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REVIEW

In-depth analysis of the interplay between oncogenic mutations and NK cell-mediated cancer surveillance in solid tumors

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ABSTRACT

Natural killer (NK) cells play a crucial role in antitumoral and antiviral responses. Yet, cancer cells can alter themselves or the microenvironment through the secretion of cytokines or other factors, hindering NK cell activation and promoting a less cytotoxic phenotype. These resistance mechanisms, often referred to as the "hallmarks of cancer" are significantly influenced by the activation of oncogenes, impacting most, if not all, of the described hallmarks. Along with oncogenes, other types of genes, the tumor suppressor genes are frequently mutated or modified during cancer. Traditionally, these genes have been associated with uncontrollable tumor growth and apoptosis resistance. Recent evidence suggests oncogenic mutations extend beyond modulating cell death/proliferation programs, influencing cancer immunosurveillance. While T cells have been more studied, the results obtained highlight NK cells as emerging key protagonists for enhancing tumor cell elimination by modulating oncogenic activity. A few recent studies highlight the crucial role of oncogenic mutations in NK cell-mediated cancer recognition, impacting angiogenesis, stress ligands, and signaling balance within the tumor microenvironment. This review will critically examine recent discoveries correlating oncogenic mutations to NK cell-mediated cancer immunosurveillance, a relatively underexplored area, particularly in the era dominated by immune checkpoint inhibitors and CAR-T cells. Building on these insights, we will explore opportunities to improve NK cell-based immunotherapies, which are increasingly recognized as promising alternatives for treating low-antigenic tumors, offering significant advantages in terms of safety and manufacturing suitability.

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1. Introduction

1.1. Introducing natural killer cells

Natural killer (NK) cells play an essential role in antitumoral and antiviral responses, being the first line of defense against cancer and viral infections.[1–3] In humans, NK cells are identified by the expression of CD56 and the absence of CD3 surface markers.[4,5] Based on the expression level of two markers, CD56 and CD16, two conventional NK cell subsets have been described in humans: $CD56^{bright}$ $CD16^{dim}$ and $CD56^{dim}$ $CD16^{bright}$ (from now on referred as $CD56^{bright}$ and $CD56^{dim}$ NK cells, respectively).

Both subsets are phenotypically and functionally distinct. Whereas the first are mainly located in secondary lymphoid organs and tissues, the second group can predominantly be found circulating in peripheral blood.[5] In terms of cytotoxicity, $CD56^{bright}$ subset is less cytolytic. Indeed, since they are the predominant producers of immunoregulatory cytokines (e.g., interferon-gamma (IFNγ), tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-10 and IL-13), they are frequently known as pro-inflammatory NK cells.[6] On the other hand, $CD56^{dim}$ NK cells, while expressing high levels of cytotoxic molecules (perforin and granzyme B) as well as CD16a receptor (also known as IgG Fc receptor IIIA, FcγRIIIA), exhibit lower cytokine production compared to $CD56^{bright}$ NK cells. Nonetheless, $CD56^{dim}$ NK cells are highly cytotoxic and proficient in performing Antibody-Dependent Cellular Cytotoxicity (ADCC).[7]

Finally, shared with some subsets of activated T cells (e.g., CD4-Th1 and γδT cells), NK cells have a central role in the production of IFNγ.[8,9] This pleiotropic cytokine regulates the expression of crucial genes implicated in regulated cell death (e.g., Bcl2-family proteins, caspases, or death receptors), inflammation, cell cycle regulation, and transcriptional activators' expression.[10–12]

Tumor cells have developed numerous highly sophisticated resistance mechanisms tied to cancer progression to avoid the multiple mechanisms of cancer immunosurveillance. These resistance mechanisms, defined by Hanahan and Weinberg as

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"hallmarks of cancer", are significantly influenced by the activation of oncogenes.[13] Oncogenes are known for their ability to promote cell transformation, which provides malignant cells with survival and proliferation advantages. More recently, they have been shown to modify the cell niche establishing immunologically 'cold' tumor microenvironments (TMEs). Cold tumors seem not to generate adequate protective immune responses and do not present good responses to some types of immunotherapies, especially those related to antigen-specific responses.[14,15] Paradoxically, oncogenic changes would also be responsible for inducing an inflammatory microenvironment characterized by epithelial production of cytokines like IL23 and CCL9 shaping the TME toward conditions that will favor the development of certain tumors. This phenomenon operates through various pathways, including facilitating malignant cell proliferation and survival, promoting angiogenesis and metastasis, reprogramming stromal cells, and disrupting adaptive and NK cell immune responses.[16–18] In those cases, only malignant cells that adapt to the cellular stress imposed by oncogenesis and the TME will progress. During this phase of selective pressure, malignant cells with specific molecular alterations that confer immunoevasion are preferentially selected.[15]

Consequently, the identification and comprehensive understanding of these genes and their impact on the immune system's response are paramount in the fight against cancer. Therefore, this review will focus on the major oncogenic driver mutations and how they modify the antitumoral potential of NK cells, with special emphasis on the regulation of NK cell recognition of tumor cells. Before that, we will briefly introduce the main mechanisms involved in NK cell-mediated control of cancer cells and tumor evasion strategies to understand better the potential impact of oncogenes in this process.

1.2. Dr. Jekyll: natural killer cells against cancer

In contrast to cytotoxic CD8+ T cells, NK cells do not require prior antigen exposure to mediate their antitumor function.[4] As shown in Figure 1a, NK cells possess several activating and inhibitory receptors. The balance between activating and inhibitory signals will determine whether NK cells will kill the target cells.[19,20]

As mentioned, NK cells are armed cytotoxic cells with high expression of perforin (PRF) and granzymes (GZMs), executors of granular exocytosis pathway. PRF is a protein that forms pores in the target cell membrane, permitting GZMs to enter inside the cell and inducing cell death.[21–23] GZMs are a family of serine-proteases comprised of (Figure 1b) five members in humans and ten in mice.[24–26] Among these, GZMB has the most potent cytotoxic activity mainly inducing apoptosis.[27–29] The cytotoxic activities of other GZMs remain controversial, but it is clear that GzmA, GzmM, or GzmK are involved in regulating the inflammatory response through extracellular mechanisms.[26,30–36]

Recently, it has been described that granular exocytosis pathway can be implicated in other types of regulated cell death, such as necroptosis and pyroptosis.[37] In addition to induce cell death, GZMs have been associated with additional biological functions, including inflammation, autoimmunity, extracellular matrix degradation, and related pathologies including sepsis, cardiovascular disease, skin disorders, arthritis of ulcerative colitis among others.[35,38,39] However, a more detailed description of these serine-proteases is out of the scope of this review, and it has been the topic of recent excellent reviews.[29,38,40,41]

Besides granular exocytosis, NK cells can induce cell death by an additional mechanism based on death ligands, which are members of the TNF superfamily of proteins (see Figure 1c).[42] The most commonly expressed death ligands in NK cells are TNFα (Tumor necrosis factor), FasL (Fas Ligand), and TRAIL (TNF-related apoptosis inducing ligand).

1.3. Mr. Hyde. Tumor immunoevasion from NK cell immunosurveillance

One of the primary functions of NK cells is to exert tumor-suppressive activity. Nonetheless, NK cells may paradoxically modulate tumor variants capable of evading NK cell immunosurveillance. In doing so, they inadvertently contribute to these tumor cells evading antitumoral mechanisms. These observations led to the development of the immunoediting theory, which is divided into three phases "the three *Es*": ***e***limination, ***e***quilibrium, and ***e***scape.[43,44]

Elimination corresponds to immunosurveillance.[45] In this initial phase, NK cells play an essential role in eliminating emerging tumor cells due to their unique capacity to rapidly recognize and kill transformed cells. As cytotoxic cells of the innate immune system, they circulate with all the necessary molecules to recognize and eliminate tumor cells without prior antigen presentation.[46,47] In the emblematic study by Imai *et al.* (2000), it was observed that low NK cell activity was associated with an increased cancer risk during an 11-year follow-up period,[48] highlighting the importance of NK cells in the initial stages of tumor cell control.

