

Role of IDO1 and GCN2–mTOR Signaling in CD8⁺ T-Cell Dysfunction in Breast Cancer

¹Priyanka Nayak

²Dr. Jaishriram Rathored*

¹Central Research Laboratory and Molecular Diagnostics

Datta Meghe Institute of Higher Education and Research

Wardha(Sawangi), India

priyankanayak898@gmail.com

²Central Research Laboratory and Molecular Diagnostics

Datta Meghe Institute of Higher Education and Research

Wardha(Sawangi), India

jaishriz@gmail.com

0000-0001-6067-7505

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Abstract

Breast cancer growth and development are determined by the interactions between malignant epithelial cells, immune cells, and metabolic processes in the tumor microenvironment. Indoleamine 2,3-dioxygenase 1 (IDO1) catalyzes the conversion of the essential amino acid tryptophan to kynurenine, which may suppress antitumor T cell responses. Accumulation of tryptophan breakdown products and decreased tryptophan levels are associated with enhanced IDO1 expression and activity, which can lead to alterations in immunological responses and metabolic reprogramming. In particular, tryptophan restriction can trigger the general control nonderepressible 2 (GCN2)-eukaryotic initiation factor 2 α (eIF2 α) stress-response pathway and suppress mechanistic target of rapamycin (mTOR)-dependent nutrient and anabolic signaling, whereas kynurenine and related metabolites can modulate several additional pathways, including aryl hydrocarbon receptor signaling. These downstream effects of tryptophan restriction are potentially important in CD8⁺ T cells and can alter their metabolic fitness, proliferation, activation, and cytotoxic effector functions, leading to impaired antitumor immunity. Overall, IDO1-driven tryptophan metabolism and the associated immunometabolic alterations may contribute to tumor immune escape in the setting of breast cancer. Although this hypothesis has been proposed, additional studies are needed to validate the causal associations between IDO1 expression, tryptophan availability and kynurenine levels, GCN2/eIF2 α and mTOR signaling, and CD8⁺ T cell responses.

Keywords: IDO1; tryptophan metabolism; CD8⁺ T cells; GCN2; mTOR

1. Introduction

Breast cancer is one of the most frequent malignancies, and it continues to be a leading cause of cancer-related morbidity and death in women worldwide (Pasi et al., 2026). Although improvements in detection and treatment have improved clinical outcomes, tumor development, drug resistance, and immune evasion remain key issues in breast cancer (BC). The tumor microenvironment (TME) is considered an essential component of the tumor system because the crosstalk between tumor cells and immunological cells, as well as metabolic factors, is involved in disease development and immune surveillance function. CD8⁺ T lymphocytes are critical players in tumor recognition and destruction; however, their function in the TME is often impaired (K. Li et al., 2021).

The metabolic environment of tumor-infiltrating lymphocytes has become an important consideration in understanding their function state. Rapidly proliferating tumor cells influence nutritional use and metabolism resulting in a competitive situation for necessary nutrients and immunomodulatory metabolites. The metabolism of tryptophan is of particular interest as it is an essential amino acid for cellular proliferation, protein synthesis, and immune cell activity. Alterations in its availability can therefore have an impact on T cells' metabolic fitness and functional activity (Chen et al., 2026) (Xu et al., 2026).

Indoleamine 2,3-dioxygenase 1 (IDO1) is a key enzyme in extrahepatic tryptophan catabolism that converts tryptophan to N-formylkynurenine, hence commencing the kynurenine pathway. IDO1 expression is triggered by inflammatory signals, mainly interferon- γ , and has been found in several tumor and immune cell types in the tumor microenvironment (Hornýák et al., 2018). Increased IDO1 activity promotes tryptophan consumption and the buildup of kynurenine metabolites, providing an immunoregulatory metabolic milieu. These features have made IDO1 a promising option for studying the metabolic processes of tumor-associated immune suppression (Wang et al., 2026).

