Title

Unleashing the potential of CD39-targeted cancer therapy: Breaking new ground and future prospects

Authors

Zhou, Qiongyan

Shao, Shengwen

Minev, Theia

et al.

Publication Date

2024-09-01

DOI

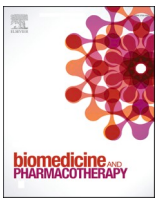
10.1016/j.biopha.2024.117285

Biomedicine & Pharmacotherapy 178 (2024) 117285

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Unleashing the potential of CD39-targeted cancer therapy: Breaking new ground and future prospects

ARTICLE INFO

Keywords:
CD39
Tumor Microenvironment (TME)
Immunotherapy
Angiogenesis
Metabolic Reprogramming

ABSTRACT

The review article titled CD39 Transforming Cancer Therapy by Modulating Tumor Microenvironment published in June 2024 in *Cancer Letters* provides a comprehensive overview of CD39's multifaceted roles in cancer, particularly its influence on immunoregulation, angiogenesis, and metabolic reprogramming within the tumor microenvironment (TME). This commentary builds on that foundation by incorporating recent advancements in CD39 research, highlighting unresolved issues, and proposing future research directions. We delve into the therapeutic potential of targeting CD39, addressing clinical translation challenges, and exploring the integration of CD39-based strategies into precision oncology.

1. Introduction

The tumor microenvironment (TME) is crucial in cancer progression and therapeutic resistance [1–4]. CD39, an ectonucleotidase, has emerged as a significant player by modulating immune responses, angiogenesis, and metabolic processes [5–7]. The original review by Xu et al. [8] provides a foundational understanding of CD39's functions and therapeutic potential. This commentary aims to expand upon these insights by discussing recent updates, analyzing current debates, and suggesting pathways for future research.

2. Recent advances in CD39 research

2.1. Immunoregulation and tumor immune evasion

CD39's role in immunoregulation is well-documented, particularly its ability to convert ATP to immunosuppressive adenosine, thereby facilitating tumor immune evasion [8,9]. Recent studies have further elucidated the mechanisms through which CD39 modulates the TME, influencing the activity of various immune cells, including T cells, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs) [10–12]. These insights have paved the way for novel therapeutic strategies targeting CD39 to enhance anti-tumor immunity. To better understand these complex interactions and their therapeutic implications, Fig. 1 illustrates the CD39 mechanism in immunoregulation and its impact on different immune cells within the TME.

This figure illustrates the role of CD39 in modulating the immune response within the TME. CD39, an ectonucleotidase expressed on the cell membrane, converts extracellular ATP to ADP and subsequently to adenosine. Adenosine, the final product of this hydrolysis, exerts several immunosuppressive effects: it suppresses the activity of effector T cells, enhances the function of regulatory T cells, inhibits the cytotoxic activity of NK cells, promotes the expansion and suppressive function of MDSCs, and impairs the antigen-presenting function of dendritic cells. These interactions collectively contribute to an immunosuppressive TME, supporting tumor growth and progression.

2.2. Angiogenesis and metabolic reprogramming

Beyond immunoregulation, CD39 significantly impacts angiogenesis and metabolic reprogramming within the TME. Recent research has highlighted the enzyme's role in promoting vascular endothelial growth factor (VEGF) secretion, thus supporting tumor vascularization [6,7,13]. Additionally, CD39's influence on metabolic pathways, such as the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways, underscores its importance in maintaining tumor cell survival under adverse conditions [14–16].

3. Current therapeutic strategies and clinical translation

3.1. CD39 inhibitors and monoclonal antibodies

Developing CD39 inhibitors, such as sodium metatungstate and monoclonal antibodies like TTX-030 and SRF617, represents a promising therapeutic avenue [17,18]. These agents block CD39's enzymatic activity, reducing adenosine production and enhancing anti-tumor immune responses. Clinical trials investigating these inhibitors have shown encouraging preliminary results, although challenges related to specificity, resistance, and side effects persist [19,20].