However, some cells occasionally manage to evade the immune system, including NK cells,[43] initiating the second phase, *equilibrium*. During this period, immune cells, notably T cells, gain major relevance, continuing to target and eliminate tumor cells.[49,50] However, some tumor cells survive by entering a quiescent state and acquiring immunosuppressive properties, such as increasing the expression of anti-apoptotic molecules (e.g., Bcl-2)[51] and reducing antigen or major histocompatibility complex (MHC) class I expression, limiting T-cell recognition and subsequent killing of the cancer cells.[52] Here, NK cells play a crucial role because their ability to recognize tumor cells that have adapted to escape T-cell killing facilitated by the absence of MHC, the principal inhibitory ligand for NK cell receptors, enabling them to kill these 'low immunogenic cells' (Figure 1a). Notably, oncogenic transformation during these stages have been shown to modulate HLA-I expression, thus, contributing to recognition of cancer cells by NK cells.[53,54]

After a while, tumor cells begin to proliferate and divide massively again, the phase is considered the *escape* phase.[45,55] Again, NK cells play a pivotal role in metastasis control and tumor progression, as observed in small cell lung cancer, where evasion of NK cells by reduction of NKG2D-ligands reflects increased aggressiveness.[56]

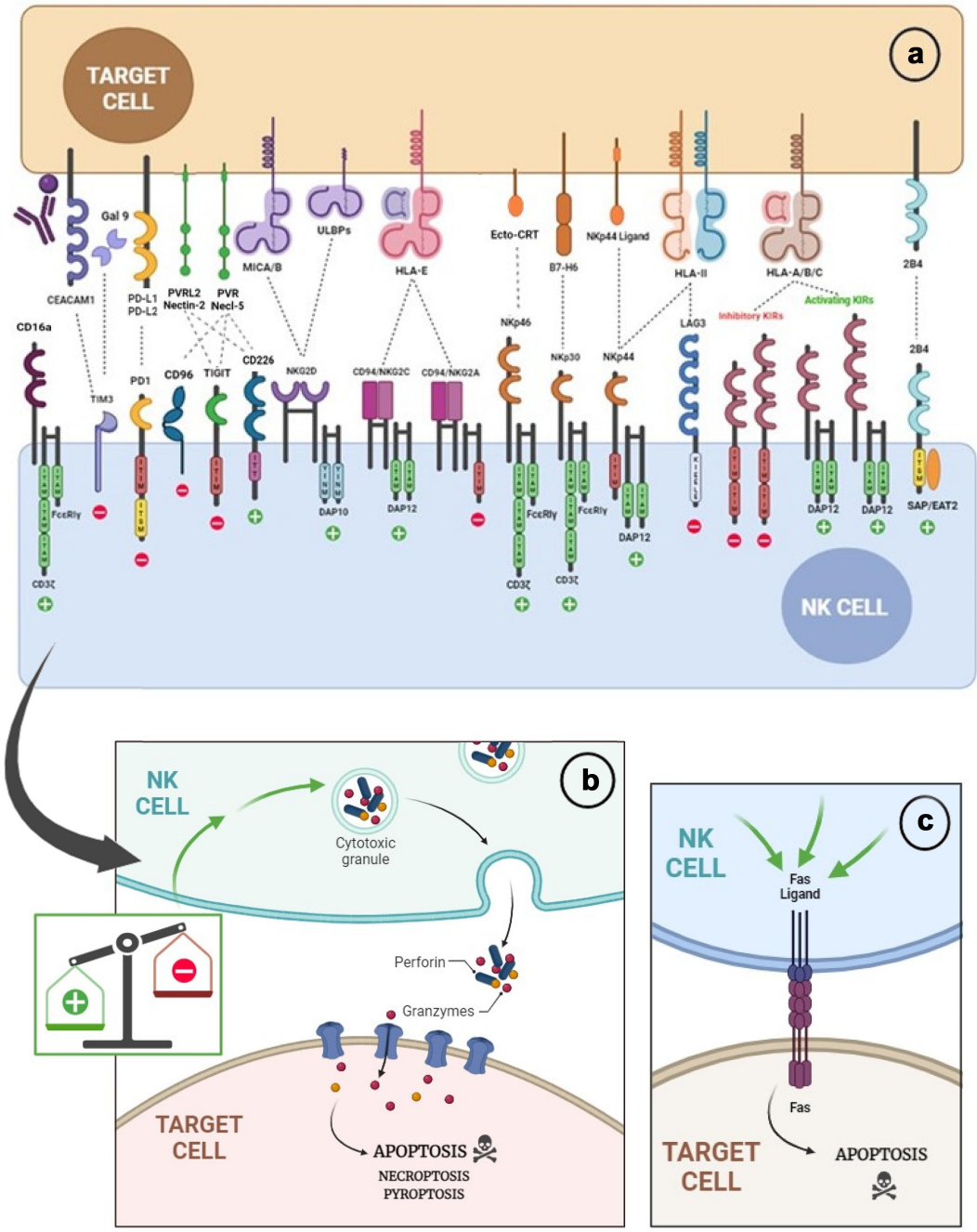

Figure 1. NK cell-mediated cytotoxicity. NK cells express several receptors on their surface that will positively or negatively regulate their activity (A). NK cells possess two main mechanisms to induce the target cell death, granular exocytosis (B) and expression of death receptors (C). Figure created with BioRender.com.

Throughout this development, the tumor microenvironment (TME) is also established and shaped to promote cancer cell immunoevasion. This results in dampening NK cell function and altering their phenotype throughout the entire tumor progression process[57,58] which will be discussed in the next section.

2. The tumor microenvironment inhibits NK cell function

As aforementioned, an additional factor that strongly affects the modulation of NK cell responses is the TME. The TME encompasses all tumor components, including the different non-tumor cell populations: immune cells, fibroblasts, and cells that comprise the blood vessels.[59,60] Within the TME, numerous complex interactions exist between extracellular matrix, nonimmune, immune and cancerous cells, each having a clear impact on tumor progression, invasion, and metastasis.[61]

These interactions collectively generate an immunosuppressive environment that hinders effective immune responses, leading to poor trafficking and immune infiltration of tumors. The most relevant TME factors regulating NK cell activity are discussed below:

2.1. The TME architecture

TME architecture plays a crucial role in orchestrating both tumor immunity and therapeutic responses. Tumor initiation

and expansion depend entirely on the organization of the TME and physiological processes like angiogenesis, immune cell infiltration, and cancer cell proliferation.

In a ground-breaking study elucidating NK cell implications in mouse skin graft rejection, it was demonstrated that their migration to peripheral tissues elicits a distinctive dampening of their cytotoxic activity, mediated by the presence of collagens and elastin. This phenotypic alteration redirects NK cell functionality toward an augmented secretion of specific chemokines and cytokines like INF, CCL2, and CXCL10, thereby assuming a supportive role in T cell priming. This intriguing reprogramming of NK cell function provides a rationale for the selective loss of MHC-I expression observed in solid cancers but not leukemias.[62]

2.2. Nutrient deprivation

The effect of the tumor microenvironment (TME) on NK cell metabolism must also be taken into account as it is crucial for their function.[63–65] During tumor progression, cancer cells must adjust their metabolic activity to maintain the high biosynthetic rates required for rapid cell growth, despite low nutrient and oxygen availability. These adaptations are essential for cancer cell survival. Metabolic remodeling is believed to be a dynamic process that varies depending on the specific needs of the tumor. However, like other tumorigenic events, this metabolic adaptation is likely influenced by the actions of oncogenes and tumor suppressors.

Unlike normal cells, cancer cells preferentially utilize the glycolytic pathway over oxidative phosphorylation (OXPHOS) for glucose metabolism.[66] This preference reduces glucose availability and contributes to an acidic pH due to lactate production.[67,68] Moreover, hypoxia is observed due to limited oxygen availability, which reduces NK cell cytotoxic activity.[69] Specifically, hypoxia reduces NK cell activity by downregulating NK cell activating receptors and cytotoxic molecules like GZMB. Additionally, amino acid availability regulates NK cell functionality and signaling by maintaining important metabolic regulators like mTOR and c-Myc.[70,71]

2.3. Immunosuppressive cells

The main immunosuppressive cells in TME are tumor-associated macrophages (TAMs), Myeloid- derived suppressor cells (MDSCs), T regulatory cells (Tregs), tumor-associated neutrophils (TANs), and cancer-associated fibroblast (CAFs), with high capacity of immunosuppressive NK cells.[59,61,72–81] Notably, MDSCs are a group of myeloid-derived suppressor cells, precursors of dendritic cells, macrophages, and granulocytes, that have the ability to regulate immune response negatively.[82–84] Indeed, cancer-expanded MDSC can induce anergy of NK cells via membrane-bound TGF-β1.[85]

CAFs are another significant source of TGF-β in the TME.[86] They play a pivotal role in ECM remodeling, as well as in cancer cell proliferation and invasion. CAFs modulate NK cells to an inactive phenotype through various mechanisms, including the recruitment of other immunosuppressive cells, such as M2 macrophages, as observed in colorectal cancer.[87] Notably, it has also been shown that oncogenes promotes transformation of normal fibroblasts into CAFs.[88] They play a pivotal role in ECM remodeling, as well as in cancer cell proliferation and invasion.[86]

2.4. Cytokine profile

The influence of the TME on NK cell responses extends to its role in modulating the secretion of specific cytokines and factors by cancer cells. It is well known that cancer cells can modify the microenvironment in their vicinity by the secretion of specific cytokines or factors that directly or indirectly prevent NK cell activation or modulation to a less cytolytic phenotype (e.g., IL-6, IL-10, TGF-β, prostaglandin E2 (PGE2), or indoleamine 2,3-dioxygenase (IDO). Remarkably, TGF-β is a master regulator of NK cell activity, promoting an immunosuppressive effect[89] galectin-9, highly expressed in many human cancers, can interact with TIM-3 on the surface of NK cells, limiting their cytotoxicity[90,91]; and the enzyme IDO which is widely present in tumors and contributes to the loss of NK cell cytotoxicity.[92] However, not all the signals block the antitumoral phenotype. Other molecules in the TME also help induce an antitumoral activity, like IL-15 mostly secreted by myeloid cells,[93] with an important role in NK cell survival, activation and proliferation.[93,94] Another activating signals in TME are the DAMPs (damage-associated molecular patterns) that trigger the production of type I IFNs, which increase NK cell antitumoral function.[95]

