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Potential Mechanisms Underlying Ferroptosis-Associated NK Cell Dysfunction and Its Regulatory Networks in the Tumor Microenvironment

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Abstract:

Ferroptosis is a regulated form of cell death characterized by iron-dependent lipid peroxidation. Its role in tumor immunity has attracted increasing attention in recent years. Natural killer (NK) cells are important antitumor immune effector cells, whereas metabolic reprogramming and oxidative stress in the tumor microenvironment (TME) may promote their functional exhaustion and ferroptotic cell death. This review summarizes the potential effects of cancer-associated fibroblasts (CAFs), the kynurenine metabolic pathway, and the tumor microenvironment itself on NK cell ferroptosis. Existing studies suggest that CAFs-induced NK cell ferroptosis can occur through dysregulated iron metabolism and ferritinophagy. In addition, the accumulation of kynurenine may further promote iron-dependent lipid peroxidation in NK cells. The amino acid transporter SLC7A5 may participate in this process by mediating kynurenine uptake, although direct evidence remains limited. Moreover, nutrient deprivation, lipid metabolic reprogramming, and redox imbalance in the TME may collectively increase the susceptibility of NK cells to ferroptosis. Ferroptosis of NK cells may be an important mechanism connecting tumor metabolic reprogramming and immune dysfunction, and is expected to become a new direction for immunotherapy intervention.

Keywords: Natural killer cells; Ferroptosis; Tumor microenvironment; Kynurenine; Cancer-associated fibroblasts.

1. Introduction

Ferroptosis has gradually attracted more attention in recent years for studies on cancer biology. Ferroptosis is an iron-dependent mode of regulated cell death caused by lipid peroxidation that has been in-

creasingly recognized as a major reason for the immune evasion of tumors and offers novel targets for anti-cancer drug development [1]. In addition to proliferating, a large number of other papers have also reported that ferroptosis can harm immune cells and thus reduce their function within the tumor microenvironment (TME).

Natural killer (NK) cells are key antitumor effector cells of the innate immune system. Recent studies have suggested that NK cell death in the TME may occur through ferroptosis, and this process is closely related to NK cell functional exhaustion [2]. The activity of immune cells is heavily influenced by the various stromal elements present in the TME, cancer-associated fibroblasts (CAFs) being a prime example. CAFs in the TME can impair the cytotoxic activity and survival of NK cells. This effect may be partly achieved by the mechanism of NK cell ferroptosis [3]. The nutritional metabolism and redox characteristics inherent in the TME itself may also reshape the ferroptosis sensitivity of NK cells and consequently influence ferroptosis-related regulatory processes in these cells.

This review focuses on and systematically discusses the multiple regulatory factors underlying NK cell ferroptosis in the TME. By integrating existing studies and pointing out key evidence gaps, this review aims to provide a new theoretical framework for clarifying the molecular basis of ferroptosis in NK cells, and to provide potential targets for tumor immunotherapy (Table 1).

2. Induction of NK Cell Ferroptosis by Cancer-Associated Fibroblasts

2.1 CAFs-Mediated Modulation of NK Cell Activity within the TME

Cancer-associated fibroblasts are the most abundant stromal cell population in the tumor microenvironment and play important roles in tumor progression and immune regulation [3]. Previous studies indicate that CAFs can suppress cytotoxicity and cytokine secretion of NK cell by releasing multiple immunosuppressive molecules, such as prostaglandin E2 (PGE2) and metabolism-related factors, such as indoleamine 2,3-dioxygenase (IDO) thereby promoting immune escape of tumor cells within the TME [4]. Although the above studies have explained the inhibitory effects of CAFs on NK cells from the perspectives of cytokine signaling and immune regulation, the direct influence of CAFs on the survival status of NK cells has not yet received sufficient attention. With further research of metabolic regulation, the regulatory mechanism of CAFs on immune cells has gradually been further explained in recent years.

