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Review

Molecular Perspectives on Innate Immune Homeostasis: Interlocking Roles of Natural Killer and Dendritic Cells

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Abstract

Innate immune homeostasis depends on the coordinated regulation of protective responses and tolerance across tissues. Although natural killer (NK) cells and dendritic cells (DCs) are traditionally viewed as cytotoxic effectors and antigen-presenting cells, respectively, accumulating evidence indicates that their reciprocal interactions actively determine the magnitude, duration, and functional direction of immune responses. This review examines the NK-DC axis as a central regulatory framework for innate immune homeostasis, integrating cellular interactions with cytokine signaling, receptor-mediated regulation, antigen presentation, and tissue-specific microenvironmental cues. We first examine NK cell development, subset specialization, activating and inhibitory receptor signaling, and effector functions, followed by analysis of DC heterogeneity, antigen processing, cross-presentation, and immunogenic versus tolerogenic programs. We then synthesize the molecular mechanisms underlying NK-DC communication, including receptor–ligand interactions, reciprocal cytokine signaling, and NK-mediated editing of DCs. Attention is given to the integration of regulatory T cells (Tregs) into this framework, in which Tregs act as downstream regulatory partners that reinforce peripheral tolerance rather than as equivalent components of the central NK-DC axis. The review further examines how checkpoint signaling, metabolic stress, hypoxia, and other features of the tissue microenvironment reshape NK-DC communication in cancer, chronic infection, and autoimmune disease. These mechanisms are considered alongside emerging therapeutic approaches, including cytokine-induced memory-like NK cells, CAR-NK therapy, immune checkpoint blockade, dendritic-cell vaccines, and tolerogenic DC-based interventions. By integrating molecular mechanisms, tissue context, disease-associated dysregulation, and therapeutic strategies, this review proposes an integrated framework for understanding how NK-DC interactions establish, maintain, and potentially restore immune homeostasis.

Keywords

Natural killer cells, Dendritic cells, Innate immune homeostasis, NK-DC crosstalk, Immune tolerance, Tumor microenvironment, Immunotherapy, Regulatory T cells

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1. Introduction

Innate immune homeostasis has emerged as a dynamic and actively regulated process rather than a passive balance between immune activation and tolerance. Although innate immunity was traditionally viewed as the host's first line of defense against infection, accumulating evidence demonstrates that innate immune cells continuously integrate microbial, metabolic, and tissue-derived signals to calibrate immune responsiveness according to physiological context. Disruption of this regulatory equilibrium contributes directly to the pathogenesis of autoimmune diseases, chronic inflammatory disorders, persistent infections, and cancer, highlighting innate immune homeostasis as a central determinant of health and disease rather than merely an early antimicrobial defense [1,2].

Among the cellular networks governing this process, mutual communication between natural killer (NK) cells and dendritic cells (DCs) has emerged as a central regulatory axis. Rather than functioning independently as cytotoxic effectors or professional antigen-presenting cells, NK cells and DCs continuously shape each other's differentiation, activation state, cytokine production, and survival through bidirectional signaling involving cytokines, chemokines, receptor–ligand interactions, and immunological synapses. This dynamic crosstalk not only determines the magnitude of innate immune responses but also influences subsequent adaptive immunity across tissue microenvironments, including the lung, gastrointestinal tract, liver, and tumor niche. Recent studies further indicate that the biological outcome of NK-DC interactions is highly context dependent, varying according to tissue-specific signals, inflammatory status, and metabolic conditions [3,4].

Regulatory T cells (Tregs) provide an additional layer of immune regulation by stabilizing the homeostatic programs initiated through NK-dendritic-cell (DC) interactions. Rather than representing an equivalent regulatory axis, Tregs function primarily as downstream modulators that reinforce peripheral tolerance by limiting excessive activation of both NK cells and DCs through inhibitory cytokines and cell-contact-dependent mechanisms. Consequently, immune homeostasis is increasingly viewed as the product of an integrated NK-DC-Treg regulatory network, in which the reciprocal NK-DC axis establishes immune set points while Tregs maintain their long-term stability. Dysregulation of this network contributes to chronic inflammation, immune exhaustion, autoimmune disease, and tumor immune escape, making restoration of coordinated innate immune regulation an emerging therapeutic objective [5]. This framework is illustrated in Figure 1.

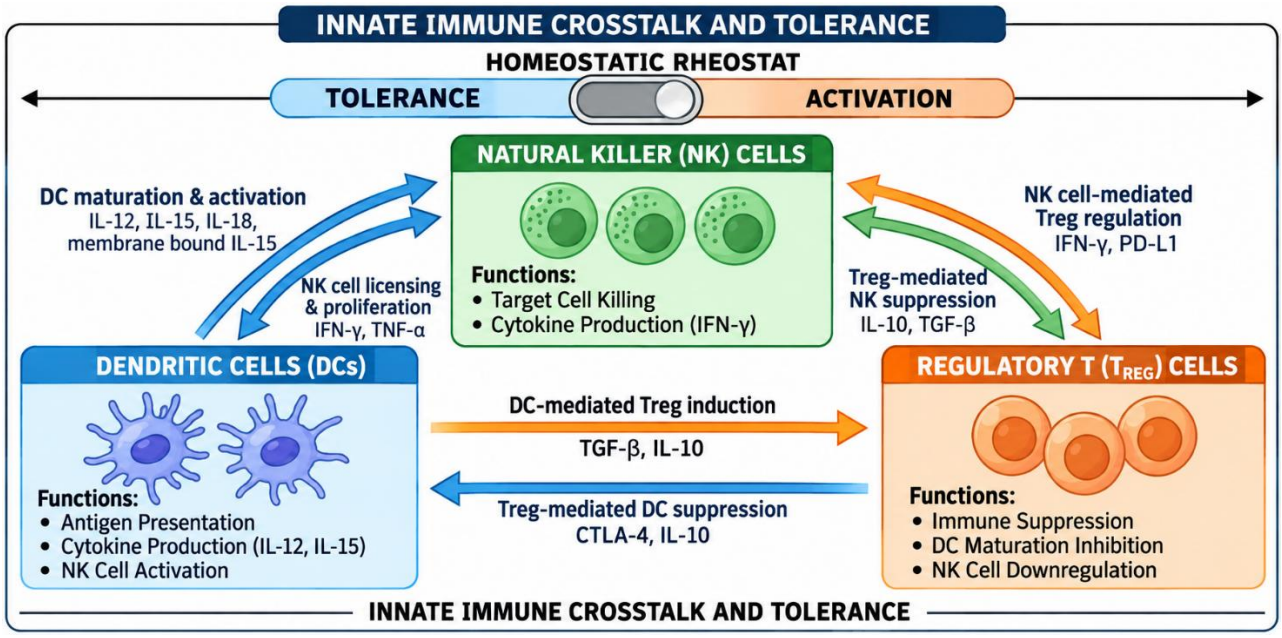

Figure 1. The NK-DC homeostatic rheostat and its regulation by downstream Treg-mediated tolerance. The figure illustrates bidirectional crosstalk between NK cells and DCs, which constitutes the primary regulatory axis controlling innate immune activation and homeostasis. Tregs are depicted as downstream modulators that reinforce peripheral immune tolerance by suppressing excessive NK cell and DC activation through inhibitory cytokines and cell-contact-dependent mechanisms.

The central premise of this review is therefore that NK-DC communication represents a context-dependent regulatory interface through which innate immune responses are calibrated, rather than a fixed pathway that uniformly promotes activation. We synthesize evidence spanning NK cell receptor signaling, DC maturation and antigen presentation, reciprocal cytokine networks, NK-mediated DC editing, immune checkpoints, metabolic regulation, and tissue-specific microenvironments. We further examine how disruption of these mechanisms contributes to autoimmune and inflammatory diseases, chronic infection, and cancer, and how emerging interventions—including NK cell engineering, checkpoint blockade, DC-based therapies, and strategies designed to restore immune tolerance—may be used to manipulate this regulatory interface.

A further objective is to identify where the current evidence remains incomplete. Although substantial mechanistic evidence supports NK-DC communication, important questions remain regarding the extent to which findings obtained from experimental systems translate to human tissues, how distinct NK and DC subsets interact *in vivo*, and how metabolic and tissue-specific signals alter these interactions during chronic disease. Addressing these gaps may be essential for developing therapies that do not simply increase immune activation but instead restore appropriate immune responsiveness while preserving tissue tolerance.

2. Molecular Basis of Innate Immune Homeostasis

Innate immune homeostasis depends on the ability of immune cells to distinguish signals that require protective responses from those that should be tolerated. This balance is not static; it is continuously adjusted according to the intensity, duration, and anatomical context of environmental and tissue-derived signals. Pattern-recognition receptors (PRRs), cytokine networks, cellular interactions, and metabolic conditions collectively determine whether innate immune activation remains transient and protective or progresses toward sustained inflammation and tissue injury. Thus, homeostasis can be viewed not simply as the absence of inflammation but as the capacity to calibrate the magnitude and duration of immune responses according to biological context [6].

PRRs provide an important upstream mechanism for this calibration. Toll-like receptors (TLRs), NOD-like receptors (NLRs), and cytosolic nucleic-acid sensors detect pathogen-associated or damage-associated molecular patterns and activate interconnected signaling pathways, including NF-κB, interferon-regulatory pathways, and inflammasome-associated responses. Importantly, PRR signaling does not produce a uniform biological outcome. The resulting response depends on the type of receptor engaged, the nature and persistence of the stimulus, the cellular compartment in which sensing occurs, and the surrounding cytokine and metabolic environment. Consequently, innate sensing can generate qualitatively different downstream programs, ranging from transient inflammatory activation to sustained immune regulation [7].

DCs are particularly important in translating these upstream signals into distinct immune states. Following innate sensing, DCs can acquire immunogenic characteristics associated with increased costimulatory capacity and production of inflammatory mediators, thereby promoting effector lymphocyte responses. Under steady-state conditions or within regulatory tissue environments, however, DCs can adopt tolerogenic programs characterized by reduced costimulatory activity and production of regulatory mediators such as IL-10 and TGF-β, favoring peripheral tolerance and regulatory T-cell responses. The immunogenic–tolerogenic distinction should therefore be regarded as a functional continuum rather than as two permanently fixed DC phenotypes, because DC behavior can change according to the strength and persistence of environmental signals [8].