2.5. Receptor-ligand interactions

Some other relevant mechanisms described for NK cell immunosuppression are the modulation or release of NK cell receptor ligands by tumor cells to avoid receptor signaling.[94,96–98] For example, already in 2013, Reiners, KS. *et al*., discovered that chronic lymphocytic leukemia patients were able to evade the antitumor activity of NK cells due to the secretion of the soluble ligand BAG6/BAT3 blocking the activating NK cell receptor NKp30.[78,97]

Similarly, NKG2D ligands, such as MICA/B (MHC class I chain- related proteins A and B) and ULBPs, are often shed by tumor cells, which blocks the activating receptor NKG2D in NK cells.[96] This process will be discussed in detail later, focusing on how oncogenes affect these ligands. NKG2DL expression on cell membranes can be reduced through proteolysis by some metalloproteinases (ADAM9, ADAM10, ADAM17), and matrix metalloproteinase (MMP9, MMP14) to form soluble NKG2DL.[99] NKG2D is a major activating receptor of NK cells, and many independent studies have shown down-regulation of NKG2D surface expression on NK cells from patients with cancer. This effect was attributable to the presence of soluble NKG2D ligands (NKG2DL)[100] and linked to anergic NK cells in several tumors. These anergic NK cells present impaired degranulation capabilities, reducing the release of PFN, GZMs, and antitumor cytokines.[85,101,102]

On the other hand, the downregulation of MHC-I is a well-known immune evasion mechanism in cancer, exposing tumoral cells to NK cell attack, since MHC-I serves as their primary inhibitory ligand. MHC class I molecules represent a fundamental molecular framework that mediates the activation

and function of cytotoxic effector cells of both the adaptive and innate immune systems, such as CD8+ T cells and NK cells. T cells are activated upon recognizing a tumor-associated neopeptide on an MHC I complex, eliminating the target cell. However, many tumors evolve to evade this recognition by downregulating MHC-I molecules on their surface. To counter this, the human immune system has developed specific killer cell immunoglobulin-like receptors (KIRs) and leukocyte Ig-like receptors (LIRs) expressed by NK cells that bind to MHC I molecules and inhibit NK cell activation. Consequently, if MHC-I expression is impaired, the inhibitory signal is reduced, facilitating the activation of the 'missing self' signaling pathway and resulting in the cytotoxic destruction of the target cell.[52,62,103,104]

MHC-I molecules are highly polymorphic, reflected by a high number of HLA-A, -B and -C alleles. Variations in MHC-I alleles pose challenges for NK cell surveillance, affecting directly their education and their ability to recognize aberrant cells.[103–105] Some alleles effectively engage inhibitory receptors, while others fail due to genetic differences. In HIV infections, individuals with poorly recognized alleles have been related to NK cell immunoescape.[105] The diverse HLA-I repertoire influences NK cell surveillance efficiency and cancer susceptibility. Understanding the regulation of HLA-NK cell interactions is crucial for immune recognition mechanisms and design of effective NK cell-based targeted therapies.

In addition to classic MHCs, non-classical HLA (HLA-E and HLA-G) have an important role in cancer. HLA-E and HLA-G are peptide-dependent MHC I molecules with low levels of heterogeneity compared to classical MHC I molecules Peptide-bound HLA-E serves as a dominant inhibitory ligand for the dimeric CD94/NKG2A receptor on NK cells and are frequently upregulated in many cancers, suggesting that this axis functions as an acquired resistance mechanism in the tumor microenvironment.[106,107]

The other non-classical HLA, HLA-G, present numerous isoforms, soluble or membrane-bound.[108] It modulates NK cell activity by engaging inhibitory receptors like KIR2DL1, KIR2DL2/3, KIR2DL4 or ILT2. HLA-G is poorly expressed on adult healthy tissues, and its expression is increased in tumor cells favoring immune-evasion.[108,109]

When discussing immunomodulatory receptors and ligands in cancer, the PD-1 and PD-L1/PD-L2 duo has gained significant attention due to their crucial clinical applications with antibodies designed to inhibit this pathway. It has been observed that both PD-1 and PD-L1 molecules are expressed in NK cells under different conditions and that these molecules regulate NK cell function. PD-1 is increased in degranulated-NK cells upon exposure to tumor cells,[110] as well as in the NK cells from cancer patients.[111] Similarly, PD-L1 expression is upregulated by IL-2 exposure,[112] highlighting the significance of this axis in NK cells, as observed during the elucidation of the anti-PD-1/PD-L1 therapies mechanism.[113] It is noteworthy that PD-1 expression in NK cells is much lower than in T cells and is not induced by stimuli such as cytokines[112] but interaction with target cells[111] which could lead to negative results when analyzing their membrane expression in NK cell cultures. Many studies still debate its expression, suggesting that it may be important to consider the models and controls used. This controversy is highlighted by observations from two groups that conducted similar experiments using the CT26 cell line in mice to study PD-1 levels in NK cells. One study concluded that NK cells lack PD-1 expression, while the other observed remarkable expression.[114,115]

With all of these mechanisms, cancer cells manage to sculpt an immunosuppressive TME for NK cells. Consequently, adoptive cell therapies, whether T or NK cell-based, are currently ineffective in treating solid tumors.[116,117] Despite NK cells continuously combating transformed cells to prevent cancer development, they are highly susceptible to changes in their environment. These environmental changes can cause NK cells to switch from their antitumor or pro-inflammatory roles to behaviors that promote tumor formation, angiogenesis, and metastasis.[118,119]

A comprehensive understanding of the mechanisms involved in NK cell-mediated cancer immunosurveillance has paved the way for investigating the impact of various components within the TME on the elimination of cancer by NK cells. Recent evidence suggests that oncogenes and tumor suppressor genes not only influence the characteristics of tumor cells but also play a crucial role in enabling cancer cells to shape the TME to evade immune-mediated destruction. However, the specific links between these changes and NK cell function during cancer immunosurveillance and immunotherapy remain underexplored despite new studies in recent years. In the following lines, we will discuss current evidence and speculate how oncogenic-driven transformation might regulate NK cell antitumoral activity.

3. Oncogenes and tumor suppressor genes in NK cell immunoevasion

3.1. A brief introduction to oncogenic transformation

Oncogenes and tumor suppressor genes are frequently mutated or modified during cancer progression. In healthy cells, there are some genes, commonly known as proto-oncogenes, which are necessary for cell growth regulation and differentiation, but when these genes, or their expression, are altered (at this point, they are termed oncogenes), they contribute to promoting cancer development.[120] The change from proto-oncogene to oncogene can result from mutations, chromosomal rearrangements, amplifications, or viral insertions. In most cases, this will likely result in uncontrollable tumor growth and apoptosis resistance.[121,122] On the other hand, tumor suppressor genes encode growth-inhibitory proteins, meaning that their loss would cause deregulation of cell proliferation. In contrast to passenger mutations, driver mutations frequently occur in cancer-related genes and are involved in oncogenic signaling pathways.[123] Most relevant and best-characterized oncogenes and tumor suppressor genes include transcription factors (Myc, fos, jun, rel), GTPases (Ras), kinases (Raf, PI3K, Stat3, Src, Syk, BTK, EGFR, VEGFR), Rb, and p53 (see Figure 2).Within the next sections, we will focus on the available evidence that links the oncogenic function of some of these genes to tumor cell evasion from NK cell function.