Abbreviations: AMPK, AMP-Activated Protein Kinase; ATP, Adenosine Triphosphate; CD39, Cluster of Differentiation 39; DCs, Dendritic Cells; MDSCs, Myeloid-Derived Suppressor Cells; MTOR, Mammalian Target of Rapamycin; NK Cells, Natural Killer Cells; TME, Tumor Microenvironment; Tregs, Regulatory T Cells; VEGF, Vascular Endothelial Growth Factor.

https://doi.org/10.1016/j.biopha.2024.117285
Received 23 June 2024; Received in revised form 27 July 2024; Accepted 8 August 2024
Available online 11 August 2024

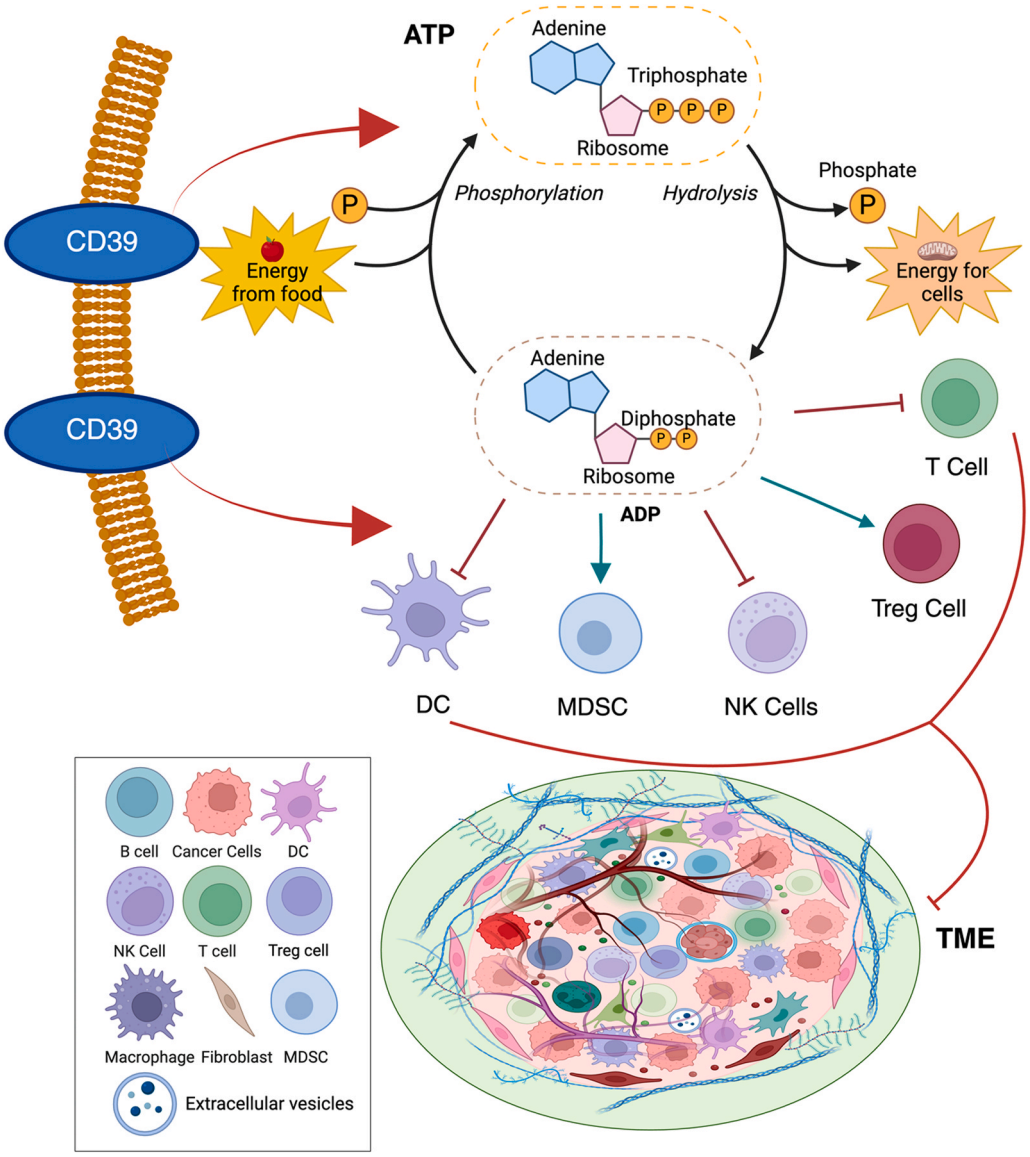


Fig. 1. CD39 Mechanism in Immunoregulation.

3.2. Gene therapy and immuno-metabolic modulators

Gene therapy approaches targeting CD39, including CRISPR-based techniques, offer another innovative strategy [21,22]. By directly altering CD39 expression, these therapies could disrupt the tumor's immunosuppressive environment. Additionally, immuno-metabolic modulators that target the CD39-adenosine pathway are being explored to exploit tumors' metabolic vulnerabilities [5,23,24].

4. Challenges and future directions

4.1. Addressing therapeutic resistance

One of the primary challenges in CD39-targeted therapy is the potential for therapeutic resistance [18,19]. Tumors may develop resistance mechanisms, such as genetic variations affecting CD39 expression or activity, necessitating combinatorial approaches to overcome these hurdles [8,25].

4.2. Personalized medicine and patient stratification

The variability in CD39 expression across different cancers highlights the need for personalized therapeutic strategies [8,26,27]. Integrating CD39 expression data into clinical workflows can help tailor treatments to individual patients, improving efficacy and minimizing adverse effects [8,28,29]. Developing comprehensive biomarker panels and employing sophisticated patient profiling techniques are essential for optimizing CD39-targeted therapies.

4.3. Ethical considerations and accessibility

Further research is needed to confirm the effectiveness of treatment targeting CD39 and related biomarkers. When discussing ethics, it's important to ensure that a wide range of patients are included in future studies to thoroughly examine how well these treatments work and how accessible they are. It's key to address any biases in how clinical trials are set up and ensure that groups who aren't often represented are part of research efforts. Also, we should think about how affordable and available these treatments will be to avoid access once they're proven effective and approved. To create strategies that work well for everyone,

