeavor to reprogram the TME for therapeutic purposes, although fraught with multifaceted challenges, holds an extraordinary promise for the evolution of cancer care. Addressing the financial, operational, and ethical considerations of such innovative treatments necessitates a collective, international effort within the research and healthcare communities. By confronting these challenges head-on, we can ensure that the groundbreaking possibilities of TME reprogramming become a reality in clinical practice, heralding a new epoch of effective and individualized cancer therapy.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Funding

This work was partially supported by a grant from the Major Science and Technology Program for Medicine and Health of Zhejiang Province, China (No. WKJ-ZJ-2012).

CRediT authorship contribution statement

SX, QW, and WM collectively conceived and designed this

comprehensive review. **SX** and **QW** made contributions to the initial draft of the manuscript. **WM** provided Supervision, graphics support, editing, and finalized the manuscript. All authors actively participated in the revision of the manuscript, carefully reviewed it, and approved the final version for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

Not applicable.

Acknowledgements

The authors extend their gratitude to Dr. Shengwen Shao for his meticulous review and edits of this manuscript. The figures were created with BioRender.com.

References

- [1] M. Nejabat, F. Hadizadeh, A. Sahebkar, The application of kinesin inhibitors in medical issues, *Curr. Rev. Clin. Exp. Pharmacol.* (2024).
- [2] L. Yao, Q. Wang, W. Ma, Navigating the immune maze: pioneering strategies for unshackling cancer immunotherapy resistance, *Cancers* 15 (24) (2023).
- [3] S. Shao, H. Miao, W. Ma, Unraveling the enigma of tumor-associated macrophages: challenges, innovations, and the path to therapeutic breakthroughs, *Front Immunol.* 14 (2023) 1295684.
- [4] K. Khalaf, D. Hana, J.T. Chou, C. Singh, A. Mackiewicz, M. Kaczmarek, Aspects of the tumor microenvironment involved in immune resistance and drug resistance, *Front. Immunol.* 12 (2021) 656364.
- [5] Y. Zhao, M. Shen, L. Wu, H. Yang, Y. Yao, Q. Yang, J. Du, L. Liu, Y. Li, Y. Bai, Stromal cells in the tumor microenvironment: accomplices of tumor progression? *Cell Death Dis.* 14 (9) (2023) 587.
- [6] D. Laha, R. Grant, P. Mishra, N. Nilubol, The role of tumor necrosis factor in manipulating the immunological response of tumor microenvironment, *Front. Immunol.* 12 (2021) 656908.
- [7] A. Mantovani, P. Allavena, F. Marchesi, C. Garlanda, Macrophages as tools and targets in cancer therapy, *Nat. Rev. Drug Discov.* 21 (11) (2022) 799–820.
- [8] P.G. Holder, S.A. Lim, C.S. Huang, P. Sharma, Y.S. Dagdas, B. Bulutoglu, J. T. Sockolosky, Engineering interferons and interleukins for cancer immunotherapy, *Adv. Drug Deliv. Rev.* 182 (2022) 114112.
- [9] H. Zhao, L. Wu, G. Yan, Y. Chen, M. Zhou, Y. Wu, Y. Li, Inflammation and tumor progression: signaling pathways and targeted intervention, *Signal Transduct. Target Ther.* 6 (1) (2021) 263.
- [10] K.E. de Visser, J.A. Joyce, The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth, *Cancer Cell* 41 (3) (2023) 374–403.
- [11] J.Y. Mun, S.H. Leem, J.H. Lee, H.S. Kim, Dual relationship between stromal cells and immune cells in the tumor microenvironment, *Front. Immunol.* 13 (2022) 864739.
- [12] Y. Xiao, D. Yu, Tumor microenvironment as a therapeutic target in cancer, *Pharmacol. Ther.* 221 (2021) 107753.
- [13] K. Liu, J.J. Cui, Y. Zhan, Q.Y. Ouyang, Q.S. Lu, D.H. Yang, X.P. Li, J.Y. Yin, Reprogramming the tumor microenvironment by genome editing for precision cancer therapy, *Mol. Cancer* 21 (1) (2022) 98.
- [14] M. Kim, N.K. Lee, C.J. Wang, J. Lim, M.J. Byun, T.H. Kim, W. Park, D.H. Park, S. N. Kim, C.G. Park, Reprogramming the tumor microenvironment with biotechnology, *Biomater. Res* 27 (1) (2023) 5.
- [15] F. De Sanctis, A. Adamo, S. Cane, S. Ugel, Targeting tumour-reprogrammed myeloid cells: the new battleground in cancer immunotherapy, *Semin. Immunopathol.* 45 (2) (2023) 163–186.