The consequences of innate sensing extend beyond individual innate-cell populations because DC-mediated antigen presentation provides an important interface between innate and adaptive immunity. Antigens acquired by antigen-presenting cells are processed and displayed as peptide–major histocompatibility complex (MHC) complexes, allowing T lymphocytes to respond according to the antigenic and costimulatory context established by the presenting cell. Consequently, the same antigen can contribute to effective immunity or tolerance depending on the maturation state and regulatory environment of DC. Disruption of these mechanisms can therefore affect multiple biological processes and has been implicated in autoimmune inflammation, metabolic disturbances, persistent infection, and malignancy [9].

NK cells add a reciprocal regulatory component to this system. Rather than acting solely as terminal cytotoxic effectors, NK cells respond to cytokines and cellular signals generated during DC activation and can, in turn, modify DC function through cytokine production and selective interactions with DC subsets. This creates a feedback relationship in which DC-derived signals influence NK cell activation while NK-derived signals can alter the functional state and quality of DC-mediated immune responses. The biological consequence of this feedback is context dependent: it can amplify protective immunity during infection or tumor surveillance, but dysregulated or persistent signaling may contribute to chronic inflammation, immune dysfunction, or inadequate immune surveillance [10].

Taken together, these mechanisms suggest that innate immune homeostasis is generated through interconnected regulatory loops rather than through isolated cellular pathways. PRRs provide upstream environmental sensing, DCs translate these signals into immunogenic or tolerogenic programs, and NK cells provide reciprocal feedback that can reinforce or constrain DC function. The resulting network establishes the functional conditions under which adaptive immunity is subsequently activated or restrained. This systems-level framework provides the basis for the following sections, which examine the molecular regulation of NK cells and DCs individually before integrating their reciprocal interactions and their dysregulation in disease.

3. Molecular and Functional Regulation of NK Cells

3.1 NK Cell Development and Subsets

NK cells develop from hematopoietic progenitors through a sequence of lineage-commitment and maturation events that establish their capacity for cytotoxicity, cytokine production, and tissue adaptation. In peripheral blood, human NK cells

are commonly divided into CD56bright and CD56dim populations. CD56dim cells constitute the majority of circulating NK cells and generally display greater constitutive cytotoxic capacity, whereas CD56bright cells are characterized by relatively strong cytokine-producing capacity and are enriched in secondary lymphoid and tissue compartments. This distinction is useful for describing major functional differences between circulating NK populations, but it should not be interpreted as an absolute separation of effector functions, because both populations can acquire overlapping functional properties following appropriate cytokine or inflammatory stimulation [3].

NK cell development involves progressive commitment from hematopoietic progenitors toward the NK/innate lymphoid lineage, followed by acquisition of characteristic receptors, signaling machinery, and effector functions. The bone marrow provides an important developmental environment, but the phenotype and function of mature NK cells are subsequently influenced by signals encountered outside the bone marrow. Cytokines, stromal interactions, and tissue-specific factors can modify receptor expression, metabolic activity, cytokine responsiveness, and effector potential, indicating that NK cell maturation cannot be understood exclusively as a fixed developmental sequence [11].

This distinction becomes particularly relevant for tissue-resident NK cells. NK populations with distinct phenotypic and functional characteristics have been identified in organs including the liver, uterus, lung, and lymphoid tissues. Compared with circulating NK cells, tissue-resident populations can exhibit specialized retention programs and effector functions adapted to local physiological requirements, including antiviral defense, vascular remodeling, and regulation of tissue inflammation. These observations indicate that the local microenvironment contributes substantially to NK cell functional specialization after lineage development and can modify the balance between cytotoxic, cytokine-producing, and regulatory activities [12,13].

The traditional CD56bright/CD56dim classification therefore provides a useful framework but does not fully capture the heterogeneity of human NK cells. Increasing evidence from high-dimensional phenotyping and transcriptomic approaches has revealed transitional and tissue-adapted populations that do not conform neatly to this binary classification. Inflammatory cytokines, tissue-derived signals, and metabolic conditions can alter NK cell functional states without necessarily representing a complete change in lineage identity. Thus, NK cell heterogeneity is better understood as the product of developmental history combined with continuous environmental adaptation, rather than as either a strictly linear maturation pathway or two completely independent cell populations [12,13].

This distinction has direct relevance to NK-DC communication. NK cells with different maturation and tissue-adaptation states may respond differently to DC-derived cytokines and receptor-mediated signals and may consequently exert different effects on DC maturation, cytokine production, or DC editing. Therefore, the functional consequences of NK-DC crosstalk are likely to depend not only on the activation state of the DC but also on which NK cell population is involved and the tissue context in which the interaction occurs. This subset- and tissue-dependent perspective provides an important framework for interpreting the molecular mechanisms of NK activation and NK-DC interactions discussed in the following sections.

3.2 Activation and Inhibitory Signaling

NK cell activation results from the integration of signals delivered by activating and inhibitory receptors, cytokine receptors, and the surrounding tissue environment. Inhibitory receptors such as killer cell immunoglobulin-like receptors (KIRs) and the CD94/NKG2A heterodimer recognize self-MHC class I molecules and normally constrain NK cell activation, thereby limiting damage to healthy cells. Conversely, loss or reduced expression of MHC class I on infected or transformed cells weakens inhibitory signaling and can favor NK cell activation through the process commonly referred to as missing-self recognition [14]. Activating receptors provide complementary information about cellular stress. For example, NKG2D recognizes stress-induced ligands, including MICA, MICB, and members of the ULBP family, which can be increased during infection, cellular stress, and malignant transformation and thereby promote NK cell cytotoxicity and cytokine production [15].

Signal integration occurs through interconnected intracellular pathways. Cytokines such as IL-2, IL-12, IL-15, and IL-18 activate JAK-STAT-dependent transcriptional programs that regulate NK cell development, survival, cytokine production, and effector differentiation. In parallel, PI3K-AKT and related signaling pathways contribute to metabolic adaptation, survival, degranulation, and cytotoxic responses downstream of activating receptors, including NKG2D and the natural cytotoxicity receptors [16]. The resulting signaling architecture allows NK cells to integrate receptor-derived information with cytokine and metabolic cues rather than relying on a single dominant activation pathway.

Inhibitory checkpoint receptors add another layer of regulation. NKG2A, TIGIT, and, in selected settings, PD-1 can constrain NK cell cytokine production and cytotoxicity, but their expression and functional importance vary considerably according to disease and tissue context. Persistent engagement of these pathways in tumors and chronic inflammatory or infectious settings can contribute to an impaired NK cell functional state [17]. Importantly, this does not necessarily imply a uniform state of irreversible “exhaustion”; NK cell dysfunction can encompass heterogeneous and potentially reversible changes in cytotoxicity, cytokine production, metabolism, receptor expression, and responsiveness to activating signals. This distinction is relevant when considering checkpoint blockade as a therapeutic strategy, because targeting a single inhibitory pathway may be effective only when that pathway represents a functionally important constraint within the disease microenvironment.

Taken together, NK cell activation is best understood as a context-dependent signaling decision produced by the convergence of receptor, cytokine, metabolic, and tissue-derived signals. This architecture allows NK cells to respond rapidly to infection or cellular transformation while maintaining safeguards against inappropriate tissue injury. It also provides a mechanistic basis for the subsequent NK-DC interactions: DC-derived cytokines can alter NK cell activation thresholds, while NK cell signaling and effector activity can reciprocally influence DC maturation and function.

3.3 Effector and Immunoregulatory Functions

NK cells combine rapid cytotoxic activity with broader immunoregulatory functions, allowing them to influence both the elimination of abnormal cells and the subsequent organization of immune responses. Their cytotoxic activity is mediated primarily through two complementary mechanisms. The first involves exocytosis of perforin- and granzyme-containing cytotoxic granules at the immunological synapse, resulting in target-cell membrane permeabilization and activation of apoptotic pathways. The second involves death-receptor signaling through NK cell expression of Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL), which engage cognate receptors on susceptible target cells and induce caspase-dependent cell death [18]. These mechanisms enable NK cells to respond rapidly to infected, stressed, or transformed cells without the antigen-specific priming required for conventional cytotoxic T-cell responses, providing an important component of early immune surveillance [19].

Beyond direct cytotoxicity, NK cells exert broad immunoregulatory functions through cytokine and chemokine production and through crosstalk with other immune cells. NK-derived IFN-γ and TNF-α activate macrophages, enhance antigen presentation by upregulating MHC and costimulatory molecules on DCs, and promote Th1-polarized T-cell responses [20]. By interacting with DCs in lymphoid organs and peripheral tissues, NK cells can drive DC maturation, influence the balance between effector T-cell priming and regulatory T-cell induction, and participate in editing of immature or dysfunctional DCs, thereby shaping the quality of adaptive immunity (discussed in detail in Section 5). In this way, NK cells function not only as cytotoxic effectors but also as key regulators at the interface of innate and adaptive immune responses [21]. Taken together, NK cells function as multifaceted regulators of immunity whose protective effects extend beyond direct elimination of infected or malignant cells. Their ability to integrate cytotoxic activity with immune regulation provides the mechanistic basis for their central role in maintaining immune homeostasis and explains why disturbances in NK cell function contribute to diverse pathological conditions discussed in subsequent sections.

Despite considerable advances, important questions remain regarding the mechanisms governing NK cell plasticity, tissue adaptation, and long-term functional reprogramming. Emerging technologies, including single-cell multi-omics and spatial transcriptomics, are expected to further refine our understanding of NK cell heterogeneity and its therapeutic implications.

4. Molecular Regulation and Immunological Roles of DCs

4.1 DC Subsets and Differentiation

DCs are distributed across blood, peripheral tissues, and lymphoid organs, where they provide an important interface between innate sensing and adaptive immune activation. Their ability to detect environmental signals, process antigens, and regulate T-cell responses places them at a critical position between tissue surveillance and antigen-specific immunity. However, DC function is strongly influenced by developmental origin and local environmental signals, making the classification of DCs according to both lineage and functional state essential for understanding their contribution to immune homeostasis [22,23]. Human DCs are broadly classified into conventional or classical DCs (cDCs) and plasmacytoid DCs (pDCs), with cDCs further divided into cDC1 and cDC2 populations. These subsets differ in developmental programs, tissue distribution, receptor expression, and functional specialization. pDCs are particularly characterized by their capacity for rapid type I interferon production following nucleic-acid sensing, whereas conventional DCs are specialized for antigen acquisition, processing, presentation, and regulation of adaptive immune responses [24,25]. This classification provides a useful framework, but it should not be interpreted as indicating completely independent or functionally rigid populations. Among conventional DCs, cDC1s are particularly efficient at antigen cross-presentation and are therefore important for initiating $CD8^+$ T-cell responses against cell-associated antigens, including those arising from infected or malignant cells. In contrast, cDC2s are generally more closely associated with the regulation of $CD4^+$ T-cell responses and helper-cell differentiation. These functional differences provide a basis for division of labor among DC subsets; however, the distinction becomes less absolute under inflammatory conditions, when cytokine exposure and tissue-derived signals can modify antigen-processing capacity, costimulatory activity, and T-cell-polarizing functions [24,25].

