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| RESEARCH ARTICLE

Application of Single-Cell RNA Sequencing Technology: Advancing Targeted Fatty Acids for Antitumor Therapy

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| ABSTRACT

The occurrence and progression of tumors are closely linked to the abnormal metabolic mechanism of fatty acids. In tumor cells, fatty acids are highly expressed and provide molecular structural substances for cells, thereby sustaining tumor growth. In previous experiments, researchers cultured cells in a fatty acid-deficient environment and analyzed the growth status of the cells in batches. These studies confirmed that fatty acids play crucial roles in tumorigenesis and have spurred research on targeted regulation for tumor therapy. However, traditional cellular and molecular experiments have certain limitations, making it difficult to resolve the key issue of metabolic heterogeneity among different subpopulations of tumor cells. This limitation has contributed to the failure of targeted therapies to achieve long-lasting therapeutic effects in the treatment of some solid tumors. In contrast, single-cell RNA sequencing (scRNA-seq) technology can analyze gene expression profiles at the single-cell level, overcoming the constraints of traditional methods, and has thus been widely applied in research on tumor metabolism. This technology can accurately identify tumor cell subpopulations with specific phenotypes (such as cancer cell subpopulations with high expression of fatty acid synthase and radiotherapy-resistant glioblastoma cell subpopulations dependent on fatty acid oxidation), clarify the remodeling effects of metabolic heterogeneity on the tumor microenvironment, and provide a detailed molecular mechanism basis for research on targeted tumor therapy. Consequently, it can effectively address the problem of metabolic heterogeneity in tumor cells. In the future, we can integrate scRNA-seq with technologies such as lipidomics and spatial transcriptomics to promote its clinical translation, guide personalized targeted therapy, and provide a precise and efficient new strategy for metabolic targeted therapy in tumors.

| KEYWORDS

Single-cell RNA sequencing technology; Fatty acids; Metabolic heterogeneity; Cancer; Targeted therapy

| ARTICLE INFORMATION

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1. Introduction

The occurrence and progression of tumors are accompanied by complex metabolic reprogramming, with abnormal regulation of fatty acid metabolism being particularly prominent. Unlike normal cells, which rely primarily on exogenous fatty acids, tumor cells fulfil their energy demand (ATP), which they require for rapid proliferation, membrane structural components (phospholipids), and signalling molecules by increasing de novo fatty acid synthesis and activating fatty acid oxidation (FAO) and other pathways. Studies have shown that when patients suffer from ovarian cancer, the levels of unsaturated fatty acids (UFAs) are significantly higher than those in healthy individuals are, and the expression levels of fatty acid-related enzymes such as stearoyl-CoA desaturase-1 (SCD1) and acyl-CoA 6-desaturase (FADS2) also increase, which are positively correlated with the oncogenic potential of ovarian cancer cells. Conversely, when drugs are used to inhibit the expression of SCD1/FADS2, the growth rate of tumors decreases, and the formation of cancer stem cells (CSCs) is inhibited [1]. This characteristic of "metabolic addiction" makes the specific regulation of fatty acid metabolism a potential target for tumor therapy.

In response, researchers have conducted many studies on the targeted regulation of fatty acids. An analysis of the mechanism of lipids in the relationship between tumors and fatty acids revealed that the mechanism controlling the degree of lipid saturation between monounsaturated fatty acids (MUFAs) and saturated fatty acids (FAs) is a key process in cellular metabolism. On the basis of these findings, the team developed a targeted SCD inhibitor (SCDi) to inhibit the growth of gliomas in vivo [2]. Additionally, other research groups have developed therapeutic strategies for glioblastoma by targeting ELOVL2 inhibition and casein kinase 1ε (CK1ε) inhibition, which significantly contribute to inhibiting tumor growth at the metabolic level [3][4].