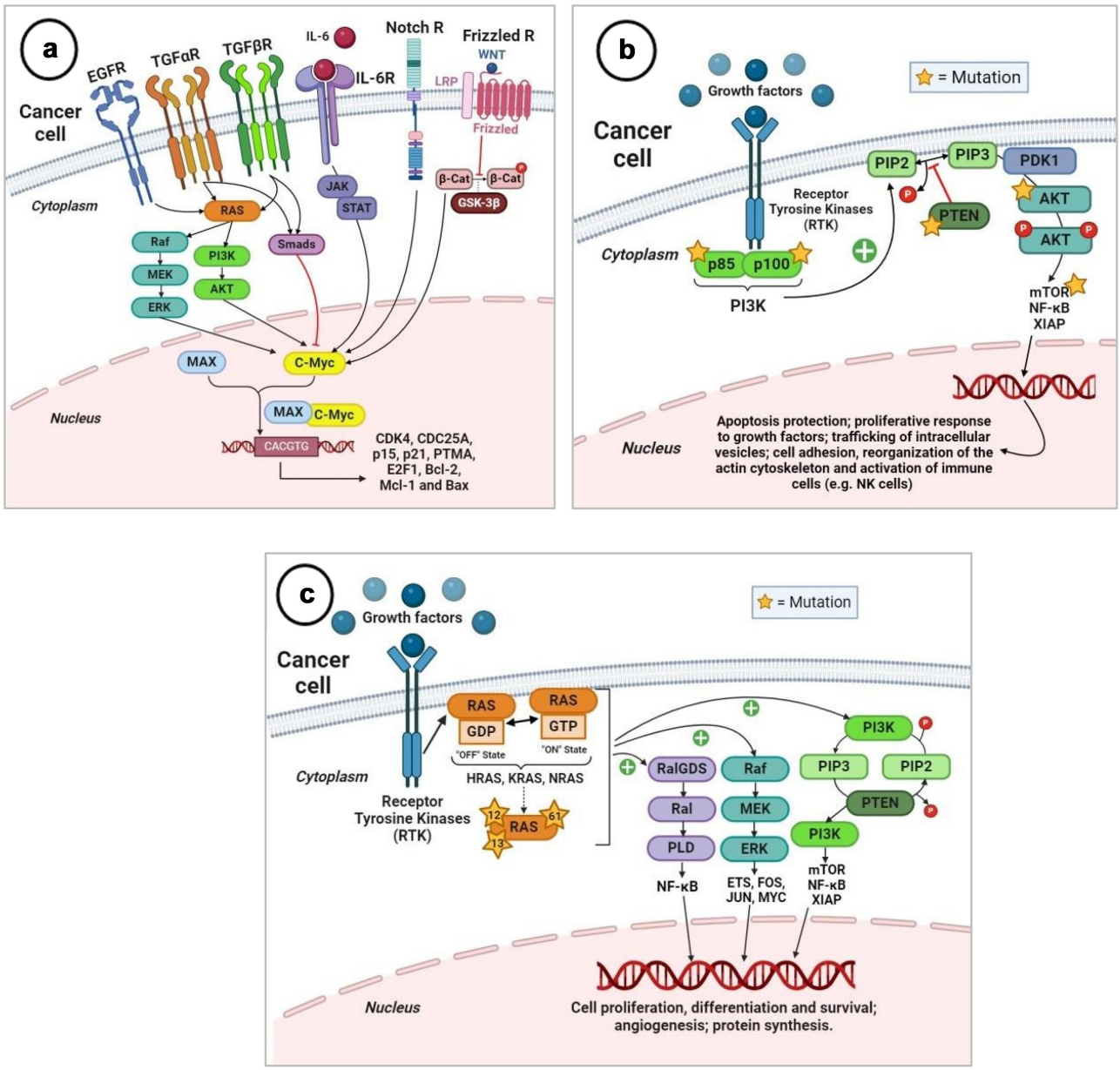

Figure 2. Oncogenic signaling pathways of myc (A), Ras (B), and PI3K (C). Figures created with BioRender.com.

3.2. Myc family

Myc alterations, including amplifications and activation, have been observed in over half of all cancer cases. Its pivotal role in regulating metabolic features, cell proliferation, growth, DNA replication, and numerous cellular processes tightly links it to multiple cancer hallmarks. It should be highlighted that similar to other oncogenes, Myc overexpression alone is usually insufficient for tumorigenesis induction.[124–126] The Myc family proteins comprise l-Myc (e.g., embryonic brains, kidney, and lung tissue), n-Myc (early developmental stages of neuronal tissues), and c-Myc (plenty of adult tissues).[127] As a transcription factor, Myc will form a dimmer with Myc-associated factor X (MAX). Once they have dimerized, they will bind E-boxes (CACGTG) to the DNA within the enhancers and promoters of target genes. Those genes encode for proteins like CDK4 (Cyclin-dependent kinase 4), the phosphatase CDC25A, p15, p21, the oncoprotein prothymosin α (PTMA), and E2F1.[128–130] Myc is also known for being able to regulate the expression of anti-apoptotic (e.g., Bcl-2 and Mcl-1) and proapoptotic proteins (e.g., Bax).[131]

Of those three Myc isoforms, c-Myc has been shown to regulate carcinogenesis and progression in many cancers like breast, cervix, colon, stomach, lungs, and multiple myeloma.[132,133] For example, in lung cancer, c-Myc is frequently dysregulated and associated with unfavorable patient survival as it activates cell cycle-driving proteins and increases the expression of anti-apoptotic proteins like Bcl-2 and Mcl-1 that could affect NK cell cytotoxicity.[134–136] While the impact of c-Myc modulation on the tumor cell death machinery in NK cell immunosurveillance has not been explicitly examined, indirect evidence suggests that the relationship is more complex than initially anticipated. The role of anti-apoptotic proteins in impeding NK cell-mediated cancer elimination remains unclear. Studies employing specific protocols, combining stimulatory cells and cytokines, have

demonstrated that activated NK cells can effectively target cancer cells expressing these proteins.[137] Conversely, a recent report indicated that under conditions of limited NK cell activation and reduced numbers, overexpression of Bcl-XL or deficiency in Bak/Bax may aid tumors in evading NK cell-induced cell death.[138] Recently it was shown that Myc could inhibit the formation of RIPK1-RIPK3 complex which is required for initiation of necroptotic cell death,[139] although it is not known if NK cells activate necroptotic cell death in cancer cells. Consequently, the role of c-Myc modulation in the tumor cell death machinery, contributing to resistance against NK cells, remains ambiguous and necessitates further investigation.

MYC amplification can also alter the TME by modifying the metabolic characteristics of the cell. Although very little is known about the metabolic features of MYCN-amplified tumors, MYCN-amplified cells display enhanced expression of proteins and genes involved in glycolysis, OXPHOS, and ROS detoxification.[140,141] This enhances these metabolic pathways, leading to nutrient deprivation and acidification of the environment, contributing to impair NK cell activity.[65,69,142]

In addition to direct modulation of cancer cell machinery, cancer cell-associated c-Myc has been shown to influence the TME and viceversa. c-Myc, which is highly expressed in breast cancer cells, can regulate angiogenesis, the function of CAFS, and the response of immune cells, including NK cells.[143] Mezquita, P. *et al.*, found that c-Myc could increase VEGF (Vascular endothelial growth factor) expression, thus inducing angiogenesis.[144]

c-Myc can also increase the expression of miR-105 in tumor cells' vesicles, leading to up-regulation of c-Myc in CAFs, and reprogramming their metabolism toward a protumoral function.[145] Although these studies did not address the impact of these changes in NK cell activity, other evidence has shown that CAFs modulate NK cell function,[59,61,72–81] and, thus, pending of experimental validation, it could be speculated that c-Myc-mediated regulation of CAFs could impact NK antitumoral function as explained below.

CAFs have been identified as key players in neutralizing the NK cells' ability to eliminate cancer cells, employing a range of intricate mechanisms.[61,72,81] These include the secretion of soluble mediators like PGE2 and TGF-β,[86] which alter NK cell activation receptors such as NKG2D, NKp30, and NKp44 as well as cytotoxic molecule expression.[146–148] Moreover, CAFs can produce IDO. Therefore, they restrict not only NK cells' cytokine production but also their cytotoxicity.[149] The role of PGE2 and IDO as NK cell activation suppressors was already described by Li, T. *et al.*, in 2012. Based on their results, these two molecules suppress the activation of NK cells, thereby promoting tumor immune escape and creating favorable conditions for tumor progression.[86] Besides this, CAFs also up-regulate immune checkpoint molecules such as PD-L1.[150] Additionally, CAFs engage in synergistic interactions with other immune cells, contributing to the recruitment of M2 macrophages within the tumor environment and cooperating with them, which enhances inhibition of NK cell function.[87] In this line, c-Myc is overexpressed in TAFs and, after its activation by Wnt ligands from cancer cells, promotes M2 polarization and tumor cell progression, albeit the impact of immunosurveillance and NK cell function was not analyzed.[143,151]

Interestingly, once activated, c-Myc induces the expression of miR-17, which excludes immune cells such as NK cells due to the down-regulation of NKG2D ligands, MICA, and MICB and the up-regulation of CCL9 and IL-23.[18,152] Both cytokines, CCL9 and IL-23, are responsible for the rapid loss of T and B cells following Myc activation. However, while CCL9 alone is mainly required for the recruitment of PD-L1+ macrophages and angiogenesis, IL-23 alone is needed for the rapid exclusion of NK cells.[18] Since NK cells express the inhibitory checkpoint PD-1, their cytotoxic activity would be inhibited or down-regulated by the action of the recruited PD-L1+ macrophages.[110] However, the impact of the PD-1/PD-L1 axis and its alternative ligand PD-L2 on NK cell function remains controversial as discussed above. On the other hand, IL-23 has been related to NK cell-mediated control of tumor initiation and metastasis control in mouse cancer models. IL-23-deficient mice showed metastatic resistance mediated by NK cells, indicating that IL-23 can suppress NK cells' surveillance, antimetastatic and immunotherapeutic activity.[153]

As previously discussed, c-Myc can modify the expression of NKG2D ligands like MICA/B and ULBPs in chronic myeloid leukemia (CML) cells, reducing NK cell recognition.[18,154] Interestingly, inhibition of c-Myc by siRNA or chemical compounds restores ligand expression and NK cell killing potential confirming a causal effect of c-Myc in NK cell mediated recognition and elimination of CML cells. Myc oncogene is well known to drive *T*- and B-lymphoid malignancies, including Burkitt's lymphoma (BL) and Acute Lymphoblastic Leukemia (ALL).[154] Recently, it was shown that Myc overexpression altered the secretion of Type I IFNs from the T/B-lymphoblasts, causing a decrease in IL-15 and its receptor, which prevented NK cell maturation.[155,156] The effects of c-Myc on NK cell activity were shown to be enhanced by expression of oncogenic $KRas^{G12D}$. In the $KRas^{G12D}$ mouse lung adenoma model, activation of Myc in this model induced more aggressive invasive adenocarcinomas by a mechanism depending on CCL9 and IL-23, which as indicated above, affected NK cell activity by recruiting PD-L1+ macrophages and depletion of NK cells.[18]

Despite all these findings, it should be noted that the role of Myc oncogene in the regulation of NK cell activity is intriguing since it has been shown that Myc activation in cancer cells triggered the up- regulation of NKG2D ligands and down-regulation of the MHC class I, both potent activating signals for NK-like cells.[18,157–159] A potential explanation for these apparently contradictory findings is that during the first stages of tumor development NK cells are prepared to eliminate cancer cells that have suffered oncogenic Myc transformation to avoid cancer progression, while, in more advanced stages, cancer cells have acquired the ability of using c-Myc to prevent NK cell action or by inducing NK cell anergy through chronic exposure to NKG2D ligands as discussed above. Further studies will be required to validate this hypothesis. Besides c-Myc, n-Myc amplification has also been established to affect the TME with potential impact on NK cell activity, although direct evidence for this is still unavailable. It was shown that n-Myc expression in neuroblastoma cells inhibited the expression of Th1-type chemokines such as CXCL9 and CXCL10, preventing the infiltration of T cells in tumors with a subsequent reduction

of IFNγ and TNFα, creating a less pro-inflammatory microenvironment.[125,160] From these results, a reduction in NK cell infiltration could also be anticipated as CXCL9/10 are potent chemoattractants of NK cells,[161,162] albeit this speculation will require experimental validation.