Table 1. Regulatory Factors, Molecular Mechanisms and Effects Related to NK Cell Ferroptosis in the Tumor Microenvironment

Regulatory factor	Key mechanisms	Related effects	Ref.
CAFs themselves	Iron-export-related molecules	Increase free iron levels in the tumor microenvironment	[5]
CAF-secreted factors	FSTL1–DIP2A–p38–NCOA4 axis	Promote iron overload, ferritinophagy, and lipid peroxidation in NK cells	[5]
KYN metabolic pathway	IDO/TDO–KYN axis	Induce ROS accumulation and lipid peroxidation	[2,7]
SLC7A5-mediated KYN transport	LAT1/SLC7A5	May increase susceptibility to KYN-related ferroptosis	[8–10]
TME metabolic pressure	Nutrient deprivation, ROS, and lipid metabolic remodeling	Increase oxidative stress, lipid peroxidation, and ferroptosis sensitivity in NK cells	[11,12]

2.2 Experimental Findings Linking CAFs to Ferroptotic Death in NK Cells

Recently, it has been discovered that CAFs can induce ferroptosis in NK cells. NK cells in the model of gastric cancer had reduced cytotoxic activity and significantly decreased cell survival [5]. Ferrostatin-1 is a ferroptosis inhibitor and thus reduces this phenomenon, but it does not interfere with the classical apoptotic pathway [5]. Therefore, it can be concluded that the main way for NK cells to undergo death in this case is ferroptosis and not apoptosis [5]. It has been found that CAFs inhibit the activity of NK cells by inducing ferroptosis and has thus provided a new direction for exploring the mechanism of immunosuppression in the TME.

2.3 Molecular Mechanisms Related to CAF-In-

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duced NK Cell Ferroptosis

It is proposed that CAF-induced NK cell ferroptosis is mainly caused by abnormal iron metabolism and an increase in oxidative stress.

CAFs can increase the amount of free iron in the TME by upregulating iron-exporting-associated molecules such as ferroportin (FPN1) and hephaestin (HEPH), which in turn results in an iron excess for NK cells [5]. CAFs can release all kinds of small molecules in the extracellular space that bind to follistatin like protein 1 (FSTL1) and then activate Disco-interacting protein 2 homolog A–p38 mitogen-activated protein kinase pathway (DIP2A-p38) in NK cells [5]. Therefore, nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy is promoted to increase the amount of free iron and lipid peroxidation in NK cells inside the cell [5]. An increase in the amount of intracellular free iron may lead to the formation of reactive oxygen species (ROS) via the Fenton reaction and thus cause damage to membrane lipids [5]. In short, based on the above results, CAFs can modulate the ferroptosis of NK cells both directly and indirectly. Not only can they change the composition of metabolites in the TME, but they can also affect NK cells via specific ligand-receptor interactions [5].

CAFs may also increase oxidative stress in NK cells through metabolic reprogramming. By remodeling local metabolism, CAFs can promote ROS accumulation and participate in forming an immunosuppressive microenvironment [3].

3. Potential Regulatory Role of the Kynurenine Metabolic Pathway in NK Cell Ferroptosis

3.1 Regulatory Role of the KYN Pathway in the TME

In the TME, reprogramming of tryptophan (Trp) metabolism is considered an important mechanism of immune regulation. Trp mainly degrades into kynurenine (KYN) through the KYN pathway, catalyzed by the rate-limiting enzymes, particularly indoleamine 2,3-dioxygenase (IDO) [6]. Upregulated IDO expression within tumor and stromal cells can enhance this process, leading to KYN accumulation in the TME [6].

3.2 Experimental Evidence for KYN-Induced NK Cell Ferroptosis

Recent studies have further linked KYN to ferroptosis. In gastric cancer model, NK cell ferroptosis can occur with the accumulation of KYN [2]. Notably, this process has been confirmed to be non-AHR-dependent and can be partially reversed by glutathione peroxidase 4 (GPX4) overexpression [2].

Compared with earlier studies of ROS-dependent NK cell death [7], this finding indicates that the KYN-induced NK cell apoptosis may not merely occur through oxidative stress, but also involves the ferroptosis as one of the mechanisms. However, whether the KYN-induced NK cell apoptosis is completely induced by ferroptosis of cells due to oxidative stress or there is also apoptosis directly caused by oxidative stress remains a question worth exploring.