The decrease in local tryptophan availability was shown to impact T-cell responses through nutrition-sensing pathways. A lack of amino acids can cause GCN2 kinase activation and induction of an integrated stress response through eIF2 α phosphorylation, while decreased nutrient availability results in the inhibition of mTOR, namely, mTOR complex 1 (mTORC1), which regulates protein synthesis, metabolism, proliferation, and survival. Therefore, activation of GCN2-eIF2 α signaling and suppression of mTOR are distinct mechanisms responsive to nutritional status that can work in parallel in the context of tryptophan restriction. Functional crosstalk between these pathways is possible under particular cellular and metabolic conditions, but the obligatory linear link between GCN2 and mTOR has not been established. Finally, these metabolic adaptations might contribute to the impaired metabolic flexibility and effector function of CD8⁺ T cells in an IDO1-rich tumor microenvironment (Solvay et al., 2023) (L. Yang et al., 2023).

Several studies have demonstrated that IDO1-mediated tryptophan depletion exerts an immunosuppressive effect on T-cell proliferation and function. GCN2-eIF2 α and mTOR are two distinct nutrient-responsive signaling pathways that might be activated by tryptophan restriction rather than a single GCN2-mTOR signaling cascade. Additionally, experimental evidence has revealed that both GCN2-dependent and GCN2-independent mechanisms can contribute to the response to tryptophan limitation. Therefore, the role of individual GCN2 and mTOR signaling components and their crosstalk in CD8⁺ T cells in the context of breast cancer must be further investigated (Sarangi, 2023).

This review addresses the role of IDO1-associated tryptophan metabolism and nutrient-sensing pathways involving GCN2-eIF2 α and mTOR in CD8⁺ T-cell dysfunction in breast cancer. First, the role of IDO1 in tryptophan metabolism and its relevance in the breast cancer tumor microenvironment are described. Then, the possibility that tryptophan restriction might activate GCN2-eIF2 α -associated stress signaling and suppress mTOR-associated anabolic activity, and the potential functional consequences of such responses on CD8⁺ T-cell proliferation, metabolism, cytokine production, and cytotoxic activity are examined. Evidence linking such mechanisms to impaired antitumor immunity and tumor immune escape is evaluated, with a distinction between findings directly demonstrated in breast cancer and those extrapolated from other experimental systems. Finally, the available evidence regarding GCN2, mTOR, and their potential cross-talk is considered, focusing on mechanistic questions in need of clarification and possible therapeutic implications.

Literature Search and Review Approach

A narrative literature search was conducted using databases including PubMed, Google Scholar and Scopus to identify literature relevant to IDO1-mediated tryptophan metabolism, GCN2-eIF2 α and mTOR nutrient sensing pathways, CD8⁺ T cell function, and breast cancer immune regulation. The literature search was conducted during August-September 2026. Searches were conducted using combinations of the terms “IDO1”, “indoleamine 2,3-dioxygenase 1”, “tryptophan metabolism”, “kynurenine”, “GCN2”, “eIF2 α ”, “mTOR”, “CD8⁺ T cells”, “T-cell dysfunction”, “immune escape”, and “breast cancer”, including “triple-negative breast cancer” where appropriate. Foundational studies were prioritized where they established key mechanisms of tryptophan sensing and T-cell regulation, while recent literature including studies published during 2025-2026 were also incorporated to reflect current developments. Original studies providing evidence in the field of breast cancer were prioritized; studies from other cancer or experimental systems were included if they provided mechanistic evidence relevant to the proposed pathway and were identified as such. This review is narrative in nature and was not conducted as a systematic review or meta-analysis.

IDO1 and Tryptophan Metabolism in Breast Cancer

Indoleamine 2,3-dioxygenase 1 (IDO1) is an intracellular heme-containing enzyme that catalyzes the first and rate-limiting step of extrahepatic tryptophan catabolism through the kynurenine pathway, converting tryptophan to N-formylkynurenine and subsequently generating kynurenine and downstream metabolites. IDO1 is induced mainly by inflammatory signals such as interferon- γ and can be expressed by tumor, immune, and stromal cells. In breast cancer, increased tryptophan-kynurenine pathway activity has been associated with an immunoregulatory tumor microenvironment. The sustained expression of IDO1 leads to decreased local tryptophan levels and elevated kynurenine metabolites, which in turn dampens immune responses by limiting nutrients for growing cells and generating inhibitory metabolites, such as those that bind to the aryl hydrocarbon receptor (Nelp et al., 2018).