Besides its direct impact on the resistance of cancer cells to NK cells and its role in shaping the TME to inhibit NK cell activity, Myc expression in immune cells can also influence NK cell function, contributing to cancer immunoevasion. One notable example is the promotion of immune- suppressive cells, such as Treg cells, which are well-established inhibitors of NK cell activity. Myc has been demonstrated to facilitate Treg cells' proliferation and functional activation by regulating their metabolism.[163,164] While the specific influence of Myc expression on Treg function and its consequent impact on NK cell inhibition have not been thoroughly investigated, recent research indicates that inhibiting Myc enhances the antitumoral activity of CD8+ T cells. This effect is achieved by suppressing Treg function, as demonstrated in a study where Myc inhibition led to increased CD8+ T cell activity.[165] These findings underscore the intricate interplay between Myc expression, Treg cells, and NK cell function in the complex landscape of cancer immunoevasion.

3.3. RAS

RAS proteins are essential components of signaling pathways coupled cell surface receptors. It is a GTPase protein, mutated in various cancers. About 20% of cancer patients carry a mutated version.[166] It belongs to a small GTPases superfamily composed of more than 150 members. This superfamily of proteins can be subclassified into RAS, RHO, RAB, and ARF families. Among them, the Ras family is encoded by three ubiquitously expressed genes: HRAS, KRAS (the most frequent mutated isoform), and NRAS. Usually, Ras aberrant functions in the context of cancer originate from single mutations at codons 12, 13, or 61 taking place in conserved sites, causing constitutive activation of Ras and its signaling pathways involving Raf/Mek/Erk, PI3K, and Ral GDS.[167]

The Ras-mutated protein form was reported to induce NKG2D ligand expression by a Raf-MAPK/MEK and PI3K signaling pathway and independently of the DNA damage sensors, which are usual triggers of NKG2D ligand expression after DNA damage and/or oxidative stress.[86,168] Furthermore, it is worth noting that the oncogene Ras has been documented to have a role in the context of non-small cell lung cancer, wherein the mutation of KRAS is associated with an elevation in the expression of PD-L1.[169,170] This finding has been associated with a better response to anti-PD-1 antibodies,[170,171] mainly due to CD8+sT cells, and the role of NK cells in these responses is still unclear.

Regarding the potential modulation of Ras mutations in cell death induced by NK cells, it should be noted that most of the studies that have directly addressed this question have found that NK cells are able to kill cancer cells using natural cytotoxicity or ADCC, irrespectively of mutations in Ras/Raf pathways.[171] Interestingly, it was found that colorectal cancer (CRC) cells with mutant KRAS showed resistance to perforin-independent ADCC in comparison with wild-type KRAS, which was linked to KRAS-mediated resistance to death receptors.[172,173] However, when total cell death induced by NK cells was analyzed, no differences were observed between wt and mutant Ras, suggesting that only those tumor cells with mutations in Ras and, in addition, resistant to the PRF/GZM pathway, might acquire survival advantaged against NK cells. Although mutations that generate PRF resistance in cancer cells have not been described so far Ras mutated tumor cells overexpressing PI-9,[174] a GZMB serpin inhibitor, could be more resistant to NK cell mediated cell death. Additionally, mutated Ras tumor cells could be more resistant to NK cell serial killing a process in which PRF and FasL pathways seem to act sequentially for optimal elimination of cancer cells, at least in vitro.[175]

In 2020 Daia, E. *et al.*, demonstrated that $KRAS^{G12D}$ is packaged into exosomes that are engulfed by macrophages via AGER (advanced glycosylation end-product specific receptor) with the subsequent polarization of macrophages into an M2 tumor-promoting state.[176] As indicated above, M2 macrophages are able to suppress NK cells killing ability by different means including cooperation with CAFs, generation of anti-inflammatory cytokines and attraction of Treg cells.[87,177,178] However, the specific role of $KRAS^{G12D}$ endocyted by macrophages on NK cell activity was not analyzed in that study.[176] Drawing insights from related studies, although not explicitly tested, one can speculate on the potential impact of oncogenic RAS variants on NK cell activity. This speculation is based on findings such as neutrophil attraction through KRAS-dependent IL-8 induction which could potentially influence NK cell activity through mechanisms like NETosis, a network extracellular trap made by DNA and proteins released by neutrophils under specific conditions.[179–183] Additionally, these RAS variants may affect NK cells by promoting the production of anti- inflammatory molecules (ARG1, ROS, NO, PGE2)[184] and facilitating IL-10/TGF-β1-dependent Treg infiltration.[185] Similarly, different studies have correlated the presence of KRAS mutations with the generation of immunosuppressive TME in CRC by recruiting MDSCs, which prevented T cell infiltration and activation, although NK cells were not analyzed.[186,187] This finding was also extended to lung adenocarcinoma.[188]

Mutations in Ras pathways have been linked to the modulation of cell death machinery, leading to an anti-apoptotic profile and HLA-I downregulation.[189–191] This alteration may potentially modulate NK cell-mediated antitumoral activity. However, the presence of Ras/Raf mutation did not affect the sensitivity of a panel of CRC cell lines to activated allogeneic NK cells; instead, it was mostly regulated by HLA-I levels independently of the driver mutation.[171]

3.4. PI3K (PIK3R1 and PIK3CA)

The phosphoinositide 3 kinase (PI3K) is a heterodimer composed of a regulatory subunit (p85), encoded by PIK3R1 gene, and a catalytic subunit (p100), encoded by PIK3CA gene. This signaling pathway responds to various extracellular signals through different tyrosine kinase-like receptors like ErbB family, or insulin-like growth factor 1 receptor (IGF1R)[192,193] generating the intermediate metabolite PiP3 by PiP2

phosphorylation that subsequently activates PKB/AKT/mTOR pathways. This pathway that is negatively regulated by the action of the PTEN phosphatase,[194] participates in several cellular processes including protection from apoptosis,[195] proliferative response to growth factors,[196,197] trafficking of intracellular vesicles, cell adhesion,[198] reorganization of the actin cytoskeleton[199] and activation of immune cells including NK[200] and T cells.[201] Notably, the PI3K-AKT-mTOR signaling pathway is the most frequently mutated in human cancer, being the following alterations the most common ones: PIK3CA, PIK3R1, PTEN, AKT, TSC1, TSC2, LKB1 (also known as STK11) and mTOR.[202] An example is breast cancer, where PTEN loss of or reduction in function is commonly found, allowing the constitutive activation of PI3K pathways, although the significance of this finding is still unclear.[192,203,204]

Like other oncogenes, the direct evidence linking mutations in the PI3K pathway to NK function is limited, with most connections being speculative. The hypotheses are primarily derived from observations of its impact on the TME and T cell function or infiltration. For instance, PI3KCA mutations have been associated with the presence of immunosuppressive molecules/cells in the TME, potentially influencing NK cell activity, although this aspect remains unexplored. Correlations have been observed, such as increased Treg, reduced T cell infiltration, increased PD-L1 expression and heightened resistance to immunotherapy in different cancer types linked to PIK3CA mutations.[192,203] In addition, similarly to Ras and Myc, speculations could be established from the studies relating PI3K mutation and regulation of cell death pathways in cancer cells, which could affect NK cell-mediated tumor cell death. For example, AKT inhibits pro-apoptotic caspase-9 and Bad and reduced expression of proapoptotic BH3-only proteins,[205] although, as indicated above, it is not clear yet the conditions at which these alterations can favor cancer immunoevasion of NK cell- mediated killing.[137,138]

While there are no studies specifically examining the influence of oncogenic mutations in the PI3K/AKT/TOR pathway on NK cell antitumoral activity, insights can be gleaned, and speculative observations can be made based on studies exploring the role of this pathway in the regulation of NK cell ligand expression. Several studies have analyzed the role of PI3K in the expression of inhibitory (classical and non-classical HLA-I) and activating (MIC, ULBP and Rae families) ligands in humans and mice. Independent studies using chemical inhibitors and activators found that activation of PI3K-AKT pathway inhibited HLA-I expression in cancer cells.[206,207] Another study found that placental- derived leptin enhanced inhibitory non-classical HLA-G molecule expression in trophoblasts by the MEK/Erk and PI3K-AKT pathways.[208] While the latter is not explicitly mentioned in a tumoral context, it is worth experimentally validating this extrapolation since, although potential differences are recognized, the interaction between mother and fetus bears notable similarities to the immune-cancer relationship. Indeed, with appropriate caution, regulating immunity at mother-fetus interface has inspired different discoveries in cancer immunoevasion.[209]

