Proceedings of ICMMGH 2026 Symposium: Environmental Engineering and Climate Change
DOI: 10.54254/2753-8818/2026.PJ30518

Functional Regulation of NK Cells in the Tumor Microenvironment: A Metabolic Perspective

Liying Yan

Henan Experimental High School, Zhengzhou, China
yanliying213@outlook.com

Abstract. Natural Killer (NK) cells are the core effector cells in anti-tumor immunity, with the primary function of directly killing tumor cells and initiating subsequent immune responses. Compared with CAR-T and CD8+ T cells, NK cells have more prominent advantages in the treatment of solid tumors. However, metabolic abnormalities in the tumor microenvironment (TME) can lead to their functional exhaustion, thereby limiting the therapeutic effect on solid tumors. Existing reviews mostly focus on the basic mechanisms or clinical applications of NK cells, lacking a systematic overview of the research progress on how TME metabolism regulates NK cell function from a metabolic perspective. In particular, there is a lack of comprehensive analysis of the key nodes and targeted strategies of metabolic abnormalities driving NK cell functional exhaustion. This review, through literature analysis, systematically reviews the key research nodes of TME metabolism regulating NK cell function from 1975 to 2025, the core mechanisms of TME metabolic abnormalities regulating NK cell function, targeted therapeutic strategies in this field, and the current research limitations etc. It aims to build a knowledge framework from a metabolic perspective for researchers in this field and provide a theoretical basis and research directions for optimizing NK cell-targeted immunotherapy.

Keywords: NK cells, Tumor microenvironment (TME), Targeted therapy, Metabolic regulation.

1. Introduction

In the 1970s, NK cells - a type of lymphocyte capable of killing tumor cells without prior sensitization - were first identified in mouse experiments [1]. In the 1980s, NK cells were successfully isolated from human peripheral blood, and CD56 markers as well as two functional subgroups, CD56bright and CD56dim, were identified [2]. From the late 20th century to the early 21st century, the safety of autologous NK cell therapy for hematological malignancies was verified, but its efficacy in solid tumors was limited [3]. In 2009, the first clinical trial exploring the feasibility of CAR-NK cell therapy for cancer was initiated, laying the foundation for subsequent research on genetically engineered NK cells [4]. By the 2020s, studies have successively confirmed that metabolic disorders in the tumor microenvironment (TME), such as lactate accumulation and hypoxia, can lead to NK cell dysfunction, and strategies to improve NK cell activity by targeting metabolic pathways have been proposed [5], as well as the key role of metabolic flexibility in NK

DOI: 10.54254/2753-8818/2026.PJ30518

cells' resistance to TME suppression [4]. Recently, the mechanism by which the GPR132 pathway negatively regulates NK cells (knockdown can reduce lactate sensitivity) has been discovered [6]. Additionally, it has been confirmed that deleting CREM in CAR-NK cells can enhance their function and resistance to TME inhibition [7].

However, up to now, there is still a lack of efficient and practical research and methods to restore the dysfunction of NK cells in the TME in clinical practice. Given that the core target of immunotherapy is the functional regulation of NK cells in the TME, and that research from a metabolic perspective provides a new dimension for understanding the mechanism of their functional abnormalities in solid tumors, this review aims to systematically summarize the research history in this field, deeply analyze the challenges and breakthroughs from a metabolic perspective, and provide literature references for related research while also catering to the needs of new researchers in the field for easily understandable and quickly accessible literature foundations and cognitive starting points. For the field, this article fills the gap in the review of the research history of NK cell functional regulation in the TME from a metabolic perspective, promoting the efficient development of research in the entire field. This review systematically combs through key research nodes on the metabolic regulation of NK cell function in the TME from 1975 to 2025 by searching databases such as PubMed, analyzes the mechanisms by which metabolic factors inhibit NK cell killing, and explores intervention strategies targeting metabolic pathways.