This poses a significant problem for the function of activated CD8⁺ T cells because their proliferation, protein production, metabolic reprogramming, and cytotoxic effector functions all depend on the availability of amino acids. IDO1 mediated restriction of tryptophan can therefore inhibit T cell proliferation and function and exert a nutrient stress that engages intracellular sensing mechanisms. Reduced tryptophan can induce the GCN2-eIF2 α stress response by accumulation of uncharged tRNA while at the same time suppressing mTOR mediated anabolic signaling. These effects may contribute to altered T cell receptor signaling, diminished biosynthetic and metabolic fitness, and decreased cytotoxic activity. GCN2 and mTOR should be regarded as distinct nutrient-responsive pathways that can operate in parallel after tryptophan restriction, rather than as a single sequential pathway; the extent of any cross-talk between them is context-dependent, and their precise contribution to IDO1-associated CD8⁺ T-cell dysfunction in breast cancer remains to be established (Ai et al., 2026) (Zhang et al., 2025).

GCN2 Signaling in CD8⁺ T Cells Under Tryptophan Deprivation

GCN2 is an amino acid stress sensing kinase which is activated by tryptophan deprivation in CD8⁺ T cells. The IDO1 mediated tryptophan degradation pathway can cause tryptophan limitation leading to accumulation of uncharged tryptophanyl-tRNA and subsequent GCN2 activation (Munn et al., 2005). Activated GCN2 will phosphorylate eIF2 α and initiate an integrated stress response, leading to reduced global protein synthesis and alterations in stress responsive gene expression. While this response could be advantageous in terms of nutrient adaptation under a transient tryptophan deprivation, prolonged tryptophan limitation will impair high biosynthetic demands of activated CD8⁺ T cells, resulting in compromised proliferation and effector functions (Rashidi et al., 2019).

In cytotoxic T cells, a prolonged stress of GCN2-associated nature could lead to reduced T-cell function. Indeed, there is evidence that tryptophan deprivation results in GCN2-dependent downregulation of the

T-cell receptor ζ -chain, leading to impaired cytotoxic function in CD8⁺ T cells (Fallarino et al., 2006). Nevertheless, GCN2 is not the only factor involved in T-cell response to amino-acid limitation, since both in vivo and in vitro experiments demonstrated the existence of GCN2-dependent and GCN2-independent pathways contributing to T-cell response to amino-acid limitation (Van de Velde et al., 2016; Zhao et al., 2023). Therefore, the activation of GCN2 and suppression of mTOR should be considered two different nutrient responsive mechanisms to IDO1-associated tryptophan restriction, which could occur simultaneously, but the extent of crosstalk between them could be context-dependent.

mTOR Signaling and Metabolic Regulation of CD8⁺ T Cells

The mechanistic target of rapamycin (mTOR) is a nutrient-responsive regulator that controls cellular metabolism, growth, and differentiation. The mTORC1 and mTORC2 complexes play distinct roles in CD8⁺ T-cell responses. Studies have shown that mTORC1 favors metabolic programming and differentiation of effector CD8⁺ T cells, whereas reduced activity promotes memory-related features. mTORC2 promotes CD8⁺ T-cell metabolic programming and memory differentiation. Thus, mTOR activity must be appropriately regulated in order to maintain a balance between effector and memory T cell states (Soliman, 2013).

mTORC1 activity is tightly linked to the metabolic status of activated CD8⁺ T lymphocytes. Higher mTORC1 activity has been linked to higher glycolytic activity and effector molecule expression, whereas lower activity is linked to greater lipid metabolism and improved long-term survival. Amino-acid transporter expression impacts mTOR location and activity during CD8⁺ T-cell activation, highlighting a link between amino-acid availability, mTORC1 signaling, and T-cell destiny. Collectively, available evidence identifies mTORC1 as a key metabolic regulator of CD8⁺ T-cell responses (K. Yang & Chi, 2012).