An important emerging consideration is therefore the extent to which DC subsets should be viewed as fixed functional categories versus populations capable of adapting to their environment. Recent high-dimensional approaches, including single-cell transcriptomic and spatial analyses, have revealed substantial heterogeneity within conventional DC populations and have identified tissue- and activation-associated transcriptional states that are not fully captured by conventional surface-marker classification. These findings do not eliminate the importance of developmental lineage but instead suggest that lineage provides the framework within which environmental signals shape functional state. Thus, DC

identity can be considered as the product of developmental programming together with tissue-specific and inflammatory adaptation.

This distinction has direct implications for immune homeostasis. The same DC lineage may promote effective immunity under conditions of infection or malignant transformation but contribute to tolerance or immune regulation under steady-state conditions. Accordingly, DC biology is better understood through the interaction between subset identity, maturation state, and tissue context, rather than through phenotype alone. This framework is particularly relevant to the NK-DC axis because different DC subsets and functional states may differ in their capacity to produce NK-regulatory cytokines, express activating or inhibitory ligands, and participate in reciprocal NK-DC interactions. The functional consequences of these differences are considered further in Sections 4.3 and 5.

4.2 Antigen Processing and Presentation

DCs acquire antigens through multiple mechanisms, including phagocytosis, macropinocytosis, and receptor-mediated endocytosis, and process the internalized material within endosomal and lysosomal compartments before loading peptide fragments onto MHC molecules. MHC class II presentation primarily enables recognition of processed extracellular antigens by $CD4^+$ T cells, whereas MHC class I presentation generally supports $CD8^+$ T-cell recognition of intracellularly derived peptides. The functional consequence of antigen presentation, however, depends not only on peptide–MHC formation but also on the maturation state of the DC and the availability of appropriate costimulatory and inflammatory signals [26,27]. An important extension of this process is cross-presentation, through which exogenous antigens are presented on MHC class I molecules to naïve $CD8^+$ T cells. This pathway is particularly relevant when the antigen originates from infected or malignant cells that are not themselves efficiently available for direct presentation by professional antigen-presenting cells. Cross-presentation therefore provides an important mechanism linking extracellular antigen acquisition to cytotoxic T-cell immunity and is especially prominent in cDC1 populations [27,28]. However, cross-presentation should not be considered synonymous with effective $CD8^+$ T-cell priming: productive activation also requires appropriate costimulatory signals, inflammatory cytokines, and DC migration to sites where naïve T cells can be engaged.

DC maturation therefore represents a critical determinant of how antigen processing is translated into an immune response. Following appropriate activation, DCs increase surface peptide–MHC complexes and costimulatory molecules and alter chemokine-receptor expression, facilitating migration toward lymphoid tissues and interaction with naïve T cells [28]. The same antigen can consequently produce different immunological outcomes depending on the context in which it is presented. Antigen presentation by an appropriately activated DC can promote effector T-cell responses, whereas presentation under steady-state or tolerogenic conditions can favor T-cell hyporesponsiveness or regulatory responses. This contextual dependence is central to the role of DCs in maintaining the distinction between protective immunity and peripheral tolerance.

The molecular basis of cross-presentation is itself heterogeneous. Cytosolic and vacuolar pathways have been described, with differences in antigen source, intracellular trafficking, proteolytic processing, and peptide loading. Their relative contribution may vary according to DC subset and inflammatory context, indicating that cross-presentation is not a single uniform pathway but a collection of mechanisms that converge on MHC class I presentation of exogenous antigen [27]. Defining how these pathways are regulated remains important for understanding why some DC populations are particularly effective at initiating antitumor $CD8^+$ T-cell responses.

Importantly, antigen processing does not occur independently of other innate immune signals. PRR activation, cytokine exposure, and interactions with NK cells can influence DC maturation and therefore modify the conditions under which processed antigens are presented to T cells. In this sense, antigen presentation represents an integration point between antigen availability, innate sensing, DC functional state, and cellular crosstalk. This provides a mechanistic bridge between the antigen-processing functions described here and the NK-DC interactions examined later in the review.

4.3 Activation and Tolerogenic Programs

DC functional state is strongly influenced by the nature and persistence of signals detected through PRRs, including TLRs, NLRs, and cytosolic nucleic-acid sensors. Recognition of pathogen-associated or damage-associated molecular patterns activates interconnected signaling pathways involving NF-κB, interferon-regulatory factors, and inflammasome-associated mechanisms. These pathways can induce increased expression of costimulatory molecules such as CD80, CD86, and CD40; production of inflammatory mediators including IL-12, IL-6, and TNF-α; and upregulation of CCR7, facilitating migration toward draining lymphoid tissues [29]. Such changes increase the capacity of DCs to provide antigen presentation together with the costimulatory and cytokine signals required for effective T-cell activation. DC-derived IL-12, IL-15, and type I interferons can additionally promote NK cell activation and functional differentiation, providing an important link between innate sensing and NK-DC communication [30].

However, DC activation should not be viewed as an irreversible transition from an inactive to an inflammatory state. Under steady-state conditions and within regulatory tissue environments, DCs can acquire functional programs that favor peripheral tolerance. These cells may exhibit reduced expression of costimulatory molecules, increased production of regulatory mediators such as IL-10 and TGF-β, and expression of immunoregulatory enzymes, including indoleamine

2,3-dioxygenase (IDO). Through these mechanisms, tolerogenic DCs can promote T-cell hyporesponsiveness, regulatory T-cell differentiation, or other forms of peripheral tolerance to self-antigens, commensal microorganisms, and innocuous environmental antigens [31]. Importantly, the distinction between immunogenic and tolerogenic DCs represents a functional spectrum rather than two permanently fixed cellular identities. The same DC population may change its functional program in response to the intensity and duration of PRR stimulation, cytokine exposure, metabolic conditions, tissue-derived signals, and interactions with other immune cells. Consequently, a phenotype that is tolerogenic under steady-state conditions may become immunogenic following an appropriate inflammatory stimulus, whereas persistent exposure to suppressive or metabolically altered microenvironments can promote dysfunctional or regulatory states.

NK cells are among the cellular partners capable of modifying this functional balance. NK-derived IFN-γ and TNF-α can enhance DC maturation and inflammatory function, whereas inhibitory interactions and the selective elimination of immature or inadequately activated DCs can influence which DC populations persist during an immune response. Conversely, DC-derived cytokines provide important signals controlling NK cell survival, activation, and effector differentiation. The resulting feedback relationship means that the immunogenic or tolerogenic state of a DC cannot be considered independently of the surrounding NK cell compartment and tissue environment. This reciprocal regulation provides a mechanistic basis for the NK-DC axis as a modulator of immune set points.

The major molecular characteristics associated with immunogenic and tolerogenic DC programs are summarized in Table 1. Importantly, these characteristics should be interpreted as functional tendencies rather than absolute phenotypic definitions, because DC states can be reshaped by environmental and cellular signals. This plasticity is central to the ability of the immune system to transition between effective host defense and restoration of tolerance while limiting unnecessary tissue damage.

Table 1. Molecular signatures of immunogenic vs. tolerogenic DCs.

Feature	Immunogenic Dendritic Cells (iDCs)	Tolerogenic Dendritic Cells (tDCs)
Surface Markers	High expression of costimulatory molecules CD80, CD86, and CD40.	Low expression of costimulatory molecules (CD80, CD86).
Antigen Presentation	High MHC II expression for potent CD4+ T-cell priming.	Low MHC II expression; bias toward T-cell anergy.
Secreted Cytokines	Pro-inflammatory: IL-12, IL-15, IL-6, TNF-α, and type I IFNs.	Anti-inflammatory: IL-10 and TGF-beta.
Enzymatic Profile	Low IDO expression.	High IDO and aromatase expression promote metabolic suppression.
Primary Function	Supports effector T-cell and NK cell activation.	Promotes regulatory T cell (Treg) differentiation and peripheral tolerance.

Thus, antigen presentation should be viewed not as a uniform cellular process but as a highly regulated mechanism whose efficiency depends on DC maturation, subset identity, and tissue microenvironment. These variables ultimately determine the quality of adaptive immune responses initiated by DCs.

4.4 Linking DC Biology to NK-DC Crosstalk

The functional programs described above—subset specialization, antigen presentation capacity, and the immunogenic versus tolerogenic axis—are not static or cell-autonomous but are continuously shaped by bidirectional interactions with NK cells. NK cells provide early cytokines, particularly IFN-γ and TNF-α, that drive DC maturation, upregulate costimulatory molecules, and enhance IL-12 production, thereby reinforcing immunogenic DC phenotypes. At the same time, NK cells can selectively eliminate immature or suboptimally activated DCs through cytotoxic editing, ensuring that only fully competent DCs participate in T-cell priming. Reciprocally, DC-derived IL-12, IL-15, IL-18, and type I interferons activate and sustain NK cell effector functions, creating an amplification loop that integrates innate sensing with adaptive immunity. This NK-DC crosstalk operates at every stage of the immune response, from steady-state surveillance and tolerance induction to pathogen challenge, tumor immunity, and resolution of inflammation [32]. Rather than representing a simple bidirectional interaction, NK-DC communication functions as a dynamic regulatory circuit that continuously adjusts immune activation according to the inflammatory environment. The outcome of this interaction depends not only on cytokine exchange but also on tissue-derived metabolic signals, cellular composition, and the activation status of both cell populations. Although the molecular basis of NK-DC crosstalk has been extensively characterized in experimental models, important differences remain between murine and human immune systems. Consequently, the relative contribution of individual signaling pathways to immune homeostasis in humans requires further clarification through translational and clinical studies.

Collectively, these observations position DCs as active coordinators rather than passive initiators of immune responses. Their ability to integrate environmental signals and reciprocally regulate NK cell activation establishes the NK-DC axis

as a central mechanism controlling the balance between immune activation and peripheral tolerance [33]. The molecular basis of this reciprocal communication is discussed in detail in the following section.