The aforementioned targeted regulatory therapeutic regimens are all derived from research based on traditional cellular and molecular experiments. Although these regimens demonstrate relatively good efficacy in inhibiting tumor growth, which is limited by challenges such as the metabolic heterogeneity of tumor cells and the complexity of the microenvironment, patients still face issues such as poor prognosis and even tumor recurrence during treatment.

The emergence of single-cell RNA sequencing (scRNA-seq) technology has overcome the limitations imposed by the challenges mentioned above. By dissociating solid tumor cells, this technology analyzes gene expression profiles at the single-cell level, revealing the metabolic heterogeneity of cell subpopulations. This enables tracking of cell state transitions and identification of tumor subpopulation cells with distinct phenotypes. In recent years, scRNA-seq technology has been widely applied in tumor metabolism research. Relevant studies have used this technology to identify tumor stem cell subpopulations with specific metabolic phenotypes, elucidate the metabolic regulatory mechanisms of tumor cells, and provide a detailed molecular mechanism basis for tumor therapy. Therefore, combining scRNA-seq with targeted metabolic regulation research can not only accurately identify different subpopulations of tumor cells and their specific phenotypes but also increase the effectiveness of targeted regulation of cellular metabolic functions within the complex tumor microenvironment, offering a reliable foundation for the development of antitumor drugs.

2. Research Progress on Fatty Acids and Tumors

Fatty acids serve as essential energy sources and structural components of cells in most species, including humans. They are vital for the production of adenosine triphosphate (ATP) and the synthesis of new lipid metabolites. Studies have demonstrated that incubating cells in medium containing lipoprotein-deficient serum results in significant growth inhibition and cell death. However, supplementing the serum with very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), or high-density lipoprotein (HDL) can partially restore the growth rate of BCR-Abl-transformed precursor B cells. These findings suggest that the presence of lipoproteins can promote the growth of tumor cells. [5] Additionally, dysregulation of fatty acid metabolism contributes to various diseases, including arteriosclerosis, diabetes, and fatty liver. In particular, the upregulation of fatty acid levels is associated with an increased risk of cancer, as fatty acids regulate multiple biological functions, including maintaining the structure of cancer cell membranes and transmitting oncogenic signals. These findings have led to the widespread recognition that fatty acids play a critical role in the pathogenesis of human malignant tumors and cancer-related diseases.

On this basis, researchers have conducted relevant studies. The Badr laboratory discovered that a group of enzymes called stearoyl-CoA desaturases (SCDs), which regulate the reversible conversion between monounsaturated and saturated fatty acids, are essential for the growth of glioblastoma (GBM). In their study, after glioma cells were treated with SCD-targeting shRNA or SCD inhibitors (SCDi), their growth rate in vivo was inhibited. Furthermore, the stem cell frequency of glioma cells in the limiting dilution assay was markedly lower than that in the control group. These findings, along with those of other related studies, not only confirm the tumor-promoting role of fatty acids but also drive the launch of many studies on targeted metabolic regulation.

However, despite the efforts of researchers in the development of SCDis, a major challenge remains during treatment: the SCD activity in glioblastoma can persist through a FOSB-mediated escape mechanism. This highlights the heterogeneity of glioblastoma, which complicates the advancement of research on targeted metabolic regulation [2].

Tumor heterogeneity is one of the hallmarks of cancer and a significant challenge in the field of oncology. It describes the diversity of cell populations both between tumors of the same type in different patients (intertumor heterogeneity) and within a single tumor (intratumor heterogeneity) and is one of the greatest obstacles to the development of drugs for targeted metabolic regulation. The experiments described above utilized traditional cellular and molecular methods to analyze metabolic processes in a bulk manner, generating metabolic data in aggregate and examining the close relationship between fatty acid metabolism and tumorigenesis from an overall perspective. On the basis of these bulk analyses, researchers have developed drugs aimed at targeted metabolic regulation to treat tumors. However, owing to the metabolic heterogeneity of tumor cells, these targeted drugs often fail to produce sustained therapeutic effects. Consequently, traditional cellular and molecular approaches are limited by tumor heterogeneity and cannot account for differences in phenotypes and metabolic processes among tumor subpopulations. This limitation adversely affects the efficacy of targeted therapies and leads to poor patient prognosis.