- [16] H. Liu, H. Zhao, Y. Sun, Tumor microenvironment and cellular senescence: understanding therapeutic resistance and harnessing strategies, *Semin. Cancer Biol.* 86 (Pt 3) (2022) 769–781.
- [17] E. Balta, G.H. Wabnitz, Y. Samstag, Hijacked immune cells in the tumor microenvironment: molecular mechanisms of immunosuppression and cues to improve T cell-based immunotherapy of solid tumors, *Int. J. Mol. Sci.* 22 (11) (2021).
- [18] Z. Tan, H. Xue, Y. Sun, C. Zhang, Y. Song, Y. Qi, The role of tumor inflammatory microenvironment in lung cancer, *Front. Pharmacol.* 12 (2021) 688625.
- [19] A.A. Bhat, S. Nisar, M. Singh, B. Ashraf, T. Masoodi, C.P. Prasad, A. Sharma, S. Maacha, T. Karedath, S. Hashem, S.B. Yasin, P. Bagga, R. Reddy, M. P. Frennaux, S. Uddin, P. Dhawan, M. Haris, M.A. Macha, Cytokine- and chemokine-induced inflammatory colorectal tumor microenvironment: emerging avenue for targeted therapy, *Cancer Commun.* 42 (8) (2022) 689–715.
- [20] T. Hirano, IL-6 in inflammation, autoimmunity and cancer, *Int. Immunol.* 33 (3) (2021) 127–148.
- [21] G. Lopez-Castejon, D. Brough, Understanding the mechanism of IL-1beta secretion, *Cytokine Growth Factor Rev.* 22 (4) (2011) 189–195.
- [22] O. Habanjar, R. Bingula, C. Decombat, M. Diab-Assaf, F. Caldefie-Chezet, L. Delort, Crosstalk of inflammatory cytokines within the breast tumor microenvironment, *Int. J. Mol. Sci.* 24 (4) (2023).
- [23] M.A. Salkeni, A. Naing, Interleukin-10 in cancer immunotherapy: from bench to bedside, *Trends Cancer* 9 (9) (2023) 716–725.
- [24] Q. Chen, X. Guo, W. Ma, Opportunities and challenges of CD47-targeted therapy in cancer immunotherapy, *Oncol. Res.* 32 (1) (2023) 49–60.
- [25] Z.W. Liu, Y.M. Zhang, L.Y. Zhang, T. Zhou, Y.Y. Li, G.C. Zhou, Z.M. Miao, M. Shang, J.P. He, N. Ding, Y.Q. Liu, Duality of interactions between TGF-beta and TNF-alpha during tumor formation, *Front. Immunol.* 12 (2021) 810286.
- [26] A.B. Baba, B. Rah, G.R. Bhat, I. Mushtaq, S. Parveen, R. Hassan, M. Hameed Zargar, D. Afroze, Transforming growth factor-beta (TGF-beta) signaling in cancer-a betrayal within, *Front. Pharmacol.* 13 (2022) 791272.
- [27] Y. Gu, Z. Zhang, P. Ten Dijke, Harnessing epithelial-mesenchymal plasticity to boost cancer immunotherapy, *Cell Mol. Immunol.* 20 (4) (2023) 318–340.
- [28] D.R. Balce, Y.T. Wang, M.R. McAllister, B.F. Dunlap, A. Orvedahl, B.L. Hykes Jr., L. Droit, S.A. Handley, C.B. Wilen, J.G. Doench, R.C. Orchard, C.L. Stallings, H. W. Virgin, UFMylation inhibits the proinflammatory capacity of interferon-gamma-activated macrophages, *Proc. Natl. Acad. Sci. USA* 118 (1) (2021).
- [29] M. Wen, Y. Li, X. Qin, B. Qin, Q. Wang, Insight into cancer immunity: MHCs, immune cells and commensal Microbiota, *Cells* 12 (14) (2023).
- [30] S. Shao, E. Risch, D. Burner, L. Lu, B. Minev, W. Ma, IFN-gamma enhances cytotoxic efficiency of the cytotoxic T lymphocytes against human glioma cells, *Int. Immunopharmacol.* 47 (2017) 159–165.
- [31] D. Jorgovanovic, M. Song, L. Wang, Y. Zhang, Roles of IFN-gamma in tumor progression and regression: a review, *Biomark. Res.* 8 (2020) 49.