Despite significant advances in understanding DC biology, several important questions remain unresolved. These include the mechanisms governing long-term DC plasticity, the influence of tissue metabolism on tolerogenic programming, and the extent to which human DC subsets mirror those characterized in experimental models. Addressing these questions will be essential for optimizing DC-targeted immunotherapies and restoring immune homeostasis in inflammatory diseases and cancer.

5. NK-DC Crosstalk: A Central Axis of Immune Regulation

Although Tregs are indispensable for maintaining peripheral immune tolerance, they function primarily as downstream regulators within the homeostatic network described in this review. The central focus remains the reciprocal interaction between NK cells and DCs, which initiate and calibrate innate immune responses. Through cytokine-mediated communication and direct cellular interactions, Tregs subsequently reinforce immune homeostasis by limiting excessive activation of both NK cells and DCs [4].

Bidirectional communication between NK cells and DCs constitutes a core regulatory axis that integrates innate sensing with adaptive immunity and maintains immune homeostasis across diverse tissue compartments [4]. Through a tightly coordinated interplay of direct cell–cell interactions, soluble mediators, and reciprocal functional editing, NK cells and DCs dynamically shape each other's activation thresholds, survival, and functional specialization, thereby tuning the quality, magnitude, and duration of downstream T-cell responses. This NK-DC crosstalk operates as a central rheostat that balances protective immunity against pathogens and tumors with tolerance to self-antigens and commensals, and its dysregulation underlies diverse pathological states, including chronic infection, autoimmunity, and cancer [34,35].

5.1 Molecular Mechanisms of NK-DC Interactions

NK cells and DCs communicate through coordinated contact-dependent and soluble signaling mechanisms that determine the magnitude, duration, and functional direction of immune responses [36]. Direct interactions are established through immunological synapses in lymphoid and inflamed tissues, where adhesion molecules such as lymphocyte function-associated antigen-1 (LFA-1) on NK cells interact with intercellular adhesion molecule-1 (ICAM-1) on DCs to stabilize cellular contacts and facilitate bidirectional signal exchange [37]. Additional receptor-ligand interactions can then determine the functional outcome of these contacts. Activating receptors, including NKp30 and DNAM-1, can recognize ligands expressed by DCs and promote NK cell activation, degranulation, and cytokine production, while interactions involving CD40-CD40L can contribute to DC activation and functional maturation [23,26]. Conversely, inhibitory receptors such as NKG2A and KIRs recognize MHC class I molecules and can restrain NK cell activation or cytotoxicity toward DCs, thereby influencing the survival and functional composition of the DC compartment [38].

These contact-dependent signals should not be interpreted as independent receptor-ligand events. Rather, they form an integrated signaling network in which activating and inhibitory inputs are interpreted together with cytokine and tissue-derived signals. The resulting outcome depends on the maturation state of the DC, the activation history of the NK cell, cytokine availability, and the local inflammatory environment. Thus, the same receptor-ligand interaction may have different consequences in steady-state tissues compared with acute infection, chronic inflammation, or cancer. This context dependence provides a mechanistic explanation for why NK-DC interactions can promote effective immune activation in one setting while contributing to regulation, tolerance, or immune dysfunction in another.

Soluble mediators provide a second major layer of NK-DC communication. DC-derived IL-12 and IL-18 strongly promote NK cell IFN-γ production and cytotoxic activity and are important components of early type 1 immune responses. IL-15, including its presentation in trans through membrane-associated IL-15Rα, supports NK cell survival, homeostatic proliferation, and acquisition of effector competence. Other cytokines, including IL-23 and IL-27, can further modify NK cell effector programs, although their effects are highly dependent on the cellular and inflammatory context [39-41]. In the reciprocal direction, NK-derived IFN-γ and TNF-α can promote DC maturation, increase expression of antigen-presentation and costimulatory machinery, and modify the subsequent capacity of DCs to prime T-cell responses [5].

The interaction therefore does not represent a simple unidirectional sequence in which DCs activate NK cells and NK cells subsequently activate DCs. Instead, NK-DC communication forms a feedback circuit in which each cell population continuously modifies the activation threshold and functional state of the other. The consequences may include amplification of antimicrobial or antitumor immunity, selective elimination of poorly activated DCs, reinforcement of regulatory programs, or attenuation of immune responses when inhibitory signals predominate [42]. The biological outcome is consequently determined by the integration of receptor-mediated recognition, cytokine signaling, cellular maturation state, and tissue-specific environmental cues.

This model provides a mechanistic basis for considering the NK-DC axis as a regulatory rheostat rather than simply an activating pathway. Its importance lies not in maximizing NK or DC activity, but in coordinating their responses so that immune activation is sufficient for pathogen or tumor control while remaining compatible with tissue integrity and restoration of immune homeostasis.

5.2 NK-Mediated Editing of DCs: Quality Control of Antigen Presentation

Activated NK cells can selectively eliminate immature or suboptimally activated DCs, whereas mature DCs with stronger expression of MHC class I and appropriate costimulatory molecules are generally more resistant to NK-mediated cytotoxicity. This phenomenon, commonly described as DC editing, is determined by the integration of activating and inhibitory signals during NK-DC contact. Activating receptors, including NKp30, NKG2D, and DNAM-1, can contribute to recognition of susceptible DCs through stress- or activation-associated ligands, whereas inhibitory receptors recognizing self-MHC class I can raise the threshold for NK cell cytotoxicity and thereby influence DC survival [43,44].

The functional significance of DC editing extends beyond the elimination of individual immature DCs. By altering the composition of the DC compartment, NK cells may influence which antigen-presenting cells remain available to interact with T lymphocytes and therefore modify the quality and magnitude of subsequent adaptive responses. This provides a potential quality-control mechanism linking innate immune surveillance to antigen presentation. However, the consequences of DC editing are likely to depend on the maturation state of DC, the strength of the NK cell response, and the surrounding tissue environment. Thus, elimination of an immature DC should not automatically be interpreted as beneficial, because immature or tolerogenic DC populations can also participate in peripheral tolerance under physiological conditions.

This context dependence is particularly relevant when considering dysregulated NK-DC interactions. Reduced NK cell cytotoxic capacity or altered expression of activating and inhibitory ligands on DCs could modify the extent of DC editing and consequently change the composition of the antigen-presenting-cell compartment. Depending on the tissue and inflammatory setting, such alterations could contribute to impaired effector T-cell priming, persistence of dysfunctional DCs, or inappropriate inflammatory or regulatory responses. These possibilities support a model in which NK-mediated DC editing functions as a calibration mechanism rather than an absolute quality-control checkpoint [45].

Accordingly, the biological importance of DC editing lies not simply in removing immature DCs but in dynamically regulating the availability and functional state of antigen-presenting cells in response to the prevailing immune environment. This mechanism provides an additional layer through which NK cells can influence the transition between effective immunity, immune regulation, and restoration of homeostasis.

5.3 NK-DC-Treg Networks in Immune Homeostasis

Tregs provide an additional layer of control within the NK-DC regulatory network by reinforcing peripheral tolerance and limiting excessive immune activation. In this framework, the NK-DC axis represents the principal regulatory interaction, whereas Tregs function as downstream and reciprocal modulators that help stabilize immune responses after their initiation. DCs are particularly important in this process because their functional state influences the balance between effector T-cell priming and regulatory T-cell differentiation [6].

Under homeostatic conditions, tissue-resident DCs generally maintain relatively low levels of costimulatory activity and can produce regulatory mediators such as TGF-β and IL-10, thereby supporting mechanisms of peripheral tolerance and Treg maintenance. At the same time, DC-derived cytokines, including IL-12 and IL-15, contribute to basal NK cell survival and functional readiness, although the magnitude and biological consequences of these signals vary according to tissue and cellular context [46-49]. Thus, immune surveillance can be maintained without requiring constitutive NK cell activation.

When PRR-mediated inflammatory signals become sufficiently strong, DCs can acquire a more immunogenic functional state, characterized by increased production of cytokines such as IL-12 and IL-18 and enhanced IL-15 trans-presentation. These signals promote NK cell activation and IFN-γ production, while NK-derived cytokines can reciprocally reinforce DC maturation and inflammatory function. This feedback can favor effector T-cell responses when effective host defense is required [50-54]. Conversely, when regulatory signals predominate, tolerogenic DC programs can support Treg maintenance, while Tregs can subsequently constrain excessive activation of DCs and NK cells through regulatory cytokines and contact-dependent mechanisms.

The resulting network should therefore not be interpreted as a symmetric three-cell circuit. Instead, it can be conceptualized as a hierarchical regulatory system in which reciprocal NK-DC interactions establish and modify immune activation states, while Tregs provide an important downstream mechanism for reinforcing peripheral tolerance and limiting prolonged activation. This distinction is particularly relevant to the proposed homeostatic rheostat model: Tregs do not replace the central NK-DC regulatory axis but contribute to its stabilization and resolution.

Importantly, the relative contribution of these interactions is likely to vary across tissues and disease states. In cancer, chronic infection, and autoimmune inflammation, persistent antigenic or inflammatory stimulation may alter NK cell function, DC maturation, and Treg activity simultaneously, making it difficult to assign a single dominant pathway to the resulting immune phenotype. Understanding how these components interact under specific tissue conditions may therefore be more informative than considering NK cells, DCs, or Tregs as isolated regulators of immune homeostasis.

5.4 Checkpoint and Metabolic Regulation of NK-DC Crosstalk

Immune checkpoint receptors on NK cells provide an important layer of negative regulation that shapes their responses to DCs and other target cells. Human NK cells express several inhibitory receptors beyond classical KIRs and NKG2A, including TIGIT, PD-1, and other molecules that can damage cytokine production and cytotoxicity when engaged in inflamed tissues and tumor microenvironment (TME). These receptors integrate with signals from activating receptors and cytokine receptors to set the activation threshold of NK cells during their interactions with DCs, thereby limiting excessive NK-mediated killing and uncontrolled inflammation [55].

DCs themselves express ligands for these checkpoint receptors and can therefore directly modulate NK cell function. For example, upregulation of PD-L1 and related inhibitory ligands on DCs during chronic inflammation or in tumors can contribute to reduced NK cell activation and impaired production of IFN-γ and TNF-α, weakening DC maturation and T cell priming in a feed-forward manner. DCs also regulate the balance of activating and inhibitory signals received by NK cells through their expression of MHC class I molecules and other surface ligands, further fine-tuning NK responsiveness in different tissue contexts. In this way, DCs both deliver activating cytokines and simultaneously present inhibitory ligands that together determine the quality of NK-DC crosstalk [56].