3.3 Potential Association Between SLC7A5 and KYN Uptake

KYN is a large neutral amino acid. Its transmembrane transport is highly likely to rely on the system L amino acid transporter. An important component of L amino acid transport machinery in activated NK cells is Solute Carrier Family 7 Member 5 (SLC7A5), also known as L-type amino acid transporter1 (LAT1) [8]. SLC7A5 participates in the regulation of amino acid uptake, c-Myc maintenance, and NK cell metabolic reprogramming [8]. SLC7A5 activity is closely associated with the metabolic and functional status of NK cells [8].

Upregulated SLC7A5 expression can promote Trp uptake by NK cells, indicating that SLC7A5 not only participates in Trp transport, but may also influence KYN-related metabolic networks [9].

Under Trp-depleted conditions, general control nonderepressible 2 (GCN2) can induce upregulation of SLC7A5 and enhance uptake of KYN by T cells, thereby further amplifying AHR signaling activation [10]. This study suggests that, in the context of Trp depletion within the TME, increased SLC7A5 expression may further increase the entry of KYN into cells [10]. Although direct evidence showing whether this process also occurs in NK cells is still scarce, taking into account the similarities between NK cells and T cells, existing studies support the following hypothesis: under long-term Trp depletion and KYN accumulation in the TME, enhanced SLC7A5-mediated KYN uptake may lead to excessive intracellular KYN accumulation in NK cells, thereby increasing their susceptibility to ferroptosis. Validating this hypothesis is crucial for understanding the mechanism of NK cell dysfunction in the tumor microenvironment, and may provide new strategies to restore NK cell antitumor activity by targeting SLC7A5 or the KYN metabolic pathway.

4. Metabolic and Redox Stress in the

Tumor Microenvironment Promotes NK Cell Susceptibility to Ferroptosis

4.1 Metabolic Stress in the TME

Pronounced metabolic reprogramming, including nutrient competition, hypoxia, and abnormal accumulation of metabolites occur in the TME. Together, these factors create an unfavorable survival environment for immune cells. For NK cells, activation and cytotoxic function depend on stable energy metabolism and redox homeostasis; therefore, NK cells are particularly sensitive to metabolic stress in the TME. Existing studies have shown that nutrient deprivation, ROS accumulation, and abnormal lipid metabolism can all lead to NK cell functional exhaustion and reduce their antitumor capacity [7,12]. These factors may alter intracellular metabolic homeostasis in NK cells and make them more susceptible to oxidative damage and ferroptosis.

4.2 Lipid Metabolic Reprogramming Increases NK Cell Sensitivity to Ferroptosis

In immune cells, lipid metabolic status is closely related to cellular immune function. For example, abnormal fatty acid accumulation can lead to lipid peroxidation damage in immune cells and impair their viability. Recent research further showed that Cluster of Differentiation 36 (CD36)-mediated abnormal lipid uptake can directly promote ferroptosis in NK cells, suggesting that lipid metabolic reprogramming in the TME itself can participate in NK cell functional exhaustion [11]. Although direct evidence in NK cells remains limited, TME-associated lipid metabolic reprogramming is likely to alter NK cell membrane lipid composition and oxidative stress levels, thereby indirectly increasing their susceptibility to ferroptosis.

4.3 Redox Imbalance Increases NK Cell Sensitivity to Ferroptosis

Disruption of redox homeostasis is a prerequisite for ferroptosis. In the TME, tumor cells and inflammatory responses can continuously produce large amounts of ROS, while antioxidant systems may be impaired by nutrient limitation or metabolic stress [12]. Current studies have shown that both tumor-derived metabolites and stromal cell signals can participate in the regulation of NK cell ferroptosis by enhancing oxidative stress [2,5,7]. Therefore, redox imbalance may act as a common convergence point for different upstream mechanisms and play a central role in NK cell ferroptosis. ROS accumulation within the TME may also increase the sensitivity of NK cells to KYN- or CAF-induced ferroptosis.