Regarding activating ligands, constitutive activation of PI3K pathways can increase the expression of various ligands from the MIC, ULBP, and Rae families in cancer cells.[210–213] Although these ligands are typically defined as stress response ligands due to their association with cellular stress, the term "stress" is challenging to define, and the specific molecular pathways underlying their activation are complex. NKG2D ligands are regulated at multiple stages of biogenesis, including transcription, RNA stabilization, protein stabilization, and cleavage from the cell membrane. Ongoing in-depth studies have provided increasingly detailed insights into the specific pathways that modulate the expression levels of these proteins.[213,214]

For example, it has been shown that HER2 signaling induces the expression of MICA/B via the PI3K/AKT pathway in breast cancer cells, enhancing their susceptibility to NK cells.[210] Similarly, the EGFR tyrosine kinase inhibitor (TKI) gefitinib has been reported to downregulate the expression of MICB and ULBP–2/5/6 in non-small-cell lung cancer cells, likely through inhibition of the PI3K/AKT pathway.[215] However, other studies have shown that EGFR TKIs, such as erlotinib and gefitinib, can enhance the susceptibility of lung cancer cells to NK cell-mediated lysis by inducing ULBP1, attributing this increase to the inhibition of the PKC pathway.[216] It is important to note that these studies used different cell lines, which may exhibit varying expression of driver oncogenes or even different sensitivities to these drugs.

In addition, treatment with vorinostat or pterostilbene upregulated MICA expression via the PI3K/AKT signaling pathway and improved the ability of NK cells to kill cancer cells.[211,212] Finally, BCR/ABL activation in chronic leukemia cells enhanced MICA expression and NK cell-dependent cytotoxicity by a pathway dependent on PI3K/mTOR.[213] Interestingly, BCR/ABL inhibition by Imatinib was shown to decrease MICA protein secretion, leading to increased susceptibility of cancer cells to NK cells. Thus, the efficacy of Imatinib in enhancing NK cell killing may not be attributed to an increase in MICA activation receptor expression, but rather to a decrease in soluble MICA levels.[213] All these findings are good examples of how drugs used in cancer treatment can affect NK cell antitumoral activity by regulating the activity of potential oncogenic proteins, providing the basis for the possible use of oncogenes as targets to enhance NK cell-based therapies.

It is worth mentioning a recent paper showing that IL-18 enhances MICA/B expression in dendritic cells favoring NK cell-DC interaction.[217] Although in a different context, since IL-18 is usually enhanced in some tumors, it is tempting to speculate on the implications of this finding in the recognition of cancer by NK cells.

As deduced from the preceding findings, PI3K activation seems to promote a shift toward NK cell activation and tumor recognition, seemingly indicating the tumor's strategy to evade T cells. However, as indicated above, additional mechanisms related to the immunosuppressive profile of TME, some of which are also regulated by the PI3K pathway, are likely to contribute to the immunoescape of NK cell immunosurveillance. Thus, interfering with these immunosuppressive pathways like TGF-β might present a chance to favor NK cell-mediated elimination of PI3K mutated tumors as mutations in this pathway appear to enhance cancer cell susceptibility to NK cells.

Beyond tumor mutations, recent findings suggest germline mutations in the PIK3CD gene can impair NK and CD8+ T cell cytotoxicity, leading to compromised immunity against herpesviruses and impaired tumor surveillance.[218]

3.5. STAT protein family: STAT3 and STAT5

STAT3, a member of the JAK-STAT signaling pathway, is constitutively activated in multiple cancers: colon, head and neck, pancreatic, breast, and hematological neoplasias.[219–222] It coordinates key cellular mechanisms like cell differentiation, proliferation, immune function, and apoptosis. However, it is also well known for its role in mediating tumor immune evasion.[223,224] For example, in multiple myeloma or CRC, STAT3 has been described to directly repress the transcription of NKG2D ligands (e.g. MICA) and therefore to inhibit the NK cell-mediated tumor surveillance. In those studies, the inhibition or knockdown of STAT3 led to a stronger NKG2D-dependent tumor cell death by NK cells.[225,226] An increase in other NK ligands (e.g. MICB or ULBP2) following STAT3 inhibition has also been reported.[227,228] Additionally, when STAT3 is constitutively active, it can trigger the release of immunosuppressive cytokines such as IL-10 or TGF-β that will recruit immune cells (e.g. Tregs), which have an immunosuppressive effect on NK cells' cytotoxicity.[229]

Besides STAT3, another member of the STAT family is commonly activated in solid cancers, the STAT5 protein. Over the years, the constitutive activation of STAT5 has been associated with hematological malignancies (e.g. leukemia) and solid tumors (e.g. breast, lung, and colorectal cancer).[230–233] Nonetheless, the way in which it promotes tumor proliferation has been less described.[234]

3.6. Tumor suppressor genes

To finish this section, we will focus on tumor suppressor genes that have been shown to directly affect NK cell antitumoral activity, specifically the retinoblastoma (Rb) and p53 genes, which control different biological processes like cell death, cell cycle, and terminal differentiation, similarly to oncogenes (see Figure 3).

Rb is frequently inactivated in many human cancers, such as retinoblastoma, breast cancer, prostate cancer, and small cell lung cancer.[235,236] The canonical pathway whereby Rb exerts its tumor suppressive is through regulating the G1/S transition during cell cycle progression. For doing so, it modulates the activity of E2F transcription factors. In most cancers, alterations in this gene lead to a more aggressive tumor cell phenotype; it promotes tumor metastatic activity and drug resistance. Since uncontrolled cell proliferation and metastasis are hallmarks of cancer cells,[13] it has been postulated that genes acting as Rb function inhibitors (e.g., CCND1 and CDK4) are identified as oncogenes. Conversely, those promoting Rb functions (e.g., cyclin-dependent kinase inhibitors like CDKN1A, CDKN1B, and CDKN2A) are tumor suppressor genes.

Again, most evidence on the role of Rb on NK cell activity is indirect from studies showing that suppression of Rb signaling affects immunomodulators involved in NK cell activity, including IL-6, CCL2, or prostaglandin-endoperoxide synthase 2 (PTGS2),[237,238] all of them negative regulators of NK cell activity by different means including direct action on NK cells or indirect regulation by promoting Treg, TAM and/or MDSCs infiltration (CCL2).[239,240] In 2015, the tumor suppressor gene Rb was established to negatively regulate NK cell cytotoxicity in mouse glioma. Deleting Rb was sufficient to enhance resistance to NK cell-mediated cytotoxicity, albeit the correlation with changes in activating and inhibitory ligands could not be well established as, apparently, deletion of Rb decreased activating ligands while increasing MHC-I.[241] Thus, further experiments will be required to analyze the mechanisms by which Rb mutations promote tumor resistance to NK cells.

p53 is a crucial tumor suppressor gene that is best known for maintaining genomic stability and inhibiting cell proliferation.[242,243] As a transcription factor, it regulates genes involved in cell cycle, apoptosis, DNA repair, and many others.[244] Loss of p53 function is frequently involved in cancer development.[245] Unlike other tumor suppressor genes (e.g. BRCA1 or Rb), which are usually inactivated by deletions or truncating mutations, most p53 mutations in cancers are missense mutations. p53 mutations origin full-length mutant p53 proteins (mutp53) with only one amino acid substitution.[246,247] These mutations present two principal effects. On the one hand, there is the loss of the wild-type p53 (wtp53) function, and on the other hand, mutp53 tends to promote tumorigenesis through the gain-of-function (GOF) mechanism. Plenty of GOF activities have been reported so far: cell proliferation promotion, metastasis, genomic instability, metabolic reprogramming, cell stemness, tumor microenvironment reshaping, immune suppression and resistance to therapy in cancer.[247–249]

The status of p53 within cancer cells profoundly influences the immune response, including regulation of PD-L1 and MHC-I expression, polarization of TAMs or inhibition of T and NK cell infiltration.[250–252] The loss of the wtp53 also has important effects on NK cell-mediated killing. In 2011 Textor, S. *et al.*, showed that NKG2D ligands expression (e.g. ULBP1 and ULBP2) are upregulated at the transcriptional level by wtp53 but not mutp53. This transcription factor binds p53-responsive elements in the ULBP1/2 genes, leading to a higher expression of these NK cell ligands, thereby enhancing NK cell NKG2D-based cytotoxicity.[253] The same findings were confirmed in 2022 by Uddin, MB *et al.*, in a murine model, showing that the p53 missense mutant G242A, which corresponds to the human G245A mutation, plays a significant role in suppressing the activation of host NK cells. This suppression enables breast cancer cells to evade immune assault and avoid rejection by the immune system.[254]