Importantly for the IDO pathway, experimental data show that IDO1-mediated tryptophan catabolism inhibits mTOR signaling, which may be reversed by increasing tryptophan availability (Newman et al., 2021). The same experimental work demonstrated that IDO1-mediated tryptophan deprivation may impact mTOR independently of GCN2, implying the presence of several nutrient-responsive mechanisms downstream of tryptophan restriction. Although evidence supports a relationship between mTOR and CD8⁺ T-cell metabolism and IDO1-mediated tryptophan depletion and mTOR regulation, their direct interaction in the breast cancer microenvironment is yet unknown (K. Li et al., 2021) (Zhang et al., 2025).

IDO1-Mediated Metabolic Regulation of CD8⁺ T-Cell Dysfunction in Breast Cancer

The breast tumor microenvironment comprises metabolically active tumor and immune cells that can modulate anticancer immune responses. IDO1 is expressed in breast cancer, although its amount varies

by molecular subtype and cellular compartment. Breast tumor studies have shown that IDO/IDO1 expression is greater in basal-like or triple-negative tumors, although IDO1 expression is also seen in a significant proportion of hormone receptor-positive breast malignancies. These findings confirm IDO1 as an important component of the breast cancer immune milieu, while its link to immune-cell infiltration appears to differ depending on tumor subtype and context (Feng et al., 2020) (Sarangi, 2023).

CD8⁺ T lymphocytes play a critical role in antitumor immunity. This can be achieved through their ability to recognize and eliminate tumor cells. This study evaluates the association between IDO1 expression and infiltration of CD8⁺ T cells in breast cancer. Although reports have demonstrated an inverse correlation between IDO1 expression and infiltration of CD8⁺ tumor-infiltrating lymphocytes, the relationship between IDO1 expression and CD8⁺ T cell infiltration in breast cancer was context dependent. Genomic studies have identified positive associations between IDO1 and CD8⁺ T cell-related immune signatures. However, an objective tissue-based analysis of 362 stage I to III hormone receptor-positive breast cancers did not identify an association between IDO1 protein expression and CD8⁺ tumor-infiltrating lymphocytes. Thus, IDO1 expression is not a reliable biomarker of impaired CD8⁺ T cell function or reduced infiltration of these cells in breast cancer. The functional properties of infiltrating CD8⁺ T cells are not necessarily reflected by their abundance.

Importantly, breast cancer studies provide direct evidence that tryptophan catabolism can impact cytotoxic T-cell responses, but the relevant enzyme and responding T-cell population vary across models. In TNBC, Greene et al. demonstrated that the tryptophan catabolite kynurenine induced death of primary human CD8⁺ T cells and that conditioned medium from anchorage-independent TNBC cells suppressed CD8⁺ T-cell viability in a TDO-dependent manner. This provides direct breast-cancer evidence linking tumor-associated tryptophan catabolism to CD8⁺ T-cell dysfunction; however, the enzyme implicated was TDO rather than IDO1 and therefore this study does not directly establish an IDO1-mediated mechanism. Conversely, studies examining IDO1 in TNBC have reported enhanced T-cell cytotoxicity and perforin production following IDO1 inhibition, but these experiments involved V γ 9V δ 2 $\gamma\delta$ T cells rather than conventional CD8⁺ $\alpha\beta$ T cells. Thus, these findings provide supportive evidence for IDO1-associated immunosuppression in breast cancer but should not be interpreted as direct validation of the proposed IDO1-GCN2/mTOR-CD8⁺ T-cell pathway. Overall, breast-cancer studies support a role for tryptophan catabolism in immune regulation, whereas the complete sequence linking IDO1-mediated tryptophan depletion to GCN2/eIF2 α and mTORC1 responses and subsequent conventional CD8⁺ T-cell dysfunction remains to be directly demonstrated in breast cancer (Greene et al., 2019).

