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Review

NKG2D as a molecular link between epithelial stress and immune activation in Crohn's disease: therapeutic implications

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disorder driven by dysregulated immune responses, epithelial barrier dysfunction, and progressive tissue damage. Despite advances in biologic therapies, treatment resistance and loss of response remain common. The activating receptor NKG2D, expressed on natural killer cells and T cell subsets, recognizes stress-induced ligands (MICA, MICB, ULBP) upregulated on intestinal epithelial cells under inflammatory conditions. In CD, sustained ligand expression promotes NKG2D-dependent cytotoxicity, pro-inflammatory cytokine release (IFN-γ, IL-17), and lymphocyte trafficking into the mucosa, perpetuating a cycle of epithelial injury and chronic inflammation. Preclinical colitis models and clinical trials with anti-NKG2D monoclonal antibodies (e.g., NNC0142-0002) demonstrate reduced disease activity, improved histological outcomes, and induction of remission in moderate-to-severe CD patients. However, challenges remain, including potential impairment of immune surveillance against infections and tumors, patient heterogeneity, and pathway redundancy. Future directions include biomarker-guided patient selection, combination therapies with anti-TNF or anti-integrin agents, and next-generation biologics such as bispecific antibodies. Understanding the cellular and molecular basis of NKG2D signaling in mucosal inflammation positions this receptor as a promising, mechanistically anchored therapeutic target in Crohn's disease.

Keywords: Crohn's disease, NKG2D receptor, Inflammatory cytokines, MICA/MICB, Therapeutic target, Mucosal inflammation.

1. Introduction

Crohn's disease is a chronic, relapsing inflammatory condition of the gastrointestinal tract that arises from a complex interaction between genetic predisposition, environmental triggers, intestinal microbiota, and immune dysregulation. The disease can affect any segment of the gastrointestinal tract and is characterized by transmural inflammation, leading to complications such as strictures, fistulas, and abscesses. The global incidence of Crohn's disease continues to rise, particularly in industrialized and newly industrializing countries, reflecting the influence of environmental and lifestyle factors [1–3].

The pathogenesis of Crohn's disease involves an inappropriate immune response to commensal microbiota in genetically susceptible individuals. Genome-wide association studies have identified numerous susceptibility genes, including those involved in innate immunity, autophagy, and epithelial barrier integrity, such as NOD2, ATG16L1, and IL23R [4–6]. These genetic alterations contribute to defective microbial handling and exaggerated immune activation.

Current treatment strategies for Crohn's disease aim to suppress inflammation and induce remission. These include corticosteroids, thiopurines, methotrexate, and biologic agents targeting tumor necrosis factor (TNF), integrins, and interleukin-12/23 pathways [7–9]. Although these therapies have improved clinical outcomes, a significant proportion of patients exhibit primary non-response or lose responsiveness over time [10,11]. Moreover, long-term immunosuppression is associated with an increased risk of infections and malignancies.

Given these limitations, there is a pressing need to identify novel therapeutic targets that address key mechanisms of disease pathogenesis. The NKG2D receptor has emerged as a promising candidate due to its central role in

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immune activation and its involvement in mucosal inflammation. Understanding the contribution of NKG2D signaling to Crohn's disease may provide new opportunities for therapeutic intervention.

2. Functions of NKG2D

The NKG2D receptor is an activating immunoreceptor encoded by the KLRK1 gene and expressed on multiple immune cell types, including natural killer cells, $CD8^+$ T cells, γδ T cells, and subsets of $CD4^+$ T cells [12–14]. Structurally, it belongs to the C-type lectin-like family and forms homodimers on the cell surface. Unlike many other receptors in this family, NKG2D does not possess intrinsic signaling capacity but relies on association with adaptor proteins to transduce intracellular signals.

The primary adaptor protein for NKG2D is DAP10, which contains a YINM motif that recruits phosphoinositide 3-kinase and Grb2-Vav1 signaling complexes [15]. This leads to activation of downstream pathways, including AKT and MAP kinase cascades, resulting in cytotoxic granule release, cytokine production, and enhanced cell survival. In natural killer cells, NKG2D acts as a primary activating receptor, while in T cells it functions as a costimulatory receptor that enhances T cell receptor-mediated activation [16,17].