Metabolic features of the tissue microenvironment impose additional constraints on NK-DC interactions. Hypoxia, nutrient depletion, and the accumulation of metabolites such as lactate or adenosine in chronically inflamed tissues and tumors can impair NK cell metabolism, reduce cytotoxicity and cytokine production, and skew DCs toward dysfunctional or tolerogenic phenotypes. Altered lipid handling and mitochondrial function in DCs can similarly influence their ability to produce IL-12, IL-15, and type I interferons, thereby indirectly affecting NK cell activation and survival. These metabolic cues act in parallel with checkpoint pathways to limit the extent of NK-DC cooperation under conditions of persistent stress [57].

In vivo, checkpoint and metabolic signals are integrated to determine the overall behavior of the NK-DC axis. In tumors, for example, high expression of inhibitory ligands on DCs and other myeloid cells, together with a hypoxic and nutrient-poor microenvironment, can drive NK cells toward an exhausted or hypofunctional state and prevent effective support for cDC1-mediated cross-priming of $CD8^+$ T cells. Conversely, therapeutic blockade of inhibitory receptors, combined with strategies that improve cytokine availability or metabolic fitness, has the potential to restore productive NK-DC crosstalk and thereby enhance both innate and adaptive antitumor responses. Similar principles are likely to apply in chronic infections and inflammatory diseases, where manipulating checkpoints and metabolic pathways may help reset dysregulated NK-DC circuits back toward homeostatic set points [58]. Together, immune checkpoint pathways and metabolic regulation represent complementary mechanisms that dynamically calibrate NK-DC communication according to tissue physiology and inflammatory status. Therapeutic strategies targeting both pathways simultaneously may therefore offer greater potential for restoring immune homeostasis than approaches directed at either mechanism alone.

6. Dysregulation of NK-DC Interactions in Disease

Disturbances in NK-DC communication have been implicated in autoimmune and inflammatory diseases, cancer, and chronic infection. However, the nature and consequences of this dysregulation differ substantially among diseases and tissues. Changes in NK cell phenotype or function, altered DC maturation, persistent inflammatory signaling, and changes in regulatory T-cell activity can collectively shift local immune set-points toward inadequate immune control or sustained inflammation. Rather than representing a single pathological mechanism, these alterations should therefore be considered context-dependent disruptions of a regulatory network, in which the relative contribution of NK cells, DCs, Tregs, and other innate immune populations varies according to disease stage and tissue environment [59].

6.1 Autoimmune and Inflammatory Disorders

Autoimmune diseases provide an important example of how disruption of innate immune regulation can contribute to persistent loss of tolerance. Alterations in NK cell phenotype and function have been reported in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS), while activated or functionally altered DC populations can promote persistent presentation of self-antigens and inflammatory T-cell responses. However, the direction and magnitude of these changes are disease- and tissue-dependent, and NK cells may exert either regulatory or pro-inflammatory effects depending on their subset and activation state [60-62]. Recent therapeutic observations provide an important translational perspective. Early clinical evidence from allogeneic CD19-targeted CAR-NK therapy in refractory SLE has demonstrated substantial B-cell depletion accompanied by clinical responses, raising the possibility that engineered NK cells could contribute to immune resetting by targeting pathogenic B-cell populations [63]. However, these findings should currently be interpreted as emerging clinical evidence rather than proof that correction of the NK-DC axis itself is responsible for therapeutic benefit. The relationship between B-cell depletion, restoration of immune tolerance, and subsequent changes in NK-DC regulatory networks remains an important area for investigation.

6.1.1 Rheumatoid Arthritis

RA illustrates a somewhat different pattern in which persistent activation of immune cells within the synovial

microenvironment contributes to chronic inflammation. Synovial DCs can acquire inflammatory phenotypes and provide signals capable of sustaining autoreactive T-cell responses, while NK cells within inflamed joints may exhibit heterogeneous functional states. Depending on their subset and local cytokine environment, NK cells can contribute to inflammatory cytokine production or exert regulatory effects [64].

Consequently, the relationship between NK cells and DCs in RA should not be reduced to a simple model of defective NK-mediated DC editing. Evidence supports broader alterations in cellular communication and inflammatory signaling within the synovial microenvironment, but the extent to which impaired DC editing specifically contributes to human RA remains incompletely established. This distinction is important when translating mechanistic observations from experimental models into therapeutic strategies.

6.1.2 Multiple Sclerosis

MS further illustrates the context dependence of NK cell function. CD56bright NK cells have been associated with immunoregulatory functions, including suppression of activated T-cell responses, whereas other NK cell populations may exhibit distinct effects depending on disease stage and inflammatory context [65]. DCs also contribute to neuroinflammation by presenting antigen and producing cytokines that can promote pathogenic T-cell differentiation. The interaction between these populations may therefore influence the balance between inflammatory amplification and immune regulation within the central nervous system and peripheral immune compartments.

Importantly, the evidence does not support a uniform model in which NK cell dysfunction invariably promotes MS progression. Instead, NK cell effects appear to vary according to subset, activation state, disease stage, and treatment status. This heterogeneity highlights the broader principle that therapeutic manipulation of NK cells in autoimmune disease should aim to restore appropriate immune regulation rather than simply increase or suppress NK cell activity.

6.1.3 Integration with Macrophage Regulation

The NK-DC axis also operates within a broader network of innate immune cells that includes monocytes and macrophages. Macrophages participate in inflammatory initiation, efferocytosis, tissue remodeling, antigen presentation, and resolution of inflammation and communicate extensively with NK cells and DCs. NK-derived IFN-γ can influence macrophage activation, while macrophage-derived cytokines can modify NK cell function and indirectly affect DC maturation [66].

Importantly, macrophage functional states should not be considered a rigid M1-versus-M2 binary. Macrophage phenotypes exist along a continuum shaped by tissue-derived signals, metabolic conditions, cytokines, and the stage of inflammation. Dysregulated macrophage activation or defective resolution can therefore sustain inflammatory signaling and alter the broader cellular environment in which NK-DC interactions occur. This places macrophages within the wider regulatory network rather than treating them as an independent pathway of immune dysfunction.

6.1.4 Therapeutic Implications

These observations have stimulated therapeutic approaches aimed not simply at suppressing inflammation but at restoring appropriate immune regulation. Tolerogenic dendritic-cell (tolDC) approaches seek to promote antigen-specific or localized tolerance by generating DCs with reduced immunogenicity and enhanced regulatory capacity. Early clinical studies have generally supported the feasibility and safety of tolDC-based approaches, although their clinical efficacy and durability remain under investigation [67].

Similarly, NK cell-directed strategies are being explored in different therapeutic contexts, including cytokine-based modulation and CAR-NK approaches. In autoimmune disease, however, the objective should not necessarily be to maximize NK cell cytotoxicity; rather, therapeutic benefit may depend on selectively modifying pathogenic immune populations while preserving or restoring regulatory functions. The recent clinical experience with CAR-NK therapy in SLE illustrates the potential of this approach but also emphasizes the need to determine how engineered NK cells influence the broader immune network over time [68].

Overall, autoimmune and inflammatory diseases illustrate that disruption of NK-DC communication is not a uniform defect but a disease- and tissue-specific alteration of immune regulation. This distinction supports a shift from nonspecific immunosuppression toward precision immunomodulation designed to restore appropriate immune set points while preserving protective immunity.

6.2 Cancer and the TME

Effective antitumor immunity depends in part on coordinated interactions between NK cells and conventional type 1 dendritic cells (cDC1s). Activated NK cells can promote cDC1 recruitment and functional maturation through chemokine and cytokine production, while cDC1s are specialized for cross-presentation of tumor-associated antigens to $CD8^+$ T cells. This reciprocal relationship provides a mechanistic link between innate tumor surveillance and adaptive antitumor immunity [69-71]. However, the contribution of this axis varies among tumor types and is strongly influenced by the composition and metabolic state of the TME.

Tumors can disrupt NK-cDC1 cooperation through multiple, overlapping mechanisms, including immunosuppressive cytokines such as TGF-β and IL-10, altered prostaglandin signaling, hypoxia, metabolic stress, and increased expression of inhibitory ligands. These conditions can reduce NK cell cytotoxicity and cytokine production while impairing the recruitment, maturation, or antigen-presenting capacity of DCs. Reduced NK-derived CCL5 and XCL1/XCL2 may limit the recruitment of cDC1s into the tumor, weakening subsequent cross-presentation and $CD8^+$ T-cell priming [70,71]. Thus, tumor-mediated suppression of NK cells can have consequences that extend beyond loss of direct cytotoxicity by simultaneously disrupting the cellular network required for effective adaptive antitumor immunity.

The NK-cDC1 relationship is therefore better understood as a reciprocal ecological interaction within the TME rather than a simple linear pathway. NK cells can contribute to cDC1 recruitment and activation, whereas cDC1-derived cytokines can sustain NK cell survival and effector function. When this feedback is maintained, it may support coordinated innate and adaptive antitumor responses. When either component becomes dysfunctional, the resulting loss of reciprocal support can favor immune escape. The magnitude of this effect is likely to depend on tumor lineage, anatomical site, stromal composition, and the relative abundance of suppressive myeloid and regulatory lymphocyte populations.

Evidence from different tumor settings further emphasizes this context dependence. In some mucosal and solid tumors, alterations in local inflammatory and metabolic conditions are associated with impaired NK cell function and reduced cDC1 abundance or activity, potentially limiting effective $CD8^+$ T-cell priming [72,73]. Across several tumor types, intratumoral NK cell and cDC1 abundance or functional signatures have also been associated with antitumor immune activity and response to immunotherapy. However, these associations should not automatically be interpreted as evidence that reduced NK-cDC1 activity is the direct cause of treatment resistance, because both populations may be influenced by common upstream features of the TME.

These observations have therapeutic implications. Strategies designed to enhance NK cell function, increase cDC1 recruitment or maturation, or restore the cytokine and chemokine signals connecting these populations are being investigated as approaches to strengthen antitumor immunity. Combining such strategies with immune-checkpoint blockade is particularly attractive because checkpoint inhibition may relieve inhibitory constraints, while NK-cDC1-directed approaches could improve the cellular and functional infrastructure required for effective T-cell priming. Nevertheless, the optimal combination is likely to be tumor- and context-specific, and clinical validation is required to determine whether restoring NK-cDC1 cooperation translates into durable therapeutic benefit. As shown in Figure 2, tumor-derived signals disrupt NK-DC communication and promote immune escape.