- [32] M. Yu, Z. Peng, M. Qin, Y. Liu, J. Wang, C. Zhang, J. Lin, T. Dong, L. Wang, S. Li, Y. Yang, S. Xu, W. Guo, X. Zhang, M. Shi, H. Peng, X. Luo, H. Zhang, L. Zhang, Y. Li, X.P. Yang, S. Sun, Interferon-gamma induces tumor resistance to anti-PD-1 immunotherapy by promoting YAP phase separation, *Mol. Cell* 81 (6) (2021) 1216–1230, e9.
- [33] A.E.R. Kartikasari, C.S. Huertas, A. Mitchell, M. Plebanski, Tumor-induced inflammatory cytokines and the emerging diagnostic devices for cancer detection and prognosis, *Front. Oncol.* 11 (2021) 692142.
- [34] C.R.F. Silveira, A.C. Corveloni, S.R. Caruso, N.A. Macedo, N.M. Brussolo, F. Haddad, T.R. Fernandes, P.V. de Andrade, M.D. Orellana, R.L. Guerino-Cunha, Cytokines as an important player in the context of CAR-T cell therapy for cancer: Their role in tumor immunomodulation, manufacture, and clinical implications, *Front. Immunol.* 13 (2022) 947648.
- [35] R. Baghban, L. Roshangar, R. Jahanban-Esfahlan, K. Seidi, A. Ebrahimi-Kalan, M. Jaymand, S. Kolahian, T. Javaheri, P. Zare, Tumor microenvironment complexity and therapeutic implications at a glance, *Cell Commun. Signal.* 18 (1) (2020) 59.
- [36] L. Bejarano, M.J.C. Jordao, J.A. Joyce, Therapeutic targeting of the tumor microenvironment, *Cancer Discov.* 11 (4) (2021) 933–959.
- [37] A. Tiwari, R. Trivedi, S.Y. Lin, Tumor microenvironment: barrier or opportunity towards effective cancer therapy, *J. Biomed. Sci.* 29 (1) (2022) 83.
- [38] B. Wu, X. Shi, M. Jiang, H. Liu, Cross-talk between cancer stem cells and immune cells: potential therapeutic targets in the tumor immune microenvironment, *Mol. Cancer* 22 (1) (2023) 38.
- [39] M.T. Bilotta, A. Antignani, D.J. Fitzgerald, Managing the TME to improve the efficacy of cancer therapy, *Front. Immunol.* 13 (2022) 954992.
- [40] D. Cao, X. Naiyila, J. Li, Y. Huang, Z. Chen, B. Chen, J. Li, J. Guo, Q. Dong, J. Ai, L. Yang, L. Liu, Q. Wei, Potential strategies to improve the effectiveness of drug therapy by changing factors related to tumor microenvironment, *Front. Cell Dev. Biol.* 9 (2021) 705280.
- [41] H. Wu, T. Ma, D. Li, M. He, H. Wang, Y. Cui, Circulating vascular endothelial growth factor and cancer risk: a bidirectional mendelian randomization, *Front. Genet.* 13 (2022) 981032.
- [42] Y. Yang, Y. Cao, The impact of VEGF on cancer metastasis and systemic disease, *Semin. Cancer Biol.* 86 (Pt 3) (2022) 251–261.
- [43] A. Romanzi, F. Milosa, G. Marcelli, R.M. Critelli, S. Lasagni, I. Gigante, F. Dituri, F. Schepis, M. Cadamuro, G. Giannelli, L. Fabris, E. Villa, Angiopoietin-2 and the vascular endothelial growth factor promote migration and invasion in hepatocellular carcinoma- and intrahepatic cholangiocarcinoma-derived spheroids, *Biomedicines* 12 (1) (2023).
- [44] T.Y.S. Ngaha, A.V. Zhilenkova, F.E. Essogmo, I.K. Uchendu, M.O. Abah, L. T. Fossa, Z.D. Sangadzhieva, D.S. V. S.R. A. N.P. Y. A. Boroda, A. Rozhkov, J. D. Kemfang Ngowa, N.B. L. I.S. M. Angiogenesis in lung cancer: understanding the roles of growth factors, *Cancers* 15 (18) (2023).
- [45] J. Garcia, H.I. Hurwitz, A.B. Sandler, D. Miles, R.L. Coleman, R. Deurloo, O. L. Chinot, Bevacizumab (Avastin(R)) in cancer treatment: a review of 15 years of clinical experience and future outlook, *Cancer Treat. Rev.* 86 (2020) 102017.
- [46] Z.J. Han, Y.B. Li, L.X. Yang, H.J. Cheng, X. Liu, H. Chen, Roles of the CXCL8-CXCR1/2 axis in the tumor microenvironment and immunotherapy, *Molecules* 27 (1) (2021).