NKG2D recognizes a diverse set of ligands that are structurally related to major histocompatibility complex class I molecules. These include MICA, MICB, and the UL16-binding protein family (ULBP1–6) [18–20]. These ligands are typically absent or expressed at low levels in healthy tissues but are rapidly upregulated in response to cellular stress, such as infection, DNA damage, oxidative stress, or malignant transformation. This mechanism allows the immune system to detect "induced self" signals and eliminate damaged or abnormal cells.

The expression of NKG2D ligands is tightly regulated at multiple levels, including transcriptional control, post-transcriptional modifications, and proteolytic shedding. Soluble forms of these ligands can be released into the extracellular environment, where they may modulate immune responses by downregulating NKG2D expression on immune cells [21]. This dynamic regulation adds complexity to the role of NKG2D in health and disease.

3. NKG2D in the pathogenesis of Crohn's disease

In Crohn's disease, dysregulation of the NKG2D pathway contributes to chronic intestinal inflammation. One of the key features of this dysregulation is the increased expression of NKG2D ligands in the intestinal mucosa. Studies have demonstrated that epithelial cells in inflamed intestinal tissue express high levels of MICA and MICB, which are rarely detected in healthy mucosa [22–24]. This upregulation is driven by inflammatory cytokines such as TNF-α and interleukin-15, as well as microbial products and cellular stress signals.

The presence of NKG2D ligands on epithelial cells leads to their recognition by NKG2D-expressing lymphocytes. This interaction triggers cytotoxic responses, including the release of perforin and granzymes, resulting in epithelial cell death [25]. The loss of epithelial integrity compromises the intestinal barrier, allowing luminal antigens and bacteria to penetrate the mucosa and further stimulate immune responses.

In addition to promoting cytotoxicity, NKG2D signaling enhances the production of pro-inflammatory cytokines. Activation of NKG2D-positive T cells has been shown to induce the secretion of interferon-γ and interleukin-17, which are key mediators of Th1 and Th17 responses [26–28]. These cytokines contribute to the recruitment and activation of additional immune cells, creating a self-amplifying cycle of inflammation.

Another important aspect of NKG2D function in Crohn's disease is its role in lymphocyte trafficking. NKG2D signaling can enhance the expression of adhesion molecules and chemokine receptors, facilitating the migration of T cells into inflamed tissues [29]. This results in the accumulation of effector cells in the intestinal mucosa, perpetuating inflammation and tissue damage.

Experimental models provide strong evidence for the involvement of NKG2D in intestinal inflammation. In murine models of colitis, blockade of NKG2D with monoclonal antibodies reduces disease severity, decreases cytokine production, and improves histological outcomes [30–32]. Conversely, overexpression of NKG2D ligands exacerbates inflammation, highlighting the pathogenic role of this pathway.

4. Therapeutic targeting of NKG2D

The NKG2D pathway represents a mechanistically attractive target for therapeutic intervention in Crohn's disease due to its upstream position in immune activation and its involvement in epithelial damage. Unlike cytokine-targeted therapies that act downstream, NKG2D blockade interferes with the initial recognition of stressed intestinal cells by cytotoxic lymphocytes, thereby interrupting a key pathogenic loop in mucosal inflammation [33,34].

The most advanced therapeutic strategy involves monoclonal antibodies directed against the NKG2D receptor. One of the best-characterized agents is NNC0142-0002, a fully human monoclonal antibody designed to block ligand binding. In a phase II randomized controlled trial, this antibody demonstrated the ability to induce clinical remission in patients with moderate-to-severe Crohn's disease who had previously failed conventional therapies [33]. Notably, patients receiving the antibody showed reductions in Crohn's Disease Activity Index scores and improvements in inflammatory biomarkers such as C-reactive protein. Histological analyses suggested decreased immune cell infiltration and reduced epithelial damage, indicating that the therapeutic effect extended beyond symptomatic improvement.