Mutp53 is also recognized for its role in inhibiting apoptosis and autophagy, thus promoting the development of apoptosis resistance features.[245,255] Hence, the wtp53 protein is also relevant for regulating GZMB-mediated apoptotic pathways by cytotoxic T and NK cells.[256] In p53-mutated breast cancer cells, Chollat-Namy, M. *et al.*, showed that the reactivation of p53 transcriptional activity by a p53-stabilizing agent (CP-31398) increased their lysis by NK cells. They could not observe a modified expression of known p53 targets related to NK cell activity, but they clearly showed an autophagy promotion and triggered the sequestration of anti-apoptotic proteins (e.g. Bcl-XL and XIAP) in autophagosomes which potentiated GZMB-induced mitochondrial outer membrane permeabilization and caspase-3 cleavage; thus promoting GZMB-induced cell death.[257]

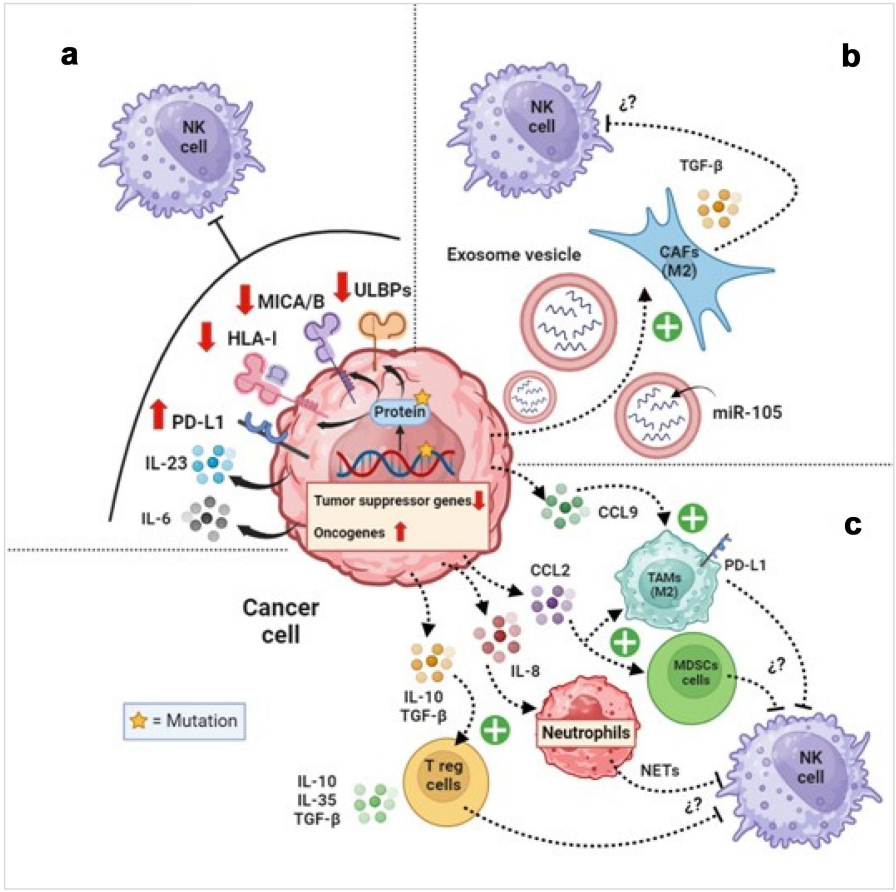

Figure 3. Effects of oncogenes and mutated tumor suppressor genes in NK cell immunosurveillance. (A) Tumor cells can directly inhibit NK cell function by secreting interleukins (e.g. IL-6 or IL-23) or by modulating the expression of NK cell receptor ligands (e.g. HLA-I, MICA/B or PD-L1). (B) Tumor cells can secrete exosome vesicles that contain specific microRNAs that will induce changes in other immune cells (e.g. TAMs or CAFs), inducing their transformation into a protumorigenic phenotype. (C) Tumor cells secret multiple molecules (e.g. CCL9, CCL2, IL- 8, IL-10 or TGF-β) that will recruit additional immune cells that have an immunosuppressive effect on the cytotoxicity of NK cells. The regular arrows show evidence already demonstrated while dotted arrows are hypothetical evidence that has not been proved yet. Figure created with BioRender.com.

This tumor suppressor gene is also well-known to regulate cell metabolism; however, how it affects metabolism-induced ligands' expression is not completely understood. Belkahla, S. *et al.*, showed that dichloroacetate (DCA) induced either OXPHOS in tumor cells and also the expression of NK ligands such as MICA/B, ULBP1, and ICAM-I in a wtp53-dependent mechanism (the opposite effect was observed in mutant or null p53). This all means that DCA can sensitize tumor cells but only those that are wtp53-expressing cells.[258]

Overall, these findings highlight the complex interplay between oncogenes and mutated tumor suppressor genes in the immune microenvironment and their effects on NK cell activating or inhibitory ligands, emphasizing the potential for targeted therapies in cancer treatment (See Table 1).

4. Strategies to overcome oncogene-mediated NK cell immunosuppression

The overexpression of anti-apoptotic proteins, or conversely, the suppression of proapoptotic proteins, is a common outcome of oncogene activation.[131] Current therapeutic strategies exploring the combinations of specific inhibitors targeting the dysregulated proteins, typically Bcl-2 or Bcl-XL, along with selectively activated NK cells, are being investigated,[137,138] proposing to establish a BH3 profile of the cancer cells to design specific trials to enhance the efficacy of adoptive NK cell therapy.[137,138] However, previous studies have proposed that a higher dose of expanded NK cells can overcome tumor resistance in hematological tumors, although this might present some limitations for patient treatment, especially in the case of solid tumors or with high tumoral burdens.[137]

However, reaching these higher doses might be plausible by designing specific trials to use NK cells as adjuvant therapy after stem cell transplant, chemotherapy, radiotherapy, or surgery to enhance tumor elimination and prevent recurrence.

KRAS and Myc alterations have also been strongly linked to the dysregulation of CDK4 activity. Besides, NK cell activation ligands were restored during the CDK4/6 inhibitor's treatment, observing an increase of ICAM1, MICA/B, and ULBPS.[260] The combination of protein inhibitors such as MEK and CDK4/6 inhibitors also induces senescence, possibly explaining the subsequent NK cell clearance, as NK cells play a crucial role in clearing cancer and senescent cells.[260,261] Therefore, the strategic use of CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, in combination with NK cell adoptive therapy or with antibodies inducing NK cell-mediated ADCC, as well as with bispecific antibodies targeting NK cells, emerges as a promising strategy to enhance the

Table 1. Regulation of NK cell ligands' expression in tumor cells. CML (chronic myeloid leukemia); CRC (colorectal cancer); MM (multiple Myeloma); NSCLC (non-small cell lung Cancer); p53-RE (p53-responsive elements).

Oncogene	NK cell ligands	Tumor/Cell Type	Pathway	References
Myc	MICA/B ↓	CML	miR17	154
	MICA/B ↑	Lung cancer	Together with $KRas^{G12D}$	18
	HLA-I	melanoma cell lines neuroblastoma cell line	mRNA ↓	158,159
Ras	NKG2D ↑	Ovarian and breast cancer	MAPK, PI3K, and DNA damage	168,259
	PD-L1 ↑	Lung cancer	MAPK and PI3K	170
	HLA-I ↓	Mesothelioma cell line	MAP kinase pathway	190,191
PI3K	HLA-I ↓	Head and neck carcinoma and colon cancer	PI3K-AKT	206,207
	MICA/B ↑	Breast cancer	Her2-PI3K-AKT	210
	MICA/B ↑	CML	cAbl-PI3K-mTOR	213
	MICA/B ↑	Cervical cancer and T-cell lymphoma	Vorinostat-PI3K-AKT Pterostilbene-PI3K-AKT	211,212
STAT3	MICA ↓	CRC cell line HT29 and MM	STAT3 binding to the MICA promoter	225,226
		CML cell line K562	JAK/STAT3	227
	ULBP2 ↓	CML cell line K562		228
	MICB ↓	Gastric adenocarcinoma		253
P53	ULBP1/2 ↑	NSCLC H1299 cell line	wtp53 binds to p53-RE	252,254
	PD-L1 ↑	Lung adenocarcinoma and breast cancer	mutp53 ⇒ PD-L1 mRNA ↑	250
	HLA-I ↑	colon cancer cell line HCT116	wtp53 ⇒*ERAP1* mRNA ↑ ⇒HLA-I	

eradication of tumor cells by NK cells. This innovative therapeutic approach offers an exciting prospect in the field of cancer immunotherapy, strengthening the potential for more effective tumor clearance and improved patient outcomes.