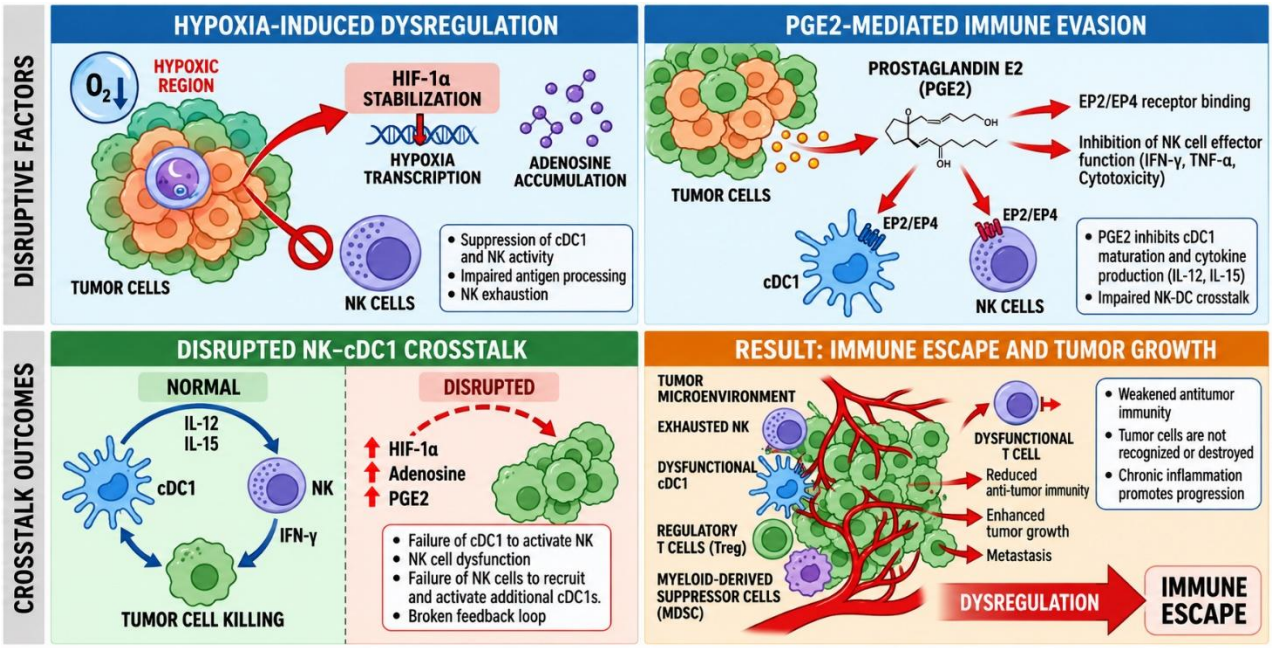

Figure 2. Dysregulation of NK-DC crosstalk in the TME. This figure illustrates key mechanisms by which the TME disrupts NK cell and dendritic cell (cDC1) interactions, leading to immune evasion. Hypoxia induces HIF-1α stabilization and adenosine accumulation, suppressing NK cell function and impairing dendritic cell activity. Tumor-derived prostaglandin E2 (PGE2) further inhibits NK cytotoxicity and cDC1 maturation via EP2/EP4 signaling. These factors disrupt NK-cDC1 crosstalk, impairing IL-12/IL-15-mediated activation and IFN-γ production. The resulting dysfunction promotes immune escape, reduced antitumor immunity, and tumor progression.

6.3 Chronic Viral Infections

In chronic infections (e.g., HIV, HCV, LCMV), persistent antigen exposure and inhibitory signaling lead to NK cell exhaustion, marked by the downregulation of NKG2D/NCRs and the overexpression of checkpoints, resulting in

functional hyporesponsiveness [74,75]. Exhausted NK cells cannot eliminate infected cells and dysregulated DCs, resulting in inadequate priming and sustenance of $CD8^+$ T cell responses. In specific models, activated regulatory NK cells actively suppress antiviral $CD8^+$ T cells through perforin-dependent cytotoxicity, promoting chronicity; the reduction of NK cells restores T cell functioning and viral control [76].

In emerging viral diseases such as COVID-19, converging data suggest that reduced numbers and functional impairment of NK cells, together with depletion or dysfunction of plasmacytoid and conventional DC subsets, contribute to the dysregulated immune responses observed in severe cases. These alterations likely disrupt normal NK-DC-T cell circuits, leading to insufficient early antiviral control and excessive later-stage inflammation. As in cancer and autoimmunity, these observations point toward strategies that aim to restore balanced NK-DC crosstalk by correcting NK dysfunction, supporting DC development and function, or modulating the cytokine milieu as potential avenues to improve outcomes in chronic and severe viral infections [77].

7. Therapeutic and Translational Implications

7.1 Adoptive NK Cell Transfer and Persistence Challenges

Adoptive NK cell therapy involves the *ex vivo* expansion, activation, and administration of autologous or allogeneic NK cells to enhance antitumor immunity. Transferred NK cells can recognize malignant cells through multiple mechanisms, including direct receptor-mediated cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC). Despite encouraging clinical and preclinical results, a major limitation of adoptive NK cell therapy is the limited persistence, expansion, and functional durability of transferred cells *in vivo*. These limitations are influenced by multiple factors, including cytokine availability, metabolic fitness, trafficking to tumor sites, host immune interactions, and the immunosuppressive TME [78].

The persistence of transferred NK cells should therefore not be considered solely a cell-intrinsic property. NK cell survival and functional competence are shaped by interactions with surrounding immune and stromal populations, including DCs and other myeloid cells. In particular, IL-12, IL-15, and other cytokine signals can influence NK cell proliferation, survival, and effector differentiation, while reciprocal NK-DC interactions may contribute to the maintenance of coordinated innate and adaptive antitumor responses. However, the extent to which endogenous DC populations directly determine the long-term persistence of adoptively transferred NK cells in patients remains incompletely established [4,9,78].

This distinction has important translational implications. Rather than viewing adoptive NK cell transfer as an isolated cellular intervention, emerging strategies increasingly consider NK cells within the broader immune network of the TME. Combination approaches incorporating cytokine support, immune-checkpoint modulation, tumor-targeting strategies, or complementary DC-directed interventions may improve NK cell trafficking, persistence, and functional activity. CAR-NK engineering represents one approach to increase tumor recognition while potentially retaining favorable safety and off-the-shelf characteristics, although limited tumor infiltration and the immunosuppressive microenvironment remain important barriers, particularly in solid tumors [79,80].

The potential contribution of tissue-resident NK cell populations provides an additional area of interest. Unlike circulating NK cells, tissue-resident populations are adapted to local cytokine, stromal, and metabolic environments and may therefore provide distinct opportunities for tissue-specific immune surveillance. Nevertheless, whether these properties can be effectively harnessed to improve the persistence or therapeutic activity of transferred NK cells remains an open question [80].

Overall, the major translational challenge is not simply to increase the number of administered NK cells but to establish a supportive immune ecosystem that permits their trafficking, persistence, and sustained effector function. This perspective places NK cell therapy within the broader NK-DC regulatory framework proposed in this review and highlights the need for combination strategies that simultaneously address cellular fitness, tissue localization, and microenvironmental suppression.

7.1.1 CAR-NK Engineering and Advantages over CAR-T Cells

Chimeric antigen receptor (CAR) engineering provides a strategy for redirecting NK cell recognition toward defined tumor-associated antigens while retaining the endogenous cytotoxic machinery and activating receptors of NK cells. CAR-NK cells have been investigated against a range of targets, including CD19, CD33, and mesothelin, using engineered receptors that couple antigen recognition to intracellular signaling pathways capable of enhancing NK cell activation and cytotoxicity [81,82].

An important potential advantage of CAR-NK therapy is its favorable safety and manufacturing profile. Compared with CAR-T cells, CAR-NK approaches have generally been associated with lower rates of severe cytokine release syndrome (CRS) and graft-versus-host disease (GvHD) in early clinical experience, although direct comparisons remain limited and depend on the cellular source, manufacturing platform, disease setting, and treatment protocol. NK cells can also be generated from allogeneic sources, including umbilical cord blood and established NK cell lines, creating the possibility

of standardized, readily available cellular products. Nevertheless, limits *in vivo* persistence and expansion remain important challenges that may restrict the durability of therapeutic responses [81-83].

The therapeutic performance of CAR-NK cells is particularly challenging in solid tumors, where antigen heterogeneity, inadequate trafficking, metabolic stress, hypoxia, and immunosuppressive signaling can restrict immune-cell activity. These limitations have encouraged combination approaches incorporating cytokine support, immune-checkpoint blockades, or strategies designed to improve tumor infiltration and persistence. Although DCs and NK cells can interact through reciprocal cytokine and chemokine signaling within the TME, the extent to which endogenous DC activity directly determines CAR-NK efficacy remains incompletely established. Therefore, the proposed integration of CAR-NK therapy with NK-DC-T-cell regulatory networks should currently be regarded as a promising mechanistic framework rather than an established clinical requirement [84].

7.1.2 Cytokine Engineering and Memory-Like NK Cell Induction

Cytokine-based approaches provide a complementary strategy to adopt NK cell therapy by enhancing NK cell proliferation, survival, metabolic fitness, and effector function. Among these approaches, IL-15 has attracted particular interest because of its central role in NK cell homeostasis and its ability to stimulate NK cell expansion without directly promoting regulatory T-cell expansion to the same extent as IL-2. Engineered IL-15 agonists and IL-15-based cytokine platforms have therefore been investigated as approaches to improve NK cell activity and persistence *in vivo* [85].

A distinct strategy involves the induction of cytokine-induced memory-like (CIML) NK cells. Brief pre-activation with IL-12, IL-15, and IL-18 can generate NK cells with enhanced IFN-γ production and increased responsiveness to subsequent stimulation. This functional reprogramming is associated with persistent epigenetic changes at loci involved in IFN-γ production and other effector programs, allowing CIML NK cells to retain enhanced functional responses after the initial cytokine exposure. These properties have generated considerable interest in CIML NK cells as a strategy for improving the durability of NK cell-based immunotherapy [81].