Mechanistically, anti-NKG2D antibodies inhibit the interaction between NKG2D-expressing lymphocytes and ligand-bearing epithelial cells. This prevents activation of cytotoxic pathways involving perforin and granzyme release, thereby preserving epithelial integrity [35]. In addition, blockade of NKG2D signaling reduces the production of pro-inflammatory cytokines, including interferon-γ and interleukin-17, which are central drivers of Th1 and Th17 responses in Crohn's disease [26,27]. Importantly, this dual effect on cytotoxicity and cytokine production distinguishes NKG2D-targeted therapy from more selective cytokine inhibitors.

Beyond receptor blockade, alternative therapeutic strategies are being explored. One approach involves targeting NKG2D ligands themselves. For example, suppression of MICA and MICB expression using RNA interference or small-molecule inhibitors has been shown in experimen-

tal systems to reduce immune activation and epithelial damage [36]. Another strategy focuses on preventing the shedding of soluble ligands, which can modulate immune responses by downregulating NKG2D expression on immune cells. Metalloproteinase inhibitors that reduce ligand shedding may therefore enhance immune regulation and restore homeostasis.

A particularly promising direction is the development of combination therapies. For instance, combining NKG2D blockade with anti-TNF agents such as infliximab may provide synergistic effects by simultaneously inhibiting upstream immune activation and downstream inflammatory cascades [37]. Similarly, combination with anti-integrin therapies could reduce lymphocyte trafficking while NKG2D blockade limits local activation. These approaches may be especially beneficial in patients with refractory disease who have failed monotherapy.

Emerging biologic platforms, including bispecific antibodies, offer additional opportunities to target NKG2D in a more precise manner. Bispecific constructs capable of simultaneously engaging NKG2D and other immune checkpoints may allow fine-tuning of immune responses, potentially enhancing efficacy while minimizing adverse effects [44]. Although these approaches are still in early stages of development, they represent an important frontier in immunotherapy for inflammatory bowel disease.

5. Advantages and limitations

Targeting the NKG2D pathway offers several conceptual and practical advantages. Because NKG2D is expressed on multiple immune cell types, including natural killer cells and various T cell subsets, its inhibition results in broad immunomodulation. This contrasts with therapies targeting individual cytokines, which may be insufficient in the context of redundant inflammatory pathways [38]. By acting upstream in the immune activation cascade, NKG2D blockade has the potential to prevent both cytotoxicity and cytokine-driven inflammation, thereby addressing multiple aspects of disease pathogenesis simultaneously.

Another advantage lies in the specificity of NKG2D ligand expression. Because these ligands are typically induced under conditions of cellular stress, targeting the NKG2D pathway may preferentially affect inflamed tissues while sparing healthy cells. This could theoretically reduce systemic immunosuppression and improve the safety profile compared to conventional therapies.

However, several important limitations must be considered. A major concern is the role of NKG2D in immune surveillance. NKG2D-mediated recognition of stressed cells is critical for the elimination of virus-infected and transformed cells. Inhibition of this pathway may therefore increase susceptibility to viral infections, particularly those involving herpesviruses, and could potentially impair tumor surveillance [39,40]. Although clinical trials to date have not identified major safety signals, long-term data are lacking and careful monitoring will be essential.

Another limitation is the heterogeneity of Crohn's disease. Patients exhibit considerable variability in terms of disease location, severity, and immunological profile. For example, some patients may have predominant Th1-driven inflammation, while others exhibit stronger Th17 responses. The extent to which NKG2D contributes to disease pathogenesis may therefore vary between individuals, influencing therapeutic response [41]. This highlights the need for predictive biomarkers to identify patients most likely to benefit from NKG2D-targeted therapy.

Genetic variability also plays a role. Polymorphisms in genes encoding NKG2D ligands, particularly MICA, can influence ligand expression and function. Certain allelic variants are associated with higher levels of soluble ligand shedding, which may affect both disease progression and response to therapy. Understanding these genetic factors may enable more personalized treatment approaches.

Another challenge is the redundancy of immune pathways. The immune system employs multiple overlapping mechanisms to detect and respond to stress signals. Even if NKG2D signaling is blocked, other activating receptors and pathways may compensate, potentially limiting therapeutic efficacy [42]. This reinforces the rationale for combination therapies that target multiple pathways simultaneously.

Finally, pharmacological considerations such as dosing, route of administration, and immunogenicity of therapeutic antibodies must be addressed. Optimizing these parameters will be critical for maximizing efficacy and minimizing adverse effects.