- [47] M. Iglesias-Escudero, N. Arias-Gonzalez, E. Martinez-Caceres, Regulatory cells and the effect of cancer immunotherapy, *Mol. Cancer* 22 (1) (2023) 26.
- [48] W. Zhu, C. Wu, S. Hu, S. Liu, S. Zhao, D. Zhang, G. Qiu, X. Cheng, J. Huang, Chemokine- and chemokine receptor-based signature predicts immunotherapy response in female colorectal adenocarcinoma patients, *Sci. Rep.* 13 (1) (2023) 21358.

- [49] M. Sarkar, T. Nguyen, E. Gundre, O. Ogunlusi, M. El-Sobky, B. Giri, T.R. Sarkar, Cancer-associated fibroblasts: the chief architect in the tumor microenvironment, *Front. Cell Dev. Biol.* 11 (2023) 1089068.
- [50] D. Yang, J. Liu, H. Qian, Q. Zhuang, Cancer-associated fibroblasts: from basic science to anticancer therapy, *Exp. Mol. Med.* 55 (7) (2023) 1322–1332.
- [51] R.S. Joshi, S.S. Kanugula, S. Sudhir, M.P. Pereira, S. Jain, M.K. Aghi, The Role of cancer-associated fibroblasts in tumor progression, *Cancers* 13 (6) (2021).
- [52] Z. Fang, Q. Meng, J. Xu, W. Wang, B. Zhang, J. Liu, C. Liang, J. Hua, Y. Zhao, X. Yu, S. Shi, Signaling pathways in cancer-associated fibroblasts: recent advances and future perspectives, *Cancer Commun.* 43 (1) (2023) 3–41.
- [53] S. Mustafa, S. Koran, L. AlOmair, Insights Into the role of matrix metalloproteinases in cancer and its various therapeutic aspects: a review, *Front. Mol. Biosci.* 9 (2022) 896099.
- [54] M. Chehelgerdi, M. Chehelgerdi, O.Q.B. Allela, R.D.C. Pecho, N. Jayasankar, D. P. Rao, T. Thamaraiyani, M. Vasanthan, P. Viktor, N. Lakshmaiy, M.J. Saadh, A. Amjad, M.A. Abo-Zaid, R.Y. Castillo-Acoba, A.H. Ismail, A.H. Amin, R. Akhavan-Sigari, Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation, *Mol. Cancer* 22 (1) (2023) 169.
- [55] H.S. Lee, W.J. Kim, The Role of Matrix Metalloproteinase in Inflammation with a Focus on Infectious Diseases, *Int. J. Mol. Sci.* 23 (18) (2022).
- [56] E.I. Buzas, The roles of extracellular vesicles in the immune system, *Nat. Rev. Immunol.* 23 (4) (2023) 236–250.
- [57] H. Xu, S. Lin, Z. Zhou, D. Li, X. Zhang, M. Yu, R. Zhao, Y. Wang, J. Qian, X. Li, B. Li, C. Wei, K. Chen, T. Yoshimura, J.M. Wang, J. Huang, New genetic and epigenetic insights into the chemokine system: the latest discoveries aiding progression toward precision medicine, *Cell Mol. Immunol.* 20 (7) (2023) 739–776.
- [58] D. Briukhovetska, J. Dorr, S. Endres, P. Libby, C.A. Dinarello, S. Kobold, Interleukins in cancer: from biology to therapy, *Nat. Rev. Cancer* 21 (8) (2021) 481–499.
- [59] A. Cavazzoni, G. Digiaco, Role of cytokines and other soluble factors in tumor development: rationale for new therapeutic strategies, *Cells* 12 (21) (2023).
- [60] B. Sun, Z. Xun, N. Zhang, K. Liu, X. Chen, H. Zhao, Single-cell RNA sequencing in cancer research: discovering novel biomarkers and therapeutic targets for immune checkpoint blockade, *Cancer Cell Int.* 23 (1) (2023) 313.
- [61] Q. Babar, A. Saeed, T.A. Tabish, M. Sarwar, N.D. Thorat, Targeting the tumor microenvironment: potential strategy for cancer therapeutics, *Biochim. Biophys. Acta Mol. Basis Dis.* 1869 (6) (2023) 166746.
- [62] S. Mayer, T. Milo, A. Isaacson, C. Halperin, S. Miyara, Y. Stein, C. Lior, M. Pevsner-Fischer, E. Tzahor, A. Mayo, U. Alon, R. Scherz-Shouval, The tumor microenvironment shows a hierarchy of cell-cell interactions dominated by fibroblasts, *Nat. Commun.* 14 (1) (2023) 5810.