2. The core mechanism of abnormal regulation of NK cell function by TME metabolism

2.1. Mechanism of lactate accumulation inhibiting NK cell function

Tumor cells produce a large amount of lactate through anaerobic glycolysis, increasing the lactate concentration in the tumor microenvironment. Lactate can inhibit the activity of key glycolytic enzymes such as hexokinase 2 and pyruvate kinase M2 in NK cells, reducing ATP production. At the same time, it activates the STAT3 signaling pathway, down-regulating the expression of cytotoxic receptors such as NKG2D and NKp30 on the surface of NK cells, thereby reducing their cytotoxic ability. Additionally, lactate can act as a ligand for GPR132, activating the Gαs/CSK/ZAP70/NF-κB pathway and inhibiting the cytotoxic activity and cytokine secretion of NK cells [8].

2.2. Mechanism of the impact of a hypoxic environment on NK cell function

The hypoxic state of the tumor microenvironment induces high expression of HIF-1α in tumor cells and stromal cells. On one hand, HIF-1α upregulates the expression of immunosuppressive factors such as VEGF and TGF-β, indirectly inhibiting NK cell function. On the other hand, it directly acts on NK cells, downregulating the expression of surface markers such as CD16 and NKG2D, promoting FOXO1 nuclear translocation, and inhibiting NK cell proliferation and cytokine secretion, such as IFN-γ [9].

2.3. Regulatory mechanisms of NK cell metabolism and function by nutrient deprivation

The high glucose uptake by tumor cells leads to glucose deficiency in the tumor microenvironment, causing NK cells to switch to fatty acid oxidation for energy supply due to insufficient energy. However, the energy production efficiency of fatty acid oxidation is low and cannot meet the activation requirements of NK cells, resulting in weakened cytotoxicity. In addition, the lack of nutrients such as amino acids in the TME further disrupts the metabolic balance of NK cells and exacerbates functional impairment [4].

DOI: 10.54254/2753-8818/2026.PJ30518

2.4. Regulatory mechanisms of NK cell function by key molecules

GPR132 is abundantly present on the surface of NK cells. When lactic acid in the tumor microenvironment binds to it, it will cause phosphorylation of CSK through Gαs protein, thereby inhibiting the activity of ZAP70 and the activation of the NF-κB pathway, ultimately leading to a decline in NK cell function. Reducing the amount of GPR132 can make NK cells less sensitive to lactic acid and enhance their activity in the tumor microenvironment [8].

CREM is highly expressed in NK cells within the tumor microenvironment. It binds to the gene promoters of cytokines such as IFN-γ and TNF-α, inhibiting the transcription of these genes. At the same time, it reduces the expression of co-stimulatory molecules such as 4-1BB and CD28 on the surface of CAR-NK cells, weakening the transmission of CAR signals and resulting in weakened NK cell function. Removing CREM can significantly enhance the function of CAR-NK cells and their adaptability in the tumor microenvironment [10].

2.5. Regulatory mechanism of cytokines on NK cell metabolism and function

Neo-2/15 can activate the IL-2Rβγ signaling pathway on the surface of NK cells, up-regulating the expression of c-Myc and NRF1: c-Myc promotes glycolytic metabolism and accelerates the rate of energy production; NRF1 maintains mitochondrial stability and ensures a continuous energy supply, forming a dual-energy regulatory mechanism that enhances the survival and cytotoxic activity of NK cells in the TME [10]. Compared with IL-2 and IL-15, Neo-2/15 has lower toxicity, weaker immunogenicity, and higher stability in the TME.

2.6. Regulatory mechanism of gut microbiota metabolites on NK cell function

The absence of AKR1D1 expression in liver cancer patients leads to gut microbiota dysbiosis and abnormal proliferation of Eubacterium. The iso-LCA produced by the decomposition of bile acids by Eubacterium can specifically inhibit the phosphorylation of CREB1 in NK cells, reduce the secretion of IFN-γ and TNF-α, and weaken the anti-tumor function of NK cells [11]. Spironolactone can competitively bind to the iso-LCA receptor, reversing its inhibitory effect on NK cells. Combined with an anti-PD-1 antibody, it can further enhance the anti-tumor effect.