Importantly, cytokine-mediated NK cell programming does not occur independently of the surrounding immune environment. IL-12, IL-15, and other cytokines produced or trans-presented by myeloid cells, including DCs, can influence NK cell survival, proliferation, and effector differentiation. However, the extent to which endogenous cDC1-derived cytokines specifically determine the persistence or therapeutic efficacy of IL-15-activated or CIML NK cells in patients remains incompletely established. Thus, the NK-DC relationship provides a biologically plausible framework for combination therapy, but it should not yet be considered a demonstrated clinical requirement for successful CIML NK cell therapy.

From a translational perspective, current approaches are increasingly exploring combinations of NK cell cytokine stimulation with other immunomodulatory strategies, including checkpoint blockade and cellular or vaccine-based therapies. The rationale is to address complementary barriers to therapeutic efficacy: cytokine stimulation may enhance NK cell fitness, whereas checkpoint inhibition or DC-directed interventions may modify inhibitory or immunosuppressive features of the TME. Nevertheless, whether coordinated manipulation of these pathways produces superior and durable clinical responses remains an important question for ongoing clinical investigation [86].

7.1.3 Checkpoint Modulation in NK Cells

Targeting inhibitory checkpoint receptors on NK cells is being investigated as a strategy to enhance NK cell antitumor activity in cancer and other settings of persistent immune stimulation. Among these receptors, NKG2A recognizes HLA-E and can deliver inhibitory signals that reduce NK cell cytokine production and cytotoxicity. NKG2A expression varies according to NK cell subset, tissue localization, and disease context, and increased expression has been reported in some tumor-infiltrating NK cell populations. These observations have provided a rationale for targeting the NKG2A–HLA-E pathway therapeutically [83].

Monalizumab, a monoclonal antibody targeting NKG2A, has been evaluated clinically both as a single agent and in combination with other anticancer therapies, including immune-checkpoint inhibitors. Early clinical studies have provided evidence of biological activity, particularly in combination regimens, although the magnitude and durability of clinical benefit vary across tumor types and treatment settings. Other inhibitory pathways, including KIR and TIGIT, are also being investigated as potential targets for relieving NK cell inhibition [84].

Importantly, checkpoint blockade should not be viewed as an isolated mechanism for restoring NK cell function. The response of NK cells to checkpoint inhibition is influenced by the broader TME, including cytokine availability, metabolic conditions, antigen-presenting-cell function, and other inhibitory pathways. Consequently, restoring NK cell activity through checkpoint blockade may be insufficient when multiple components of the antitumor immune network remain dysfunctional. Combination strategies that simultaneously address NK cell inhibition and other barriers to immune activation therefore represent a rational area of investigation. However, the extent to which specific DC-directed interventions are required to maximize the clinical efficacy of NK cell checkpoint blockade remains to be established [87].

7.2 Dendritic Cell-Centered Strategies

7.2.1 DC Vaccine Development and NK-Licensing Optimization

DC vaccines represent an established investigational approach for enhancing antigen-specific antitumor immunity. These vaccines commonly involve the generation of DCs *ex vivo* from monocytes or hematopoietic progenitors, followed by loading with tumor-associated antigens through approaches such as peptide pulsing, tumor lysates, or nucleic-acid-based antigen delivery. Subsequent maturation is intended to enhance antigen presentation, migration, and costimulatory capacity, enabling vaccine-derived DCs to promote tumor-specific $CD4^+$ and $CD8^+$ T-cell responses [87,88].

Beyond their role in antigen presentation, DCs can interact with NK cells through reciprocal cytokine and receptor–ligand signaling. IL-12 and other inflammatory mediators produced by appropriately activated DCs can enhance NK cell effector functions, while NK-derived signals can influence DC maturation and functional specialization. This provides a biological rationale for designing DC vaccines that promote coordinated innate and adaptive responses rather than optimizing antigen presentation alone. However, the extent to which deliberate enhancement of NK cell activation improves the clinical efficacy of DC vaccination remains incompletely established [4,9,87].

Current DC-vaccine research is therefore increasingly focused on improving antigen delivery, maturation, migration, and the ability of vaccine-induced DCs to function within immunosuppressive TME. Strategies include optimized antigen-loading platforms, DC-targeted delivery systems, RNA-based approaches, and combinations with immune-checkpoint blockade or other immunomodulatory therapies. These approaches are intended to overcome limitations such as inadequate DC maturation, inefficient tumor-antigen presentation, and suppression within the TME [87-90].

Importantly, the concept of NK-DC synchrony should currently be regarded as a mechanistically supported therapeutic framework rather than an established predictor of clinical response. Although reciprocal NK-DC interactions can enhance antitumor immune coordination, clinical outcomes are also determined by tumor antigenicity, DC migration, T-cell competence, metabolic constraints, checkpoint signaling, and the composition of the TME. Future clinical studies should therefore determine whether deliberate optimization of NK-DC interactions provides measurable benefit beyond conventional DC vaccination strategies.

7.2.2 Tolerogenic Dendritic Cell Therapies in Autoimmunity and Inflammation

Whereas immunogenic DC-based strategies aim to enhance antitumor or antimicrobial immunity, tolDC therapy seeks to restore peripheral tolerance by selectively reducing pathogenic immune activation. TolDCs can be generated *ex vivo* from monocyte-derived DC precursors using tolerogenic conditioning approaches that include IL-10, TGF-β, vitamin D_3, dexamethasone, and other immunomodulatory signals. These conditions can promote relatively stable regulatory phenotypes characterized by reduced immunogenicity and enhanced capacity to modulate autoreactive T-cell responses [91].

Phenotypically, tolDCs generally exhibit reduced expression of costimulatory molecules and enhanced production of regulatory mediators, including IL-10, while their capacity to promote regulatory T-cell responses may contribute to restoration of peripheral tolerance. However, tolDC phenotypes are heterogeneous and depend on the differentiation protocol, maturation stimulus, antigen exposure, and tissue environment. Consequently, no single molecular phenotype should be considered universally representative of all therapeutic tolDC products [89,90].

Critically, tolDC-mediated suppression of adaptive immunity requires selective restraint of NK cell activation; indeed, excessive NK activation can eliminate tolerogenic DCs or induce their differentiation back toward pro-inflammatory states through IFN-γ and TNF-α production (Section 5). This molecular requirement has driven development of tolDC therapies that simultaneously incorporate NK-suppressive signals (e.g., HLA-E upregulation to engage inhibitory NKG2A receptors) or are combined with partial NK checkpoint blockade to calibrate rather than eliminate NK-mediated immune surveillance [35].

Autologous tolDC therapy has shown clinical promise in early-phase trials in rheumatoid arthritis, type 1 diabetes, and transplantation, with preliminary evidence of sustained remission or tolerance induction. The next frontier involves designing tissue-specific tolDC therapies that exploit local microenvironmental signals (e.g., tolerogenic lipid mediators in the gut, hypoxia in the liver) to maximize in situ homeostatic impact while minimizing off-target immunosuppression [92].

7.2.3 DC-Targeting Strategies via Nanotechnology and Antibody-Antigen Conjugates

Direct targeting of DCs *in vivo* represents an emerging strategy to enhance immunotherapy efficacy while reducing systemic cytokine exposure and off-target immune activation. Nanoparticle-based DC targeting involves formulation of antigens, adjuvants, or immunomodulatory molecules into lipid nanoparticles (LNPs), poly (lactic-co-glycolic acid) (PLGA) particles, or virus-like particles (VLPs) engineered to selectively traffic to lymphoid tissues and be taken up by DC subsets [93].

LNP-formulated mRNA vaccines, such as those used in SARS-CoV-2 immunization, preferentially activate cDC1 and

pDC subsets in draining lymph nodes, triggering robust type I interferon and IL-12 responses. Mechanistically, the biophysical properties of nanoparticles (size 50-200 nm, surface charge, and ligand modifications) and the choice of immunogenic lipid components determine trafficking patterns and DC subset activation profiles [94].

Antibody–antigen conjugate strategies represent an alternative approach, wherein monoclonal antibodies specific for DC surface receptors (e.g., anti-DEC-205, anti-Clec9A, anti-XCR1) are linked to tumor antigens or immunomodulatory cargo, enabling targeted delivery and cross-presentation to $CD8^+$ T cells. Critically, both nanoparticle and antibody–antigen approaches enhance NK-cDC1 crosstalk in lymphoid tissues and tumors by promoting coordinated cDC1 maturation and IL-12 production, which in turn activate NK cells to produce IFN-γ and facilitate downstream $CD8^+$ T-cell priming (Section 5) [95].

Recent preclinical and early clinical data combining nanoparticle DC vaccines with checkpoint blockade show enhanced tumor regression compared to checkpoint inhibition alone, supporting the rationale for integrated NK-DC-targeted approaches in solid malignancies [89].

7.3 Combinatorial NK-DC Approaches

7.3.1 DC Vaccines Combined with NK Adoptive Transfer and Activation

A rational combination of NK cell and DC-centered strategies is based on the complementary functions of these cell populations. Adoptive NK cell transfer can provide immediate cytotoxic activity, whereas DC vaccination can enhance tumor-antigen presentation and promote subsequent adaptive immune responses. Combining these approaches may therefore create reciprocal interactions in which NK cell-derived cytokines support DC maturation, while DC-derived cytokines promote NK cell activation and persistence [87,96].

Mechanistically, NK cell-derived IFN-γ and TNF-α can enhance DC maturation and inflammatory cytokine production, whereas activated DCs can support NK cell function through cytokines including IL-12 and IL-15. This reciprocal communication provides a biological rationale for combining DC vaccination with NK cell-based therapy. However, the magnitude and therapeutic relevance of this interaction depend on the maturation state of the DCs, the functional competence of the transferred NK cells, and the characteristics of the TME [87].

Preclinical studies provide evidence that combining DC vaccination with NK cell-based approaches can enhance antitumor immune responses compared with either strategy alone. Nevertheless, translation of these findings to clinical practice remains challenging because tumor heterogeneity, inadequate immune-cell trafficking, immunosuppressive cytokines, and limited persistence of transferred cells can restrict therapeutic efficacy. Thus, the potential benefit of NK-DC combination therapy should be considered a promising investigation strategy rather than an established clinical standard [87,97].