- [63] C. Liu, D. Chu, K. Kalantar-Zadeh, J. George, H.A. Young, G. Liu, Cytokines: from clinical significance to quantification, *Adv. Sci.* 8 (15) (2021) e2004433.
- [64] M. Schrevel, E.M. Osse, F.A. Prins, J. Trimbs, G.J. Fleuren, A. Gorter, E. S. Jordanova, Autocrine expression of the epidermal growth factor receptor ligand heparin-binding EGF-like growth factor in cervical cancer, *Int. J. Oncol.* 50 (6) (2017) 1947–1954.
- [65] Z. Jia, D. Ragoonanan, K.M. Mahadeo, J. Gill, R. Gorlick, E. Shpal, S. Li, IL12 immune therapy clinical trial review: novel strategies for avoiding CRS-associated cytokines, *Front Immunol.* 13 (2022) 952231.
- [66] R. Derynck, S.J. Turley, R.J. Akhurst, TGFβ biology in cancer progression and immunotherapy, *Nat. Rev. Clin. Oncol.* 18 (1) (2021) 9–34.
- [67] B. Chen, C. Mu, Z. Zhang, X. He, X. Liu, The love-hate relationship between TGF-β signaling and the immune system during development and tumorigenesis, *Front. Immunol.* 13 (2022) 891268.
- [68] V.C. Talayero, M. Vicente-Manzanares, A primer on cancer-associated fibroblast mechanics and immunosuppressive ability, *Explor. Target Antitumor Ther.* 4 (1) (2023) 17–27.
- [69] M. Geindreau, F. Ghiringhelli, M. Bruchard, Vascular endothelial growth factor, a key modulator of the anti-tumor immune response, *Int. J. Mol. Sci.* 22 (9) (2021).
- [70] Z.L. Liu, H.H. Chen, L.L. Zheng, L.P. Sun, L. Shi, Angiogenic signaling pathways and anti-angiogenic therapy for cancer, *Signal. Transduct. Target Ther.* 8 (1) (2023) 198.
- [71] S. Dash, A.K. Sahu, A. Srivastava, R. Chowdhury, S. Mukherjee, Exploring the extensive crosstalk between the antagonistic cytokines- TGF-beta and TNF-alpha in regulating cancer pathogenesis, *Cytokine* 138 (2021) 155348.
- [72] J. Han, L. Dong, M. Wu, F. Ma, Dynamic polarization of tumor-associated macrophages and their interaction with intratumoral T cells in an inflamed tumor microenvironment: from mechanistic insights to therapeutic opportunities, *Front. Immunol.* 14 (2023) 1160340.
- [73] S.S. Peri, Y.K. Narayanaa, T.D. Hubert, R. Rajaraman, F. Arfuso, S. Sundaram, B. Archana, S. Warrior, A. Dharmarajan, L.R. Perumalsamy, Navigating tumour microenvironment and wnt signalling crosstalk: implications for advanced cancer therapeutics, *Cancers* 15 (24) (2023).
- [74] Q. Wang, X. Shao, Y. Zhang, M. Zhu, F.X.C. Wang, J. Mu, J. Li, H. Yao, K. Chen, Role of tumor microenvironment in cancer progression and therapeutic strategy, *Cancer Med.* 12 (10) (2023) 11149–11165.
- [75] C. Roma-Rodriguez, R. Mendes, P.V. Baptista, A.R. Fernandes, Targeting tumor microenvironment for cancer therapy, *Int. J. Mol. Sci.* 20 (4) (2019).
- [76] J. Xu, L. Bian, D. You, Z. Li, T. Wang, Y. Li, X. Ren, Y. He, PDGF-BB accelerates TSCC via fibroblast lactates limiting miR-26a-5p and boosting mitophagy, *Cancer Cell Int.* 24 (1) (2024) 5.
- [77] H. Luo, X. Xia, L.B. Huang, H. An, M. Cao, G.D. Kim, H.N. Chen, W.H. Zhang, Y. Shu, X. Kong, Z. Ren, P.H. Li, Y. Liu, H. Tang, R. Sun, C. Li, B. Bai, W. Jia, Y. Liu, W. Zhang, L. Yang, Y. Peng, L. Dai, H. Hu, Y. Jiang, Y. Hu, J. Zhu, H. Jiang, Z. Li, C. Caulin, J. Park, H. Xu, Pan-cancer single-cell analysis reveals the heterogeneity and plasticity of cancer-associated fibroblasts in the tumor microenvironment, *Nat. Commun.* 13 (1) (2022) 6619.