6. Future perspectives

The future development of NKG2D-targeted therapies in Crohn's disease will depend on advances in several key areas, including biomarker discovery, therapeutic design, and clinical implementation. One of the most important priorities is the identification of biomarkers that can predict response to therapy. Potential candidates include tissue expression levels of NKG2D ligands, circulating concentrations of soluble MICA and MICB, and the frequency of NKG2D-expressing immune cells in peripheral blood and intestinal tissue [43]. Integration of these biomarkers into clinical practice could enable stratification of patients and more precise targeting of therapy.

Another promising area is the development of next-generation biologics. Bispecific antibodies that simultaneously target NKG2D and other immune pathways may offer enhanced efficacy by modulating multiple aspects of immune activation. For example, a bispecific antibody targeting both NKG2D and interleukin-23 signaling could theoretically suppress both cytotoxic and cytokine-mediated inflammation. Similarly, antibody–drug conjugates could deliver targeted immunomodulatory agents directly to NKG2D-expressing cells.

Gene-editing technologies such as CRISPR/Cas9 also hold potential for modulating the NKG2D pathway. By selectively altering the expression of NKG2D ligands in intestinal epithelial cells, it may be possible to reduce immune activation without systemic immunosuppression. Although still largely experimental, such approaches could represent a paradigm shift in the treatment of inflammatory bowel disease.

The role of the microbiome in regulating NKG2D signaling is another area of active investigation. Microbial metabolites and components can influence the expression of NKG2D ligands and the activation of immune cells. Modulation of the microbiome through diet, probiotics, or fecal microbiota transplantation may therefore indirectly affect NKG2D-mediated pathways and provide complementary therapeutic strategies.

Long-term clinical studies will be essential to establish the safety and efficacy of NKG2D-targeted therapies.

Particular attention should be paid to the risk of infections and malignancies associated with chronic inhibition of immune surveillance mechanisms [45]. In addition, studies comparing NKG2D-targeted therapies with existing biologics will be needed to define their optimal place in treatment algorithms.

Ultimately, integration of NKG2D-targeted therapies into clinical practice will require a personalized medicine approach that considers individual patient characteristics, disease phenotype, and molecular profile. Such an approach has the potential to improve outcomes and reduce the burden of Crohn's disease.

Conclusions

The accumulated experimental and clinical evidence supports several key conclusions regarding the role of NKG2D in Crohn's disease pathogenesis and therapy. First, NKG2D functions as a critical upstream regulator linking epithelial stress responses to immune activation, thereby acting as a central amplifier of mucosal inflammation rather than a secondary effector pathway. Second, aberrant expression of NKG2D ligands, particularly MICA and MICB, in intestinal epithelial cells represents a fundamental pathogenic mechanism that promotes cytotoxic lymphocyte activation, epithelial barrier disruption, and chronic inflammatory signaling.

Third, therapeutic blockade of the NKG2D pathway demonstrates clinically relevant efficacy, including the ability to induce remission and reduce inflammatory activity in patients with moderate-to-severe Crohn's disease, supporting its validity as a pharmacological target. Fourth, due to its upstream position in immune regulation, inhibition of NKG2D provides broader immunomodulatory effects compared to single-cytokine-targeted therapies and may therefore overcome resistance observed with current biologics.

Fifth, despite these advantages, NKG2D-targeted strategies require careful safety evaluation, as long-term inhibition may impair immune surveillance against infections and malignancies. Sixth, interindividual variability in ligand expression and immune network redundancy suggests that NKG2D-directed therapies will likely be most effective within a stratified or combination treatment framework rather than as universal monotherapy.

Finally, future therapeutic development should focus on biomarker-guided patient selection, combination regimens integrating NKG2D blockade with established biologics, and advanced targeting approaches such as bispecific antibodies or gene-modulating technologies. Collectively, these findings position NKG2D not only as a promising therapeutic target but also as a mechanistically informative axis for understanding immune dysregulation in Crohn's disease.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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Use of artificial intelligence tools

Some sentences in this manuscript were revised with the assistance of artificial intelligence, based language models to improve clarity and readability. All intellectual content, interpretations, and conclusions are solely the responsibility of the authors.

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