Under these circumstances, single-cell RNA sequencing (scRNA-seq) technology has emerged as a promising solution. Through scRNA-seq analysis, we can identify cancer cell subpopulations with specific phenotypes, such as those with high expression of fatty acid synthesis genes, thereby distinguishing differences between cell subpopulations. Furthermore, we can accurately capture dynamic metabolic changes in stem cell subpopulations, effectively address the challenge of metabolic heterogeneity in tumor cells within cancer research and identify directions for the development of targeted therapies.

3. Overview of single-cell RNA sequencing technology

In recent years, single-cell RNA sequencing technology has advanced rapidly and has gradually become the preferred sequencing technology for researchers in the field of the tumor immune microenvironment. The core principle of this technology involves isolating individual cells, extracting RNA, constructing a complementary DNA (cDNA) library, and performing sequencing to ultimately obtain the gene expression profile of each cell. The technical process can be divided into five key steps: sample preparation, single-cell isolation, RNA amplification, sequencing, and data analysis. The coordination of these steps determines the resolution and reliability of the resulting data.

In their research, Ye et al. compared six software packages that implement this analysis technology, including BASiCS, Brennecke, scLVM, scran, scVEGs, and Seurat, all of which are highly variable gene (HVG) detection methods. They discussed the differences and potential issues among these methods and ultimately reported that scran demonstrates excellent clustering performance, a stable number of HVG detections, good average independence, and favorable runtime. Moreover, this study confirmed that single-cell RNA sequencing (scRNA-seq) technology enables RNA sequencing at the single-cell level, allowing for the investigation of RNA expression differences between individual cells and providing more biological insights than traditional methods do [6].

4. Application of single-cell RNA sequencing technology

In recent years, single-cell RNA sequencing technology has been extensively applied in tumor research.

To investigate cell diversity and the microenvironment composition in hepatocellular carcinoma (HCC), Liang et al. conducted a series of experiments. They generated single-cell RNA sequencing (scRNA-seq) data from HCC tumor tissues and performed single-cell transcriptomic analysis to identify the cell types present in the HCC samples. On the basis of these data, they concluded that, compared with those in reference cells (endothelial cells and fibroblasts), DNA insertions in hepatocytes occur mainly on chromosomes 1, 2, 3, 6, 7, and 20, whereas deletions are found mainly on chromosomes 1, 4, 5, 12, 14, 15, and 19. Additionally, Liang et al. performed subclustering analysis on 2,334 hepatocytes, confirming the intratumor heterogeneity of HCC. They also identified a hepatocyte cluster, termed C4, which exhibits high proliferative activity and characterized this clustered cell as a malignant proliferating cell [7].

In another study investigating the drug resistance mechanisms of circulating tumor cells, researchers utilized RNA-seq data derived from prostate cancer CTCs as a proof of concept. The experiment introduced and validated our aggregation framework, which suggested mechanisms of resistance to androgen deprivation therapy, and summarized the results at both the individual patient and treatment group levels. Notably, the other three methods employed in the study were unable to be used to research cell-specific transcriptional dynamics. The unique advantage of this method lies in its ability to enable interpretation and discovery at the single-cell, intrapatient, and intratreatment group levels while also facilitating robust cross-group comparisons [8].

Single-cell RNA sequencing (scRNA-seq) technology has also been used in experiments investigating the transcriptional heterogeneity of organ-specific metastasis in human gastric cancer (GC). Hai et al. collected a total of 10 samples from 6 GC patients. In their study, freshly resected biopsies were divided into two parts: one for scRNA-seq analysis and the other for pathological and histological evaluation. Finally, analysis of the scRNA-seq data revealed significant variation in the proportion of each cell lineage among different primary tumors and metastases. Using these data, researchers have identified rare tumor types in primary GC, intratumor subclones, and extensive reprogramming within the tumor microenvironment (TME), revealing the heterogeneity of GC. Importantly, this single-cell resolution analysis characterized the features of GC peritoneal dissemination by investigating peritoneal carcinomatosis. Additionally, Wang et al. applied this technology to analyze the tumor cell lineages in GC peritoneal carcinoma, demonstrating the diversity of cancer cell states [9].