involving patients' input and engaging with the community during the research process is crucial.

5. Conclusion

CD39's diverse roles within the TME make it a promising target for cancer therapy [8,18]. While significant progress has been made in understanding its functions and developing therapeutic strategies, many challenges remain [30,31]. Future research should focus on elucidating the complex interactions between CD39 and the TME, overcoming therapeutic resistance, and integrating CD39-based strategies into precision oncology. By addressing these issues, we can unlock the full therapeutic potential of CD39 and improve outcomes for cancer patients. Successful validation and implementation of CD39-targeted therapies could significantly enhance personalized treatment approaches and lead to better clinical outcomes for patients suffering from various cancers.

Funding

No funding was received for this work.

CRediT authorship contribution statement

Theia Minev: Writing – review & editing, Visualization. **Shengwen Shao:** Writing – original draft, Investigation, Data curation. **Wenxue Ma:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Investigation, Data curation, Conceptualization. **Qiongyan Zhou:** Writing – original draft, Investigation, Data curation.

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.

Acknowledgements

The authors thank Professor Suling Xu for her thorough review and comments.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

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Qiongyan Zhou
Department of Dermatology, The First Affiliated Hospital of Ningbo University School of Medicine, Ningbo, Zhejiang 315020, China

Shengwen Shao
Institute of Microbiology and Immunology, Huzhou University School of Medicine, Huzhou, Zhejiang 313000, China

Theia Minev
Cure Science Institute, San Diego, CA 92121, USA

Wenxue Ma*
Department of Medicine, Sanford Stem Cell Institute and Moores Cancer Center, University of California San Diego, La Jolla, CA 92093, USA

* Corresponding author.
E-mail address: wma@health.ucsd.edu (W. Ma).