- [78] J. Deckers, T. Anbergen, A.M. Hokke, A. de Dreu, D.P. Schrijver, K. de Bruin, Y. C. Toner, T.J. Beldman, J.B. Spangler, T.F.A. de Greef, F. Grisoni, R. van der Meel, L.A.B. Joosten, M. Merckx, M.G. Netea, W.J.M. Mulder, Engineering cytokine therapeutics, *Nat. Rev. Bioeng.* 1 (4) (2023) 286–303.
- [79] S. Muhammad, T. Fan, Y. Hai, Y. Gao, J. He, Reigniting hope in cancer treatment: the promise and pitfalls of IL-2 and IL-2R targeting strategies, *Mol. Cancer* 22 (1) (2023) 121.
- [80] N. Stanilov, T. Velikova, S. Stanilova, Navigating the cytokine seas: targeting cytokine signaling pathways in cancer therapy, *Int. J. Mol. Sci.* 25 (2) (2024).
- [81] D. Wu, B. Jia, M. Jia, H. Zhao, H. Zhao, J. Zhou, Comparative efficacy and safety of systemic therapy for advanced hepatocellular carcinoma: a systematic review and network meta-analysis, *Front. Oncol.* 13 (2023) 1274754.
- [82] J.A. Chesney, A. Ribas, G.V. Long, J.M. Kirkwood, R. Dummer, I. Puzanov, C. Hoeller, T.F. Gajewski, R. Gutzmer, P. Rutkowski, L. Demidov, P. Arenberger, S.J. Shin, P.F. Ferrucci, A. Haydon, J. Hyngstrom, J.V. van Thienen, S. Haferkamp, J.M. Guiler, B.L. Rapoport, A. VanderWalde, S.J. Dieder, J. R. Anderson, S. Treichel, E.L. Chan, S. Bhatta, J. Gansert, F.S. Hodi, H. Gogas, Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma, *J. Clin. Oncol.* 41 (3) (2023) 528–540.
- [83] C. Robert, W.J. Hwu, O. Hamid, A. Ribas, J.S. Weber, A.I. Daud, F.S. Hodi, J. D. Wolchok, T.C. Mitchell, P. Hersey, R. Dronca, R.W. Joseph, C. Boutros, L. Min, G.V. Long, J. Schachter, I. Puzanov, R. Dummer, J. Lin, N. Ibrahim, S.J. Dieder, M. S. Carlino, A.M. Joshua, Long-term safety of pembrolizumab monotherapy and relationship with clinical outcome: a landmark analysis in patients with advanced melanoma, *Eur. J. Cancer* 144 (2021) 182–191.
- [84] H.A. Tawbi, D. Schadendorf, E.J. Lipson, P.A. Ascierto, L. Matamala, E. Castillo Gutierrez, P. Rutkowski, H.J. Gogas, C.D. Lao, J.J. De Menezes, S. Dalle, A. Arance, J.J. Grob, S. Srivastava, M. Abaskharoun, M. Hamilton, S. Keidel, K. L. Simonsen, A.M. Sobieski, B. Li, F.S. Hodi, G.V. Long, R.- Investigators, Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma, *N. Engl. J. Med.* 386 (1) (2022) 24–34.
- [85] B. Li, J. Jin, D. Guo, Z. Tao, X. Hu, Immune checkpoint inhibitors combined with targeted therapy: the recent advances and future potentials, *Cancers* 15 (10) (2023).
- [86] L. Luo, C. Lin, P. Wang, D. Cao, Y. Lin, W. Wang, Y. Zhao, Y. Shi, Z. Gao, X. Kang, Y. Zhang, S. Wang, J. Wang, M. Xu, H. Liu, S.L. Liu, Combined use of immune checkpoint inhibitors and phytochemicals as a novel therapeutic strategy against cancer, *J. Cancer* 14 (12) (2023) 2315–2328.
- [87] R.J. Walsh, R. Sundar, J.S.J. Lim, Immune checkpoint inhibitor combinations-current and emerging strategies, *Br. J. Cancer* 128 (8) (2023) 1415–1417.
- [88] M. Makarew, J.K. Rotow, Genotype versus phenotype: defining predictive biomarkers of immunotherapy response, *J. Thorac. Oncol.* 18 (12) (2023) 1615–1617.
- [89] E. Sanz-Garcia, E. Zhao, S.V. Bratman, L.L. Siu, Monitoring and adapting cancer treatment using circulating tumor DNA kinetics: current research, opportunities, and challenges, *Sci. Adv.* 8 (4) (2022) eabi8618.
- [90] Y. Bao, D. Zhang, H. Guo, W. Ma, Beyond blood: advancing the frontiers of liquid biopsy in oncology and personalized medicine, *Cancer Sci.* (2024).