In general, single-cell RNA sequencing (scRNA-seq) is a powerful and effective tool for analyzing cellular heterogeneity and identifying functional subpopulations. This technology can help address the challenge of tumor cell heterogeneity and advance research on targeted drug therapies for cancer.

5. Combination of single-cell RNA sequencing technology and targeted regulation of fatty acid metabolism

It has been reported that adipocyte-related molecules promote cancer cell metastasis by regulating cancer cell metabolism. Miranda et al. demonstrated that salt-inducible kinase 2 (SIK2) plays a crucial role in adipocyte-induced ovarian cancer metastasis. These studies indicate that lipid metabolism in the tumor microenvironment (TME) is regulated by complex processes involving cancer cells, adipocytes, and surrounding cells. Therefore, in this study, clarifying the interactions between cancer cells and surrounding stromal cells within the ovarian cancer microenvironment will provide useful insights for developing new therapeutic strategies for ovarian cancer [10]. Perhaps we can apply single-cell RNA sequencing technology to analyze differences among various cell subpopulations at the single-cell level. Ultimately, data obtained from this technology may facilitate the development of targeted regulatory drugs that specifically modulate fatty acid metabolism pathways, enabling the precise elimination of ovarian cancer cells.

In addition to its application at the metabolic level, Dan et al., in their study of the bone marrow microenvironment in pre-B acute lymphoblastic leukemia (B-ALL), discovered through the use of single-cell RNA sequencing technology that monocytes may contribute to B-ALL development via leukemia-induced inflammatory responses in the bone marrow of patients [11]. The introduction of single-cell RNA sequencing has significantly advanced experimental progress. Therefore, we aimed to apply scRNA-seq technology to tumor research. By using sc-RNA sequencing to analyze cellular and molecular data at the single-cell level, we can develop drugs that target fatty acid metabolism with greater therapeutic efficacy and precision, thereby advancing the potential of tumor therapy.

6. Conclusions and prospects

The synthesis and metabolism of fatty acids are closely linked to tumorigenesis. Therefore, research focused on the targeted regulation of fatty acid metabolism for tumor therapy holds great promise. Analysis and validation through the aforementioned experiments demonstrated that the application of single-cell RNA sequencing (scRNA-seq) technology can significantly advance tumor research. This technology addresses a critical limitation of traditional cellular and molecular methods: the metabolic heterogeneity of tumor cells. Naturally, the introduction of scRNA-seq alone is not sufficient; we need to combine it with interdisciplinary approaches. By combining scRNA-seq technology with fields such as lipidomics and spatial transcriptomics, we can more effectively investigate how to specifically regulate lipid metabolism through targeted drugs to inhibit tumor growth. In addition to cross-omics integration, it is essential to translate theoretical findings into clinical practice. After extensive experimental validation of efficacy and safety, these insights should be applied clinically to promote advancements in tumor therapy research.