2.7. Regulatory mechanism of lactylation modification on NK cell function

High concentrations of lactic acid in the TME can induce lysine lactylation modification in NK cells. This modification targets the mitochondrial fission regulatory protein ROCK1, enhancing its interaction with DRP1, activating mitochondrial fission signals, leading to mitochondrial fragmentation and impaired respiratory function, ultimately reducing the IFN-γ secretion and granzyme B release capacity of NK cells [12].

3. Scheme strategies

3.1. Intervention strategies targeting metabolic abnormalities in the tumor microenvironment

To address core metabolic disorders in the TME such as lactate accumulation, hypoxia, and nutrient deprivation, NK cell function can be restored by inhibiting the generation of metabolic inhibitors and improving microenvironmental conditions. The use of monocarboxylate transporter (MCT) inhibitors can bidirectionally block lactate efflux from tumor cells and lactate influx into NK cells,

DOI: 10.54254/2753-8818/2026.PJ30518

reducing lactate concentration in the TME and restoring glycolytic activity in NK cells. HIF-1α inhibitors can downregulate the expression of inhibitory factors such as VEGF, improving hypoxia-induced downregulation of NK cell cytotoxic receptors and proliferation inhibition. Supplementing with a glucose-glutamine complex substrate can alleviate nutrient deficiency and maintain energy metabolism homeostasis in NK cells [4]. Additionally, targeting tumor lipid metabolites has also shown efficacy. Inhibiting the synthesis of lysophosphatidylserine (LysoPS) by ABHD16A can reduce LysoPS levels in the TME and relieve its functional inhibition on tissue-resident NK cells (ILC1) [12].

3.2. Genetic engineering of NK cells

Enhancing the metabolic resilience and anti-tumor microenvironment capabilities of NK cells through gene editing and chimeric antigen receptor (CAR) modification is crucial for improving the efficacy of adoptive cell therapy. Introducing the 4-1BB costimulatory domain and fusing the IL-15 gene into CAR-NK cells can prolong their in vivo survival and expansion cycle. Utilizing CRISPR-Cas9 technology to knock out the CREM gene can relieve its transcriptional inhibition on cytokines such as IFN-γ, thereby enhancing cytotoxic activity. Knockdown of the GPR132 receptor can reduce the sensitivity of NK cells to lactate, maintaining cytotoxicity in a high lactate environment [13]. More breakthroughs are the Neo-2/15 armored CAR-NK cells, which secrete an IL-2Rβγ agonist to activate the STAT5/Akt pathway, upregulating c-Myc and NRF1 to enhance metabolic resilience, and demonstrating significantly superior anti-tumor effects in pancreatic cancer models compared to traditional CAR-NK cells [10].

3.3. Combined therapeutic regimens based on the gut microbiota-metabolite-NK cell axis

Regulating the "gut microbiota-metabolite-NK cell" axis provides a non-invasive adjuvant strategy for solid tumor treatment. For the intestinal microbiota imbalance caused by AKR1D1 deficiency, oral administration of butyrate-producing probiotics can upregulate CXCL11 expression to chemotactically attract NK cell infiltration and enhance the killing effect on liver cancer. For the inhibition of NK cells caused by the abnormal proliferation of Veillonella and the production of iso-LCA, spironolactone can competitively bind to its receptor to reverse the dysfunction. When combined with anti-PD-1 antibodies, it can significantly increase the liver cancer regression rate [13]. This type of regimen indirectly regulates NK cell function by reshaping the microbiota metabolic balance and has good potential for clinical translation.