- [91] L. Guo, D. Kong, J. Liu, L. Zhan, L. Luo, W. Zheng, Q. Zheng, C. Chen, S. Sun, Breast cancer heterogeneity and its implication in personalized precision therapy, *Exp. Hematol. Oncol.* 12 (1) (2023) 3.
- [92] P.J. Dziubanska-Kusibab, E. Nevedomskaya, B. Haendler, Preclinical anticipation of on- and off-target resistance mechanisms to anti-cancer drugs: a systematic review, *Int. J. Mol. Sci.* 25 (2) (2024).
- [93] N. Wang, T. Ma, B. Yu, Targeting epigenetic regulators to overcome drug resistance in cancers, *Signal. Transduct. Target Ther.* 8 (1) (2023) 69.
- [94] B. Victor, C. Croix, F. Gouilleux, G. Prie, Targeted therapeutic strategies for the treatment of cancer, *Cancers* 16 (2) (2024).
- [95] J. Yang, H. Kang, L. Lyu, W. Xiong, Y. Hu, A target map of clinical combination therapies in oncology: an analysis of clinicaltrials.gov, *Discov. Oncol.* 14 (1) (2023) 151.
- [96] X. Chen, J. Zhang, L. Jiang, F. Yan, IBIS: identify biomarker-based subgroups with a Bayesian enrichment design for targeted combination therapy, *BMC Med. Res. Method.* 23 (1) (2023) 66.
- [97] T. Pichler, F. Mumm, N. Dehar, E. Dickman, C. Diez de Los Rios de la Serna, A. Dinkel, K. Heinrich, M. Hennink, A.D. Parviainen, V. Raske, N. Wicki, A. C. Moore, Understanding communication between patients and healthcare professionals regarding comprehensive biomarker testing in precision oncology: a scoping review, *Cancer Med.* (2024).
- [98] C. Riviere-Cazaux, L.P. Carlstrom, B.J. Neth, I.E. Olson, K. Rajani, M. Rahman, S. Ikram, M.A. Mansour, B. Mukherjee, A.E. Warrington, S.C. Short, T. von Zglinicki, D.A. Brown, S. Burma, T. Tchkonja, M.J. Schafer, D.J. Baker, S. H. Kizilbash, J.L. Kirkland, T.C. Burns, An untapped window of opportunity for glioma: targeting therapy-induced senescence prior to recurrence, *NPJ Precis. Oncol.* 7 (1) (2023) 126.
- [99] H. Chen, W. Yang, Z. Ji, Machine learning-based identification of tumor-infiltrating immune cell-associated model with appealing implications in improving prognosis and immunotherapy response in bladder cancer patients, *Front. Immunol.* 14 (2023) 1171420.
- [100] C. Wang, Q. Yu, T. Song, Z. Wang, L. Song, Y. Yang, J. Shao, J. Li, Y. Ni, N. Chao, L. Zhang, W. Li, The heterogeneous immune landscape between lung

- adenocarcinoma and squamous carcinoma revealed by single-cell RNA sequencing, *Signal. Transduct. Target Ther.* 7 (1) (2022) 289.
- [101] V.M. Nelakurthi, P. Paul, A. Reche, Bioinformatics in early cancer detection, *Cureus* 15 (10) (2023) e46931.
- [102] A. Blanco-Gonzalez, A. Cabezon, A. Seco-Gonzalez, D. Conde-Torres, P. Antelo-Riveiro, A. Pineiro, R. Garcia-Fandino, The role of AI in drug discovery: challenges, opportunities, and strategies, *Pharmaceuticals* 16 (6) (2023).
- [103] I.N. Weeraratna, A.R. Kamble, A. Luharia, Artificial intelligence applications for biomedical cancer research: a review, *Cureus* 15 (11) (2023) e48307.
- [104] Q. Gao, L. Yang, M. Lu, R. Jin, H. Ye, T. Ma, The artificial intelligence and machine learning in lung cancer immunotherapy, *J. Hematol. Oncol.* 16 (1) (2023) 55.
- [105] S. Quazi, Artificial intelligence and machine learning in precision and genomic medicine, *Med. Oncol.* 39 (8) (2022) 120.
- [106] T. Ivanisevic, R.N. Sewduth, Multi-omics integration for the design of novel therapies and the identification of novel biomarkers, *Proteomes* 11 (4) (2023).
- [107] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, *Nat. Rev. Drug Discov.* 20 (2) (2021) 101–124.