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References

[1]Xuan Y, Wang H, Yung MM, Chen F, Chan WS, Chan YS, Tsui SK, Ngan HY, Chan KK, Chan DW. SCD1/FADS2 fatty acid desaturases equipoise lipid metabolic activity and redox-driven ferroptosis in ascites-derived ovarian cancer cells. Theranostics. 2022 Apr 24;12(7):3534-3552. doi: 10.7150/thno.70194. PMID: 35547771; PMCID: PMC9065188.
[2]Miska J, Chandel NS. Targeting fatty acid metabolism in glioblastoma. J Clin Invest. 2023 Jan 3;133(1):e163448. doi: 10.1172/JCI163448. PMID: 36594473; PMCID: PMC9797338.
[3] Gimple RC, Kidwell RL, Kim LJY, Sun T, Gromovsky AD, Wu Q, Wolf M, Lv D, Bhargava S, Jiang L, Prager BC, Wang X, Ye Q, Zhu Z, Zhang G, Dong Z, Zhao L, Lee D, Bi J, Sloan AE, Mischel PS, Brown JM, Cang H, Huan T, Mack SC, Xie Q, Rich JN. Glioma Stem Cell-Specific Superenhancer Promotes Polyunsaturated Fatty-Acid Synthesis to Support EGFR Signaling. Cancer Discov. 2019 Sep;9(9):1248-1267. doi: 10.1158/2159-8290.CD-19-0061. Epub 2019 Jun 14. PMID: 31201181; PMCID: PMC6785242.
[4] Varghese RT, Young S, Pham L, Liang Y, Pridham KJ, Guo S, Murphy S, Kelly DF, Sheng Z. Casein Kinase 1 Epsilon Regulates Glioblastoma Cell Survival. Sci Rep. 2018 Sep 11;8(1):13621. doi: 10.1038/s41598-018-31864-x. PMID: 30206363; PMCID: PMC6134061.
[5] Liu Q, Luo Q, Halim A, Song G. Targeting lipid metabolism of cancer cells: A promising therapeutic strategy for cancer. Cancer Lett. 2017 Aug 10;401:39-45. doi: 10.1016/j.canlet.2017.05.002. Epub 2017 May 17. PMID: 28527945.
[6] Yip SH, Sham PC, Wang J. Evaluation of tools for highly variable gene discovery from single-cell RNA-seq data. Brief Bioinform. 2019 Jul 19;20(4):1583-1589. doi: 10.1093/bib/bby011. PMID: 29481632; PMCID: PMC6781572.
[7] Liang J, Chen W, Ye J, Ni C, Zhai W. Single-cell transcriptomics analysis reveals intratumoral heterogeneity and identifies a gene signature associated with prognosis of hepatocellular carcinoma. Biosci Rep. 2022 Feb 25;42(2):BSR20212560. doi: 10.1042/BSR20212560. PMID: 35169832; PMCID: PMC8881646.

[8] Schissler AG, Li Q, Chen JL, Kenost C, Achour I, Billheimer DD, Li H, Piegorsch WW, Lussier YA. Analysis of aggregated cell–cell statistical distances within pathways unveils therapeutic-resistance mechanisms in circulating tumor cells. Bioinformatics. 2016 Jun 15;32(12):i80-i89. doi: 10.1093/bioinformatics/btw248. PMID: 27307648; PMCID: PMC4908332.
[9] Jiang H, Yu D, Yang P, Guo R, Kong M, Gao Y, Yu X, Lu X, Fan X. Revealing the transcriptional heterogeneity of organ-specific metastasis in human gastric cancer using single-cell RNA Sequencing. Clin Transl Med. 2022 Feb;12(2):e730. doi: 10.1002/ctm2.730. PMID: 35184420; PMCID: PMC8858624.
[10] Yoon H, Lee S. Fatty Acid Metabolism in Ovarian Cancer: Therapeutic Implications. Int J Mol Sci. 2022 Feb 16;23(4):2170. doi: 10.3390/ijms23042170. PMID: 35216285; PMCID: PMC8874779.
[11] Anderson D, Skut P, Hughes AM, Ferrari E, Tickner J, Xu J, Mullin BH, Tang D, Malinge S, Kees UR, Kotecha RS, Lassmann T, Cheung LC. The bone marrow microenvironment of pre-B acute lymphoblastic leukemia at single-cell resolution. Sci Rep. 2020 Nov 5;10(1):19173. doi: 10.1038/s41598-020-76157-4. PMID: 33154494; PMCID: PMC7645756.