MICA/B and ULBPs are potent activator ligands for the NK cell receptor NKG2D. As indicated above their down-regulation has consistently been observed in numerous studies across various cancer contexts related to oncogenes or tumor suppressors genes.[157,259] Therefore, diverse approaches attempt to target the NKG2D axis for cancer immunotherapies. Additionally, in NKG2D ligand down- regulation, their cleavage and release as soluble forms also significantly influence NK cell activity. This impact is two-fold: not only does it directly result in the down-regulation of activation signals, but it also reshapes NK cells toward a pro-inflammatory phenotype. While membrane-bound NKG2D ligands boost NK cell cytotoxicity, soluble NKG2D ligands promote the expression of cytokines such as GM-CSF, IL-10, or CCL4, as well as the activation of pro-inflammatory signaling pathways like PKC-θ and ADAP.[262] In 2011, another study uncovered a possible new immunotherapy approach. Since ULBP1 and ULBP2 are direct p53 target genes, treating tumor cells with RITA (Reactivation of p53 and Induction of Tumor cell Apoptosis) would reactivate wild-type p53 and therefore would up- regulate the NKG2D ligands' expression. This novel design would enhance NK cell cytotoxicity.[253]

Considering that p53 inactivating mutations are frequently found in human tumors and the dependency of the GZMB-dependent apoptotic pathway of T and NK cells in the wtp53 protein, reactivating the function of p53 will be an interesting approach. Chollat-Namy, M. *et al.*, showed in their study that the pharmacological reactivation of a wt-like p53 function in p53-mutated breast cancer cells using a small molecule (CP-31398) increases their sensitivity to NK-mediated lysis.[257] This tumor suppressor gene is also well-known to regulate cell metabolism. However, due to the already described association between wtp53 and NK cell ligands, treatment with DCA, or similar drugs could decrease tumors with high proliferation as well as increase the effectiveness of CAR NK cell or allogeneic NK cell therapies.[258]

The up-regulation of the immune checkpoint PD-L1 often occurs due to genetic alterations within cancer cells, including Ras and p53 mutations. Furthermore, the expression of PD-1 on NK cells has been documented, raising concerns about the capacity of PD-L1 engagement to attenuate NK cell function.[110,111,113] The development of immunotherapy has paved the way for a robust research focus on blocking the PD-1/PD-L1 inhibitory pathway, yielding remarkable results in various cancer types. Interestingly, the effectiveness of this therapy is not solely rooted in releasing the brake to the immune system; it also involves directing immune cells, primarily NK cells, by tagging the tumor with antibodies capable of inducing ADCC.[115]

As previously discussed, in some cancers tumor cells reduce the MHC-I expression to avoid T-cell recognition and their subsequent killing.[52] However, NK cells can recognize these "low immunogenic cells" and kill them. In a mouse model of carcinogen-induced Non-Small Cell Lung Cancer it was shown that knocking out STAT3 led to down-regulation of MHC I making those cells more susceptible to NK cell-mediated death.[263] Moreover, as already mentioned, tumors that harbor a constitutive activation of STAT3 release classical immunosuppressive cytokines (e.g. IL-10 and TGF-β), thus impairing tumor immune surveillance.[229] This is why STAT3 inhibitors are gaining increasing therapeutic interest.[264]

Beyond activation or inhibition ligands, NK cell activity is also modulated by chemokines. Modulating the secretion of chemokines, such as CXCL9 and CXCL10, can significantly impact NK cell tumor infiltration. Hence, the observed down-regulation of CXCL9 due to oncogenic activity is not only associated with reduced NK cell infiltration across various types of cancer[265] but also directly links the low number of infiltrated NK cells in CXCL9-deficient tumors to the worst prognosis in cholangiocarcinoma,[161] opening the door to immunotherapy by targeting the CXCL9/CXCR3 axis to promote lymphocyte infiltration.

Altered gene expression in tumor cells typically triggers adopting a migratory and invasive phenotype, collectively

known as epithelial-mesenchymal transition (EMT). During EMT, significant phenotypic changes occur in cancer cells, leading to highly invasive properties. Among these changes, the regulation of cell-cell adhesion markers, such as epithelial cadherin and cell adhesion molecule 1, is altered,[266] which can enhance NK cell cytotoxicity,[267] contributing to a better understanding of the pivotal role NK cells play in controlling metastasis.

The generation of reactive oxygen species (ROS) within tumors is a common characteristic resulting from the activation of oncogenes or the inactivation of tumor suppressors, such as the Rb gene. ROS directly suppresses NK cell activity. Various NK cell priming protocols have been explored to counteract NK cell ROS inactivation, yielding NK cells enriched in the ROS scavenger thioredoxin (Trx1). These Trx1-enriched NK cells exhibit protection against ROS, mirroring the observation of Trx1+ NK cells in lung cancer patients with ROS. According to this observation, when dividing these patients, smokers display higher ROS levels and worse prognoses compared to nonsmokers.[268,269]

5. Concluding remarks and future perspectives

In general, how mutations responsible for carcinogenesis shape the TME and modulate the antitumoral activity of NK cells remains largely unknown. The only clear fact is that NK cells have a genuinely complex regulation. Although they do not require prior antigen exposure, their antitumoral function relies entirely on different activating and inhibitory signals. Several NK cell ligands have been described; some potentiate NK cell activity, while others have an immunosuppressive effect. As already discussed here, the TME is crucial as it strongly affects NK cell cytotoxicity. Especially in an anti-inflammatory context, several cell populations (e.g. TAMs, MDSCs, Tregs or CAFs) and molecules (e.g. IL-6, IL-10, TGF-β, PGE2 or IDO) are known for their negative impact on NK cell activity, thus promoting tumor progression. It is well known that several of those molecules have been secreted by cancer cells with the aim of modifying the microenvironment on their beneath.

It should be noted that NK cell functionality can also be altered by tumoral cell genetic components: oncogenes and tumor suppressor genes. During cancer progression, these genes are frequently mutated, ranging from loss of wild-type functions to overactivation of genes or acquisition of new functions. However, not everything is well understood. Some contradictions remain ambiguous and necessitate further investigation. For example, the activation of Myc in cancer cells has been proven to trigger the up-regulation of NKG2D ligands and down-regulation of MHC genes, both potent activating signals for NK-like cells. Why this is not enhancing NK cell activity is still not clear. We hypothesize that during the first stages of tumor development, NK cells are ready to eliminate cancer cells that have suffered oncogenic Myc transformation, while, in more advanced stages, cancer cells have acquired additional ability by using another oncogene to avoid NK cell action.

There is no doubt that oncogenes are capable of modulating NK cell death machinery. They can inhibit apoptosis (e.g. increasing anti-apoptotic proteins, Bcl-2 or Mcl-1, or down-modulating pro- apoptotic proteins, caspase-9, Bad or BH3-only proteins); down-regulate NK cell activating ligands (e.g. MICA/B or ULBPs); up-regulate NK cell inhibitory ligands (e.g. PD-L1); generate resistance to the PRF/GZM pathway and promote immunosuppressive cytokines secretion (e.g. IL-10 or TGF-β); aiding angiogenesis and recruitment of negative regulators of NK cells. Nonetheless it is still not clear if this is enough per se to enhance resistance to NK cytotoxicity. In any case, whether the acquisition of cell death mutations due to oncogenic activation would enhance NK cell tumor escape in the context of other immunosuppressive factors such as TGF-β or hypoxia remains to be analyzed.

In addition to the aforementioned, it should be highlighted that many of the studies conducted in this area are based on mouse models. Although these models have allowed important advances in the field of immunity and cancer, they are not perfect. Compared to humans, these models exhibit different ligand expression and regulation, which clearly limits their translation to human NK cell biology. There are also discrepancies in innate and adaptive immunity between the two species, which must be considered when using mice as preclinical models of human diseases.

It is also crucial to recognize that drugs designed to target oncogenes in cancer cells may inadvertently impact immune cell functions, including NK cells, due to shared characteristics with tumor cells, such as high proliferative rates and metabolic remodeling. This suggests that these drugs could influence the antitumor activity of immune cells, potentially inducing the opposite effect to what is desired, highlighting the intricate interplay between tumor cell genetics and immune cell responses, which underscores the need for comprehensive consideration of immune modulation in cancer therapy. Understanding the potential effects of these drugs on both cancer sensitivity to NK cells and the sensitivity of NK cells to the drugs themselves is crucial for optimizing treatment strategies and improving patient outcomes.

Despite the critical role of NK cells in antitumoral immunity, the direct impact of oncogenes on NK cell function has been largely overlooked in cancer research. While numerous studies have dissected the influence of oncogenes within the tumor microenvironment and on tumor cell death pathways, the focus has primarily been on T cells, leaving a significant gap in our understanding of NK cell biology. This disparity is evident in the limited number of papers exploring the direct effects of oncogenes on NK cell-mediated antitumoral responses, particularly within the context of the TME or tumor cell death mechanisms.

However, addressing this knowledge gap holds immense potential for enhancing cancer elimination strategies. By elucidating how oncogenes modulate NK cell activity, we can leverage this understanding to develop more comprehensive immunotherapeutic approaches that simultaneously target both T and NK cells. This integrated approach becomes increasingly crucial in light of the frequent tumor recurrences observed following CAR T cell-based immunotherapies. Moreover, emerging evidence suggests that while oncogenes may suppress T cell activity, they inadvertently render tumor cells more susceptible to NK cell recognition and elimination.

This paradoxical effect underscores the importance of exploiting the vulnerabilities of tumor cells to NK cell-mediated cytotoxicity. By capitalizing on strategies tumor cells employ to evade T cell surveillance, we can potentially enhance their visibility to NK cells, thus augmenting the overall antitumoral response.

In essence, unlocking the mechanisms by which oncogenes modulate NK cell function represents a promising avenue for refining cancer immunotherapy strategies. Through a concerted effort to investigate the direct impact of oncogenes on NK cells within the complex TME, we can pave the way for developing innovative therapeutic interventions that harness the synergistic capabilities of both innate and adaptive immune responses. By bridging the gap between T cell-centric research and the understudied realm of NK cell biology, we can aspire to achieve more durable and effective outcomes in the fight against cancer.

Disclosure statement

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