To distinguish direct breast-cancer evidence from mechanistic evidence from other experimental systems, the available studies were categorized on the basis of tumor model, cell type, tryptophan-catabolizing enzyme, measured metabolic or signaling endpoint, T-cell outcome, and relevance to the proposed mechanism (Table 1).

Table 1. Evidence supporting tryptophan-catabolism-mediated T-cell dysfunction and its connection to the hypothesized IDO1–GCN2/mTOR pathway

Model / disease	Enzyme & cell type	Key finding	Relevance / limitation
Hormone receptor-positive (HR⁺) breast cancer	Indoleamine 2,3-dioxygenase 1 (IDO1); CD8 ⁺ tumor-infiltrating lymphocytes (TILs)	IDO1 expression showed no significant association with CD8 ⁺ TIL levels	Direct breast-cancer evidence; IDO1 expression alone does not establish CD8 ⁺ dysfunction (Carvajal-Hausdorf et al., 2017).
Triple-negative breast cancer (TNBC)	Tryptophan 2,3-dioxygenase (TDO); CD8 ⁺ T cells	Kynurenine induced CD8 ⁺ T-cell death; TNBC-conditioned medium reduced CD8 ⁺ viability	Direct TNBC/CD8 ⁺ evidence, but involves TDO rather than IDO1 (Greene et al., 2019).
Triple-negative breast cancer (TNBC)	Indoleamine 2,3-dioxygenase 1 (IDO1); V γ 9V δ 2 $\gamma\delta$ T cells	IDO1 inhibition increased T-cell cytotoxicity and perforin production	Direct TNBC/IDO1 evidence, but cells were V γ 9V δ 2 $\gamma\delta$ T cells, not conventional CD8 ⁺ T cells (P. Li et al., 2021).
Experimental tumor/immune models	Indoleamine 2,3-dioxygenase (IDO); T cells	Tryptophan depletion can activate GCN2/eIF2 α stress signaling	Supports the GCN2 component, but evidence is not specific to breast-cancer CD8 ⁺ T cells.
Experimental tumor models	Indoleamine 2,3-dioxygenase (IDO); immune/tumor cells	Tryptophan catabolism suppresses mTOR-related nutrient signaling	Supports the mTOR component, but does not establish a linear GCN2→mTOR pathway in breast cancer.

Integration of IDO1–GCN2–mTOR Signaling in Breast Cancer Immune Escape

The evidence provided supports individual elements of the proposed metabolic model, but these should not be interpreted to represent a single experimentally-established linear pathway, as found in breast cancer. IDO1 can promote tryptophan catabolism and reduced tryptophan availability can activate amino-acid stress responses, including GCN2–eIF2 α (Fallarino et al., 2006; Zhao et al., 2023), while

independently, tryptophan availability can also impact mTOR-dependent nutrient signaling (Metz et al., 2012). Both can influence the metabolic and functional capacity of T cells and thus provide a potential mechanistic basis for impaired CD8⁺ T-cell responses under conditions of chronic metabolic stress (Van de Velde et al., 2016).

However, the evidence becomes less certain when these individual observations are integrated into a breast-cancer-specific mechanism. Breast-cancer studies directly support a role for tryptophan catabolism in immune regulation, but some studies implicate TDO rather than IDO1, and others examine $\gamma\delta$ T cells rather than conventional CD8⁺ $\alpha\beta$ T cells (Greene et al., 2019; P. Li et al., 2021). Similarly, evidence for GCN2 activation and mTOR suppression is derived substantially from experimental systems outside breast cancer (Fallarino et al., 2006; Metz et al., 2012). These findings therefore support the proposed model mechanistically, but do not establish that IDO1-mediated tryptophan depletion simultaneously activates GCN2/eIF2 α and suppresses mTORC1 in breast-cancer-infiltrating CD8⁺ T cells.