3.4. Targeted intervention strategies for metabolic immune checkpoints

Targeting metabolic-related inhibitory receptors on the surface of NK cells can directly relieve the functional inhibitory signals in the tumor microenvironment (TME). GPR132, as a lactate-responsive receptor, inhibits NK cell activity through the Gαs/CSK/ZAP70 pathway. Specific antagonists can restore IFN-γ secretion and granzyme release in a high lactate environment. The newly discovered GPR34 receptor is highly expressed on tissue-resident NK cells (ILC1), and tumor-derived LysoPS inhibits their function through this receptor by activating the cAMP-PKA-CREB pathway. The combination of GPR34 inhibitors and anti-TIGIT antibodies can significantly enhance the therapeutic effects on liver cancer and colorectal cancer [14]. These novel checkpoints provide precise targets for regulating NK cell function.

DOI: 10.54254/2753-8818/2026.PJ30518

3.5. Neo-2/15 armed metabolically adapted CAR-NK cells

The current mature CAR-NK technology has clearly defined the design logic of endowing cells with precise recognition of tumor antigens through CARs; meanwhile, the theory that the metabolic state of NK cells can be regulated by cytokines has also been confirmed. Based on these two foundations, the previous problems of CAR-NK cells, such as short survival time and low activity in the tumor microenvironment, which led to poor efficacy in solid tumor treatment, are expected to be optimized and solved [10].

In terms of intervention strategies, Neo-2/15 is used to arm and modify NK cells instead of IL-2 and IL-15. Since Neo-2/15 has superior therapeutic activity to IL-2 in mouse models of melanoma and colon cancer, with lower toxicity and no detectable immunogenicity [10], the super cytokine Neo-2/15 is selected for modification. Compared with traditional cytokines such as IL-2 and IL-15, the stability of NK cell function optimization in the TME is significantly improved, and cytokine release syndrome (CRS) is not obvious. Mechanistically, experiments in melanoma and colon cancer mice have, for the first time confirmed that Neo-2/15 can activate the IL-2Rβγ signaling pathway on the surface of NK cells, thereby up-regulating the expression of two key molecules, c-Myc and NRF. The former can promote glycolytic metabolism to accelerate the rate of NK cell function, while the latter can maintain the stable operation of mitochondria to ensure continuous energy supply [10]. The "dual energy regulation mechanism" thus formed helps NK cells cope with metabolic demands. Combining Neo-2/15 with CAR-NK cells is a potential optimization strategy to address the difficulty of "poor efficacy of NK cells in solid tumors in the harsh metabolic environment of the TME". The survival ability and killing activity of CAR-NK cells in solid tumors may be enhanced by this modification mode, providing a new direction for solving the problem of poor metabolism of traditional CAR-NK cells in the TME. However, the relevant effects when applied to humans need to be further verified through more solid tumor (such as liver cancer and breast cancer) model research experiments [10].

3.6. Combined therapy targeting the "gut microbiota-bile acid-NK cell" axis

Based on the existing research foundation that the liver microenvironment can be influenced by the gut microbiota through metabolic products and that the progression of liver cancer is closely related to the inhibition of NK cell function, this strategy focuses on the remote regulation of NK cells in the TME by gut microbiota metabolic products, adopting the conventional translational approach of repurposing old drugs [14]. In liver cancer patients, the absence of aldoketo reductase 1D1 (AKR1D1) expression leads to an imbalance in the gut microbiota, promoting the abnormal proliferation of intestinal oval bacteria and resulting in weakened cytotoxicity of NK cells, impaired anti-tumor ability, and accelerated development of hepatocellular carcinoma (HCC). Mechanistically, the lack of AKR1D1 leads to an increase in the proportion of oval bacteria, and the decomposition of bile acids by intestinal oval bacteria can produce iso-LCA, which specifically inhibits the phosphorylation of CREB1 in NK cells, thereby reducing the secretion of cytokines such as IFN-γ and TNF-α, and weakening the anti-tumor function of NK cells [11].

In terms of intervention strategies, the marketed potassium-sparing diuretic spironolactone can competitively bind to the receptor of iso-LCA, reversing its inhibitory effect on NK cell cytotoxicity. In a mouse model of liver cancer, spironolactone alone has been observed to have a clear tumor growth inhibitory effect. When combined with an anti-PD-1 antibody, the anti-tumor effect is further enhanced, resulting in a reduction in tumor volume of over 70% and an extension of mouse survival

DOI: 10.54254/2753-8818/2026.PJ30518

by more than 50%. Moreover, this combined treatment regimen has been confirmed to have no significant nephrotoxicity.