Importantly, the effectiveness of this approach is likely to be tissue- and microenvironment-dependent. In tumors with adequate immune-cell infiltration, combined NK and DC activation may reinforce endogenous antitumor immunity, whereas poorly inflamed or immunosuppressive tumors may require additional interventions to overcome barriers such as TGF-β signaling, hypoxia, metabolic dysfunction, or immune-checkpoint pathways. Consequently, future combination strategies may need to integrate NK cell activation, DC vaccination, and microenvironmental reprogramming according to the immunological characteristics of individual tumors.

7.3.2 Cytokine and Checkpoint Combinations to Overcome NK and DC Exhaustion

A complementary therapeutic strategy is to target the inhibitory and cytokine pathways that contribute to NK cell dysfunction within chronically inflamed and malignant tissues. Tumor-associated factors, including immunosuppressive cytokines and metabolic constraints, can reduce NK cell cytotoxicity and alter DC function, while inhibitory checkpoint pathways such as NKG2A, TIGIT, and PD-1 further constrain NK cell responses [53,55,85].

Cytokine-based approaches may therefore complement checkpoint inhibition by providing stimulatory signals required for NK cell survival, proliferation, and effector function. IL-15 has emerged as an important therapeutic cytokine because of its ability to promote NK cell expansion and functional activity. Preclinical and early clinical investigations are evaluating IL-15-based strategies, including IL-15 agonists, in combination with immune-checkpoint blockade to determine whether simultaneous enhancement of stimulatory signaling and relief of inhibitory pathways can improve antitumor responses [38,76,85].

The biological rationale for such combinations is based on the integration of activating and inhibitory signals rather than on a single molecular pathway. Checkpoint blockades can reduce inhibitory signaling, whereas cytokine stimulation can support NK cell metabolic fitness, persistence, and cytokine production. Enhanced NK cell activity may, in turn, influence DC maturation and antigen-presentation programs through cytokine-mediated communication, potentially reinforcing NK-DC cooperation. However, the extent to which this mechanism translates into durable clinical benefit is likely to depend on the functional state of the DC compartment and the characteristics of the TME [4,32,55].

Similarly, cytokine combinations such as IL-12 and IL-18 can strongly enhance NK cell IFN-γ production and have been investigated as approaches for generating highly functional NK cell states. Nevertheless, systemic cytokine administration

may be limited by toxicity and excessive immune activation, highlighting the need for controlled delivery or engineered cellular platforms [37,39,82].

Importantly, these principles should not be interpreted as evidence that simultaneous checkpoint blockade and cytokine stimulation universally restore the entire NK-DC circuit. Rather, they provide a mechanistic framework for testing whether coordinated manipulation of stimulatory and inhibitory pathways can re-establish productive NK-DC communication. Future studies should determine which combinations are most effective in specific tumor and inflammatory contexts and whether biomarkers of NK cell and DC functional status can guide patient selection.

7.3.3 Tissue-Specific NK-DC Targeting in Defined Disease Contexts

An emerging consideration in NK-DC-directed therapy is that the functional state of these cells is strongly influenced by the tissue microenvironment. Tissue-resident NK cells and DC populations acquire distinct phenotypic and functional properties in response to local cytokines, stromal signals, metabolic conditions, and inflammatory stimuli. Consequently, therapeutic strategies designed to modify NK-DC interactions may need to account for tissue-specific differences rather than assume that a uniform systemic intervention will produce equivalent effects across organs [77,98,99].

In the lung and gastrointestinal tract, for example, local immune networks must simultaneously maintain barrier integrity and provide effective antimicrobial and antitumor surveillance. Similarly, tumors arising in different anatomical sites can differ substantially in their immune-cell composition, metabolic environment, and degree of immune suppression. These differences may influence NK cell recruitment and function, DC maturation and antigen presentation, and the extent of productive NK-DC communication. Therefore, strategies aimed at enhancing NK-DC activity should be evaluated in relation to the specific cellular and molecular characteristics of the target tissue [70,77].

In cancer, this principle is particularly relevant because the abundance and functional state of NK cells and DC subsets can vary substantially between tumor types and between individual tumors. Approaches that enhance cDC1 recruitment or function, restore NK cell activity, or modify suppressive myeloid and metabolic pathways may therefore have different therapeutic effects depending on the TME [67,69,70]. Rather than applying a single universal NK-DC intervention, future therapeutic development should prioritize combinations that are selected according to tissue-specific immune phenotypes and validated biomarkers.

Overall, tissue specificity represents an important translational consideration for NK-DC-directed immunotherapy. Integrating information on tissue-resident immune-cell populations, local inflammatory and metabolic conditions, and the functional state of NK and DC compartments may enable more precise interventions while reducing the risk of excessive systemic immune activation. However, many proposed tissue-specific strategies remain investigational, and their therapeutic value requires validation in well-designed preclinical and clinical studies.

7.4 Systems and Precision Medicine Approaches

Effective NK-DC-directed immunotherapy will increasingly require a systems-level framework that considers interactions among immune-cell states, tissue context, metabolic conditions, and therapeutic interventions rather than relying on individual biomarkers or cell populations. Advances in single-cell and spatial technologies provide opportunities to characterize NK- and DC-cell heterogeneity and to identify cellular states and interaction patterns associated with effective or dysfunctional immune responses [98-100].

Single-cell RNA sequencing, spatial transcriptomics, and epigenomic approaches can characterize NK- and DC-cell populations within tissues and TME while simultaneously providing information about their activation states, functional programs, and spatial relationships. These approaches may help identify regulatory programs associated with cDC1 function, NK cell activation or dysfunction, and immunosuppressive microenvironments. However, the identification of molecular signatures does not by itself establish that these pathways are therapeutically actionable, and functional validation remains essential before such signatures can be translated into clinical interventions [98-100].

Computational approaches may provide an additional framework for integrating these complex datasets. Mathematical and mechanistic models can potentially describe cytokine feedback, cellular interactions, and changes in immune-cell states and may therefore assist in generating hypotheses regarding treatment combinations or dosing strategies. Nevertheless, such models remain dependent on the quality and biological assumptions of the underlying data and should be considered complementary to experimental and clinical validation rather than substitutes for it.

A major translational opportunity is therefore the development of biomarker-guided patient stratification. Integrating NK- and DC-cell abundance, receptor expression, transcriptional states, metabolic characteristics, and functional measurements could potentially distinguish patients more likely to benefit from NK-centered, DC-centered, or combined approaches. Importantly, these proposed signatures remain investigational, and prospective studies are required to determine whether they can reliably predict therapeutic response [98-101].

Overall, a systems-immunology perspective may provide a framework for moving NK-DC-directed therapy from empiric intervention toward biologically informed treatment selection. The principal challenge is to translate increasingly complex molecular and spatial datasets into clinically practical biomarkers that can identify the dominant regulatory defect in an individual patient and guide selection of the most appropriate therapeutic strategy.

8. Limitations and Future Directions

This review has several limitations that should be considered when interpreting the proposed NK-DC homeostatic framework. First, although substantial experimental and clinical evidence supports reciprocal communication between NK cells and DCs, the strength and biological consequences of these interactions vary considerably according to tissue, disease stage, cellular phenotype, and experimental context. Therefore, the NK-DC axis should not be regarded as a uniform regulatory mechanism across all diseases.

Second, much of the mechanistic evidence describing NK-DC interactions is derived from *in vitro* experiments and animal models, whereas direct evidence from human tissues and longitudinal clinical studies remains comparatively limited. Differences between murine and human NK- and DC-cell biology may further restrict the direct translation of experimental findings to patients. Consequently, some of the therapeutic concepts discussed in this review remain mechanistically plausible or investigational rather than clinically established.

Third, the considerable heterogeneity and plasticity of NK and DC populations present an additional challenge. Conventional classifications based on surface markers may not fully capture functional states within individual tissues. Emerging single-cell and spatial approaches are beginning to resolve this complexity; however, standardized biomarkers that reflect the functional state of the NK-DC axis in individual patients have not yet been established.

Fourth, the proposed integration of Tregs into the NK-DC framework should be interpreted as a regulatory extension rather than evidence that Tregs are equivalent to NK cells and DCs as primary components of the axis. The available evidence supports important reciprocal interactions between these populations, but the relative contribution of each component may differ substantially according to tissue and disease context.

Finally, although several therapeutic strategies, including CAR-NK cells, cytokine-based NK modulation, DC vaccines, tolerogenic DC approaches, and immune-checkpoint targeting, are advancing rapidly, evidence supporting rational NK-DC combination therapies remains incomplete. Optimal treatment combinations, sequencing, dosing, patient-selection biomarkers, and long-term safety require further validation in well-designed preclinical and prospective clinical studies.

Future research should therefore prioritize human tissue-based and longitudinal studies, functional rather than purely phenotypic biomarkers, and integrated single-cell, spatial, metabolic, and clinical analyses. Such approaches may clarify when NK-DC interactions promote protective immunity versus tolerance or pathology and may ultimately enable more precise, tissue-specific therapeutic manipulation of innate immune homeostasis.

9. Conclusion

This review highlights the NK-DC axis as an important regulatory component of innate immune homeostasis. Rather than functioning as isolated immune-cell populations, NK cells and DCs engage in reciprocal communication through cytokines, receptor–ligand interactions, and cellular contact, allowing immune responses to be adjusted according to tissue and inflammatory context. Tregs represent an additional downstream component that reinforces peripheral tolerance and helps stabilize these immune set points.

Disruption of this network has been implicated in cancer, autoimmune and inflammatory diseases, and chronic infection, although the nature and clinical significance of NK-DC dysfunction differ considerably between diseases and tissues. This context dependence is an important limitation of the current evidence and argues against assuming that a single therapeutic strategy will uniformly restore immune homeostasis.

Emerging approaches, including CAR-NK therapy, cytokine-based NK modulation, DC vaccines, tolerogenic DC strategies, and immune-checkpoint targeting, provide opportunities to manipulate different components of this regulatory network. However, many NK-DC combination strategies remain investigational, and their efficacy, optimal sequencing, and safety require further validation in disease-specific clinical studies.

Future research should therefore focus on defining tissue-specific NK-DC interactions, validating biomarkers that reflect functional rather than merely phenotypic immune states, and determining which patients are most likely to benefit from targeted or combinatorial interventions. Integration of single-cell and spatial technologies with functional and clinical data may ultimately facilitate a more precise understanding of NK-DC regulation and support the development of individualized approaches to immune modulation.

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Author Contributions

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Conflict of Interest

The authors declare that they have no conflict of interest.

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