IDO1-Mediated Tryptophan Depletion as the Initiating Metabolic Stress

Following T-cell receptor activation, CD8⁺ T cells undergo rapid metabolic and biosynthetic reprogramming to support clonal expansion and acquisition of effector functions. Increased IDO1-mediated tryptophan catabolism can disturb this requirement by limiting extracellular tryptophan available to tumor-infiltrating lymphocytes. The resulting deficiency is not simply a shortage of a protein-building substrate; it can also be sensed through intracellular nutrient-responsive pathways (Wang et al., 2026).

Two key adaptive responses to this metabolic stress are the activation of the GCN2-eIF2 α stress pathway and suppression of mTOR-dependent anabolic signaling. These responses should not be presented as an established linear GCN2-to-mTOR pathway but rather as distinct nutrient-responsive pathways that can operate in parallel after altered tryptophan availability, with context-dependent cross-talk between them (X. Li et al., 2025). The proposed link between tryptophan depletion by IDO1, GCN2-eIF2 α cascade, suppression of mTOR, and subsequent CD8⁺ T cell dysfunction is summarized in Figure 1.

GCN2-eIF2 α Activation During Tryptophan Restriction

When Intracellular tryptophan becomes limiting, reduced tryptophanyl-tRNA charging can cause an expansion of the pool of uncharged tRNA. GCN2 functions as an amino-acid stress sensor in this situation and once activated it can phosphorylate eIF2 α , which then initiates an integrated stress response that decreases protein translation and modifies the expression of some stress-adaptive genes. While these mechanisms can help adapt to a temporary nutrient shortage, chronic amino-acid

deprivation may impair the ability of activated cytotoxic T cells to meet their large biosynthetic demands (Van de Velde et al., 2016).

For CD8⁺ T cells, enhanced persistent translational stress could account for decreased proliferation and reduced production of proteins required for effective activation and cytotoxicity. Tryptophan depletion was furthermore associated with a GCN2-dependent downregulation of CD3 ζ , providing a potential mechanistic link between amino acid stress and defective T-cell receptor signaling. Nonetheless, GCN2 was unlikely to be the sole mediator, because proliferative dysfunction under profound tryptophan restriction was also manifest in a GCN2-independent manner (Qin et al., 2021).

Suppression of mTOR-Dependent Effector Metabolism

In addition to that, IDO1-mediated tryptophan catabolism can down-regulate mTOR signaling, a distinct nutrient-responsive pathway that operates in parallel with GCN2-eIF2 α stress signaling; the extent of cross-talk between the two pathways is context-dependent. mTOR (mostly mTORC1) is a nutrient sensor that connects cellular growth, proliferation, survival, metabolism, and effector functions to nutrient status; metabolic and nutrient signals are critical for the metabolic reprogramming that fuels clonal expansion, and mTORC1 activation is mandatory for antigen-specific CD8⁺ T cell effector functions, especially those related to antitumor activity (Metz et al., 2012).

Experimental studies suggest that IDO1-mediated tryptophan depletion can suppress mTOR signaling, whereas increasing tryptophan availability may reverse this effect. Thus, it could also be an independent nutrient-responsive consequence of tryptophan restriction and that this effect could be independent of GCN2 (Metz et al., 2012). However, this evidence comes primarily from experimental cellular systems that do not demonstrate that IDO1-mediated tryptophan depletion suppresses mTOR specifically in breast-cancer-infiltrating CD8⁺ T cells. The relevance of this mechanism to CD8⁺ T-cell dysfunction in breast cancer remains to be established.

Convergence on CD8⁺ Cytotoxic T-Cell Dysfunction

The functional importance of these pathways is evident by the observation that simultaneous impairment of both can limit the effectiveness of CD8⁺ T-cell responses. GCN2-eIF2 α -associated stress can cause reduction of translation while reduced mTOR activity can lead to decreases in anabolic metabolism and effector programming. Thus, the persistent limitation of tryptophan could compromise several requirements for an effective CD8⁺ T-cell response including clonal expansion, T-cell receptor-associated signaling, metabolic fitness, cytokine production, and cytotoxic activity (Jiang et al., 2020).