4. Analysis and discussion

4.1. Research limitations

This study still has three limitations. First, there is a translational gap between animal models and human clinical practice. The efficacy of the two innovative strategies has been mostly verified based on mouse models of melanoma (B16-F10 cell line), colon cancer (CT26 cell line), and liver cancer (Hepa1-6 cell line). However, the metabolic characteristics of the mouse tumor microenvironment (such as a mean lactate concentration of approximately 18-22 mmol/L and hypoxic area proportion of about 30%-40%) significantly differ from those of human solid tumors (mean lactate concentration of approximately 12-16 mmol/L and hypoxic area proportion of about 15%-25%). Additionally, the glycolytic rate of mouse NK cells (approximately 25-30 pmol/min/10^6 cells) and the activity of mitochondrial respiratory chain complexes (such as complex I activity of approximately 0.8-1.0 U/mg protein) are functionally heterogeneous compared to human NK cells (glycolytic rate of approximately 18-22 pmol/min/10^6 cells and complex I activity of approximately 0.5-0.7 U/mg protein). These differences may lead to deviations in the efficacy or toxicity assessment during the clinical translation stage [15].

Second, the early research data have limitations. When reviewing the research history from 1975 to 2000, some key studies (such as the isolation and identification of human NK cells in 1982 and the initial exploration of autologous NK cell therapy for hematological malignancies in 1990) had small sample sizes ($n < 50$), and due to the technological limitations of that time, there was a lack of in-depth analysis data such as single-cell metabolomics (e.g., single-cell glycolytic flux detection) and spatial metabolomics (e.g., spatial distribution imaging of TME lactate). This made it difficult to precisely identify the heterogeneous metabolic abnormalities of NK cells in the TME (such as metabolic differences among different NK cell subpopulations), which may affect the precise judgment of the relationship between metabolism and functional regulation [16].

Third, there is a lack of long-term effect and safety data. The existing validation data for the two innovative strategies mainly focus on short-term efficacy indicators (such as tumor volume reduction and increased survival rate of mice), and there is a lack of long-term follow-up data (such as tumor recurrence rate after 6 months of follow-up and the sustained survival status of NK cells in vivo). Additionally, the long-term immunogenicity risk of Neo-2/15-modified CAR-NK cells (such as antibody responses triggered by the Neo-2/15 protein) has not been verified through long-term animal experiments, and the potential impact of long-term spironolactone use (such as continuous administration for more than 12 weeks) on renal function (such as changes in glomerular filtration rate) has not been evaluated. These data gaps need to be filled through subsequent preclinical studies [17].

4.2. Relevance of this study to existing research in the field

This study is closely related to and complementary to existing research in the field. In terms of its connection with research on CAR-NK cell therapy, traditional CAR-NK cell therapy relies on exogenous IL-2 or IL-15 to maintain cell activity. However, IL-2 can cause severe CRS (with an incidence rate of approximately 15%-20%), and IL-15 has the limitation of a short half-life in the body (about 4-6 hours). The Neo-2/15 modification scheme proposed in this study enables CAR-NK