- [108] A. Hoeben, E.A.J. Joosten, M.H.J. van den Beuken-van Everdingen, Personalized medicine: recent progress in cancer therapy, *Cancers* 13 (2) (2021).
- [109] J. Zhao, Y. Shi, G. Cao, The application of single-cell RNA sequencing in the inflammatory tumor microenvironment, *Biomolecules* 13 (2) (2023).
- [110] L. Bonati, L. Tang, Cytokine engineering for targeted cancer immunotherapy, *Curr. Opin. Chem. Biol.* 62 (2021) 43–52.
- [111] S. Liu, Q. Sun, X. Ren, Novel strategies for cancer immunotherapy: counter-immunoediting therapy, *J. Hematol. Oncol.* 16 (1) (2023) 38.
- [112] S. Uddin, A. Ahmad, Proteomic dissection of exosome cargo: progress and future perspectives, *Cancers* 15 (17) (2023).
- [113] C. Zhang, C. Qin, S. Dewanjee, H. Bhattacharya, P. Chakraborty, N.K. Jha, M. Gangopadhyay, S.K. Jha, Q. Liu, Tumor-derived small extracellular vesicles in cancer invasion and metastasis: molecular mechanisms, and clinical significance, *Mol. Cancer* 23 (1) (2024) 18.
- [114] J.W. Clancy, C. D'Souza-Schorey, Tumor-derived extracellular vesicles: multifunctional entities in the tumor microenvironment, *Annu. Rev. Pathol.* 18 (2023) 205–229.
- [115] A. Forder, C.Y. Hsing, J. Trejo Vazquez, C. Garnis, Emerging role of extracellular vesicles and cellular communication in metastasis, *Cells* 10 (12) (2021).
- [116] S. Yu, X. Li, M. Ma, R. Yang, J. Zhang, S. Wu, The immunological contribution of a novel metabolism-related signature to the prognosis and anti-tumor immunity in cervical cancer, *Cancers* 14 (10) (2022).
- [117] D. Trapani, L. Kraemer, H.S. Rugo, N.U. Lin, Impact of prior authorization on patient access to cancer care, *Am. Soc. Clin. Oncol. Educ. Book* 43 (2023) e100036.
- [118] R. Borgert, Improving outcomes and mitigating costs associated with CAR T-cell therapy, *Am. J. Manag. Care* 27 (13 Suppl) (2021) S253–S261.
- [119] A. Gajra, A. Zalski, A. Sannareddy, Y. Jeune-Smith, K. Kapinos, A. Kansagra, Barriers to chimeric antigen receptor T-cell (CAR-T) therapies in clinical practice, *Pharm. Med.* 36 (3) (2022) 163–171.
- [120] L. Riva, C. Petrini, A few ethical issues in translational research for gene and cell therapy, *J. Transl. Med.* 17 (1) (2019) 395.
- [121] M. Wu, Q. Huang, Y. Xie, X. Wu, H. Ma, Y. Zhang, Y. Xia, Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation, *J. Hematol. Oncol.* 15 (1) (2022) 24.
- [122] L. Xia, L. Oyang, J. Lin, S. Tan, Y. Han, N. Wu, P. Yi, L. Tang, Q. Pan, S. Rao, J. Liang, Y. Tang, M. Su, X. Luo, Y. Yang, Y. Shi, H. Wang, Y. Zhou, Q. Liao, The cancer metabolic reprogramming and immune response, *Mol. Cancer* 20 (1) (2021) 28.
- [123] A. Erdmann, C. Rehmann-Sutter, C. Bozzaro, Patients' and professionals' views related to ethical issues in precision medicine: a mixed research synthesis, *BMC Med. Ethics* 22 (1) (2021) 116.
- [124] D.M. Berwick, The moral determinants of health, *JAMA* 324 (3) (2020) 225–226.
- [125] C.J. Bashor, I.B. Hilton, H. Bandukwala, D.M. Smith, O. Veisheh, Engineering the next generation of cell-based therapeutics, *Nat. Rev. Drug Discov.* 21 (9) (2022) 655–675.
- [126] C. Liu, M. Yang, D. Zhang, M. Chen, D. Zhu, Clinical cancer immunotherapy: current progress and prospects, *Front. Immunol.* 13 (2022) 961805.
- [127] R.C. Wang, Z. Wang, Precision medicine: disease subtyping and tailored treatment, *Cancers* 15 (15) (2023).
- [128] Y.W. Kwon, H.S. Jo, S. Bae, Y. Seo, P. Song, M. Song, J.H. Yoon, Application of proteomics in cancer: recent trends and approaches for biomarkers discovery, *Front. Med.* 8 (2021) 747333.



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