Consequently, CD8⁺ T cells can be present in the breast tumor microenvironment but be insufficient for optimal malignant cell clearance. The distinction is crucial; the quantity of tumor-infiltrating CD8⁺ T cells is not always indicative of retained cytotoxic capability, because infiltration does not necessarily translate into efficient tumor-cell death. (Xie et al., 2024). The key metabolic and signaling mechanisms

related with IDO1-mediated tryptophan restriction and their potential implications on CD8⁺ T-cell activity and tumor immune escape are outlined in (Table 2).

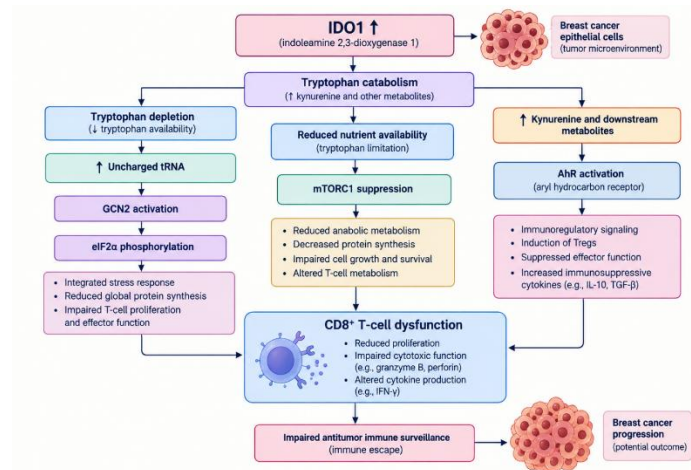


Figure 1. Proposed mechanism of IDO1-mediated tryptophan depletion, GCN2 activation, and mTOR suppression leading to CD8⁺ T-cell dysfunction and immune escape in breast cancer.

Table 2. Functional implications of IDO1-associated tryptophan limitation on nutrient-sensing pathways and CD8⁺ T-cell responses

Metabolic/signaling event	Principal mechanism	Expected effect in CD8 ⁺ T cells	Relevance to immune escape	References
Increase in IDO1 activity	Increased tryptophan catabolism	Reduced extracellular tryptophan	Nutrient-restricted TME	(Munn et al., 2005)
Decrease in Tryptophan	Accumulation of uncharged tryptophanyl-tRNA	Amino-acid stress	Impaired T-cell fitness	(Munn et al., 2005)
GCN2 activation	eIF2α phosphorylation	Reduced translation/stress adaptation	Reduced proliferation and effector capacity	(Van de Velde et al., 2016)
Reduction in mTOR/mTORC1 activity	Reduced anabolic signaling	Reduced metabolic and effector programming	Weakened antitumor response	(Metz, Rust, DuHadaway, et al., 2012)

Increase in Kynurenine	Metabolite-dependent signaling, including AhR	Additional immunoregulatory effects	Promotes immunosuppressive conditions	(Liu et al., 2024)
Combined metabolic stress	Multiple parallel mechanisms	↓ proliferation, cytokine production and cytotoxicity	Reduced tumor-cell killing	(Rashidi et al., 2019)

From Metabolic Dysfunction to Breast-Cancer Immune Escape

The metabolic consequences of IDO1-associated tryptophan catabolism may contribute to an immunosuppressive tumor microenvironment in breast cancer (Sarangi, 2023). Instead of one sequential pathway, the existing evidence reveals several potentially converging effects on T-cell metabolism, stress response, and effector function. Tryptophan limitation can trigger GCN2-dependent stress responses in cytotoxic T cells, while IDO1-mediated tryptophan catabolism can also affect mTOR-dependent nutrient signaling via a separate mechanism (Metz, Rust, Duhadaway, et al., 2012; Van de Velde et al., 2016). The relative contribution of these mechanisms to impaired tumor-cell function may depend on tumor subtype, cellular context, and the extent of local metabolic stress.