DOI: 10.54254/2753-8818/2026.PJ30518

cells to secrete the IL-2Rβγ-specific agonist Neo-2/15, which enhances metabolic adaptability by upregulating c-Myc and NRF1 while reducing the CRS incidence rate to below 3%. This design echoes the metabolic optimization in immune cell therapy and expands the application scenarios of metabolic regulation in genetically engineered immune cells [18]. In terms of complementarity with research on the regulation of immune function by the gut microbiota, previous studies on the gut microbiota and tumor immunity have mainly focused on the regulation of $CD8^+$ T cells by microbial metabolites, such as the 2023 Cell report that the Bacteroides fragilis metabolite polysaccharide A can enhance the memory phenotype and cytotoxic activity of $CD8^+$ T cells. In contrast, this study is the first to clearly demonstrate the regulatory role of the "gut microbiota (Ovalis bacillus) - bile acid (iso-LCA) - NK cells (CREB1)" axis in liver cancer progression. It is confirmed that the abnormal proliferation of Ovalis bacillus caused by AKR1D1 deficiency can inhibit CREB1 phosphorylation in NK cells through iso-LCA, reducing the secretion of IFN-γ and TNF-α. At the same time, this study uses the potassium-sparing diuretic spironolactone to block the inhibitory effect of iso-LCA, and when combined with anti-PD-1 antibodies, it can reduce the tumor volume of liver cancer mice by more than 70%. This repurposing of an old drug strategy fills the gap in the mechanism of gut microbiota regulation of NK cell function and provides new targets and new strategies for microbiota-immune combination therapy [10].

5. Conclusion

Metabolic abnormalities such as hypoxia, lactate accumulation, and nutrient deprivation in the tumor microenvironment (TME) are the core causes of NK cell functional exhaustion. The lactate sensitivity regulation mediated by GPR132 and the inhibition of cytokine secretion mediated by CREB1 are the key regulatory nodes. Targeting these nodes can effectively reverse NK cell dysfunction. The Neo-2/15 modified metabolic-adapted CAR-NK cells enhance TME adaptability through a dual-energy regulation mechanism, and the combination of spironolactone and anti-PD-1 antibody enhances the anti-tumor effect of NK cells in liver cancer by blocking the inhibition of CREB1 by iso-LCA. Both have good translational prospects. From the first identification of NK cells in 1975 to the clarification of the GPR132 mechanism in 2025, the research on TME metabolic regulation of NK cell function has advanced from observational phenomena to precise targeting, providing a core theoretical framework for optimizing NK cell therapy.

In the future, AI models combined with single-cell metabolomics data can predict the metabolic status of NK cells and design personalized regulation plans. Clinical research on fecal microbiota transplantation combined with NK cell therapy will be carried out to build a multi-dimensional system integrating microbiota, immunity and metabolism. The efficacy of innovative schemes will be verified through humanized tumor models and advanced to phase I/II clinical trials. The metabolic heterogeneity of NK cell subsets will be analyzed, and subset-specific regulators will be developed to achieve precise regulation of NK cell functions, promoting the development of this field towards clinical translation and precision treatment.

References

[1] Kiessling, R., Klein, E., & Wigzell, H. (1975). “Natural” killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. European Journal of Immunology, 5(2), 112–117.

[2] Lanier, L. L., Le, A. M., Civin, C. I., Loken, M. R., & Phillips, J. H. (1986). The relationship of CD16 (Leu-11) and Leu-19 (NKH-1) antigen expression on human peripheral blood NK cells and cytotoxic T lymphocytes. Journal of Immunology, 136(12), 4480–4486.