5. Conclusion

Research on NK cell ferroptosis has made some progress in recent years, but there are still many knowledge gaps. A general overview of the molecular network regulating ferroptosis in NK cells has not been put forward. It has not been determined whether this process is related to the old antioxidant defence system of GSH-GPX4 or to lipid metabolism. Another problem is whether the mechanism is generalizable to various types of tumours and different microenvironments, or if it is different to some extent. There is no relevant experiment to cite.

Regulation of NK cell ferroptosis may be a new way to advance the field of translational medicine for cancer immunotherapy. To inhibit ferroptosis in NK cells in the tumour microenvironment may help maintain the number and function of these cells and strengthen the overall anti-tumour immune response. At the same time, one can also change metabolic reprogramming in the TME to modulate the survival environment of various immune cells in the TME and strengthen their cooperation with NK cells to fight cancer. Clinical Feasibility and Safety of the above Strategies also need to be examined.

In short, NK cell ferroptosis is an essential way by which metabolic reprogramming promotes immune dysfunction, so it can lead to a better understanding of the suppression of the immune system in the TME. In the future, it would be beneficial to have a more specific definition of the metabolic and signaling pathways involved in NK cell ferroptosis, understand how these pathways differ in various tumour environments, and begin to explore clinical intervention points. The above studies will provide new theoretical foundation and therapeutic goal for the development of cancer immunotherapy.

References

[1] Zhan, F., Hu, Y., Jiang, X., et al., The Progress of Ferroptosis of Immune Cells in the Tumor Microenvironment and Its Impact on Tumorigenesis and Development. Immun Inflamm Dis, 2026. 14(1): p. e70333.

[2] Cui, J.X., Xu, X.H., He, T., et al., L-kynurenine induces NK cell loss in gastric cancer microenvironment via promoting ferroptosis. J Exp Clin Cancer Res, 2023. 42(1): p. 52.

[3] Yang, D., Liu, J., Qian, H., et al., Cancer-associated fibroblasts: from basic science to anticancer therapy. Exp Mol Med, 2023. 55(7): p. 1322–1332.

[4] Li, T., Yang, Y., Hua, X., et al., Hepatocellular carcinoma-associated fibroblasts trigger NK cell dysfunction via PGE2 and IDO. Cancer Lett, 2012. 318(2): p. 154–61.

[5] Li, T., Yang, Y., Hua, X., et al., Cancer-associated fibroblasts impair the cytotoxic function of NK cells in gastric cancer by

ISSN 2959-409X

inducing ferroptosis via iron regulation. Redox Biol, 2023. 67: p. 102923.

[6] Platten, M., Nollen, E.A.A., Rohrig, U.F., et al., Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. Nat Rev Drug Discov, 2019. 18(5): p. 379–401.

[7] Song, H., Park, H., Kim, Y.S., et al., L-kynurenine-induced apoptosis in human NK cells is mediated by reactive oxygen species. Int Immunopharmacol, 2011. 11(8): p. 932–8.

[8] Loftus, R.M., Assmann, N., Kedia-Mehta, N., et al., Amino acid-dependent cMyc expression is essential for NK cell metabolic and functional responses in mice. Nat Commun, 2018. 9(1): p. 2341.

[9] Venkateswaran, N., Lafita-Navarro, M.C., Hao, Y.H., et al., MYC promotes tryptophan uptake and metabolism by the kynurenine pathway in colon cancer. Genes Dev, 2019. 33(17-18): p. 1236–1251.

[10] Solvay, M., Holfelder, P., Klaessens, S., et al., Tryptophan depletion sensitizes the AHR pathway by increasing AHR expression and GCN2/LAT1-mediated kynurenine uptake, and potentiates induction of regulatory T lymphocytes. J Immunother Cancer, 2023. 11(6).

[11] Shi, L., Huang, X., Han, X., et al., NAD (+) precursor supplementation reverses CD36-mediated lipid accumulation and ferroptosis to restore antitumor function of NK cells in DLBCL. Pharm Sci Adv, 2026. 4: p. 100111.

[12] Sun, J., Pan, S., Wang, N., et al., Interplay between natural killer cells and ferroptosis: novel insights in tumor immunity and therapeutic potential. Cell Commun Signal, 2026. 24(1).