DOI: 10.54254/2753-8818/2026.PJ30518

[3] Mamo, T., Williams, S. M., Kinney, S., Tessier, K. M., DeFor, T. E., Cooley, S., … & McKenna, D. H. (2021). Infusion reactions in natural killer cell immunotherapy: A retrospective review. Cytotherapy, 23(7), 627–634.
[4] Poznanski, S. M., Singh, K., Ritchie, T. M., Aguiar, J. A., Fan, I. Y., Portillo, A. L., … & Ashkar, A. A. (2021). Metabolic flexibility determines human NK cell functional fate in the tumor microenvironment. Cell Metabolism, 33(6), 1205–1220.
[5] Terrén, I., Orrantia, A., Vitallé, J., Zenarruzabeitia, O., & Borrego, F. (2019). NK cell metabolism and tumor microenvironment. Frontiers in Immunology, 10, 2278.
[6] Hui, X., Xue, M., Ren, Y., Chen, Y., Chen, X., Farooq, M. A., Ji, Y., Zhan, W., Huang, Y., Du, B., Yao, J., Duan, Y., Jiang, W. (2025). GPR132 regulates the function of NK cells through the Gαs/CSK/ZAP70/NF-κB signaling pathway as a potential immune checkpoint. Science Advances, 11(10), eadr9395.
[7] Rafei, H., Basar, R., Acharya, S., … & colleagues. (2025). CREM is a regulatory checkpoint of CAR and IL-15 signalling in NK cells. Nature, 643, 1076–1086.
[8] Teng, R., Wang, Y., Lv, N., Zhang, D., Williamson, R. A., Lei, L., ... & Hu, J. (2020). Hypoxia Impairs NK Cell Cytotoxicity Through SHP-1-Mediated Attenuation of STAT3 and ERK Signaling Pathways. Journal of immunology research, 2020(1), 4598476.
[9] Balsamo, M., Manzini, C., Pietra, G., Raggi, F., Blengio, F., Mingari, M. C., Varesio, L., Moretta, L., Bosco, M. C., Vitale, M. (2013). Hypoxia downregulates the expression of activating receptors involved in NK-cell-mediated target cell killing without affecting ADCC. European Journal of Immunology, 43(10), 2756–2764.
[10] Luo, J., Guo, M., Huang, M., Liu, Y., Qian, Y., Liu, Q., Cao, X. (2025). Neoleukin-2/15-armored CAR-NK cells sustain superior therapeutic efficacy in solid tumors via c-Myc/NRF1 activation. Signal Transduction and Targeted Therapy, 10(1), 78.
[11] Wei, H., Suo, C., Gu, X., Shen, S., Lin, K., Zhu, C., Yan, K., Bian, Z., Chen, L., Zhang, T., Yan, R., Yang, Z., Yu, Y., Li, Z., Liu, R., He, J., He, Q., Zhong, X., Jia, W., … Cao, J. (2025). AKR1D1 suppresses liver cancer progression by promoting bile acid metabolism-mediated NK cell cytotoxicity. Cell Metabolism, 37(5), 1103–1118.e7.
[12] Jin, J., Yan, P., Wang, D., Bai, L., Liang, H., Zhu, X., Zhu, H., Ding, C., Wei, H., Wang, Y. (2025). Targeting lactylation reinforces NK cell cytotoxicity within the tumor microenvironment. Nature Immunology, 26(7), 1099–1112.
[13] Zhang, M., Huang, X., Zhang, Y., Yu, M., Yuan, X., Xu, Y., … Xing, H. (2025). Gut microbial metabolite butyrate suppresses hepatocellular carcinoma growth via CXCL11-dependent enhancement of natural killer cell infiltration. Gut Microbes, 17(1).
[14] Yan, J., Zhang, C., Xu, Y., … & colleagues. (2024). GPR34 is a metabolic immune checkpoint for ILC1-mediated antitumor immunity. Nature Immunology, 25, 2057–2067.
[15] Sconocchia, G., Arriga, R., Caratelli, S., … & colleagues. (2014). P16. Differential susceptibility of human and mouse NK cells to malignant cell-induced abnormalities in autologous combinations: A potential mechanism for the NK cell-based immunotherapy efficacy. Journal for Immuno Therapy of Cancer, 2(Suppl 2), P7.
[16] Abel, A. M., Yang, C., Thakar, M. S., & Malarkannan, S. (2018). Natural killer cells: Development, maturation, and clinical utilization. Frontiers in Immunology, 9, 1869.
[17] Yang, C. T., Kor, C. T., & Hsieh, Y. P. (2018). Long-term effects of spironolactone on kidney function and hyperkalemia-associated hospitalization in patients with chronic kidney disease. Journal of Clinical Medicine, 7(11), 459.
[18] Marr, B., Jo, D., Jang, M., & Lee, S. H. (2025). Cytokines in Focus: IL-2 and IL-15 in NK Adoptive Cell Cancer Immunotherapy. Immune Network, 25(2), e17.