The accumulation of kynurenine could provide an additional layer of immunoregulation through the activation of the aryl hydrocarbon receptor (AhR) and related downstream effects. Hence, the IDO1-associated immune regulation is likely to involve a decreased availability of tryptophan for immune cells, plus the accumulation of kynurenine-pathway metabolites, which could affect the cellular and tumor environment differently depending on the context (Liu et al., 2024). These metabolite-driven effects would provide an alternative branch of the proposed model rather than a linear cascade of signaling events.

Ultimately, it is essential to consider the suggested IDO1-tryptophan-GCN2/mTOR-CD8⁺ T connection as a hypothetical mechanism rather than a proven pathway in breast cancer (Metz, Rust, Duhadaway, et al., 2012; Van de Velde et al., 2016). Indeed, the individual studies demonstrated the association of tryptophan metabolites, GCN2/eIF2 α signaling, mTOR-dependent nutritional regulation, and T-cell dysfunction; however, the direct evidence of their simultaneous occurrence in CD8⁺ T cells in breast cancer is still lacking (Metz, Rust, Duhadaway, et al., 2012; Van de Velde et al., 2016). Therefore, further integrated studies in breast-cancer models are required to define if these mechanisms are interconnected, independent, or possess diverse contributions to immune dysfunction.

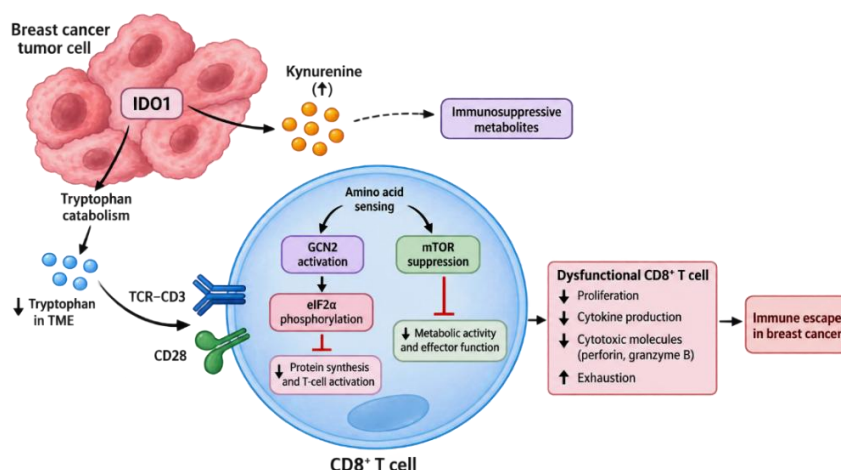


Figure 2. Proposed pathway of IDO1-mediated tryptophan depletion, GCN2 activation, and mTOR inhibition leading to CD8⁺ T-cell malfunction and immunological escape in breast cancer.

Therapeutic Implications of Targeting the IDO1–GCN2–mTOR Metabolic Axis

Targeting the metabolism of tryptophan can affect the metabolic immune suppression in the tumor microenvironment. The inhibition of IDO1 has been explored as a way to reduce tryptophan catabolism and improve antitumor immunity. The mechanism by which IDO1 inhibition works is not always reflected in the clinical outcome, which shows that the activity of the pathway can be insufficient to predict the therapeutic outcome. The context of tumors, the presence of compensatory tryptophan-catabolizing pathways, and the contribution of downstream kynurenine signaling to the progression of disease determine the effectiveness of treatment (Wen et al., 2026).

The therapeutic relevance of downstream nutrient-sensing pathways should be tempered with caution as well. Experimental evidence suggests that tryptophan restriction can trigger GCN2-associated stress responses, whereas IDO1-dependent tryptophan catabolism can suppress mTOR-dependent nutrient signaling via an alternative mechanism (Metz et al., 2012; Van de Velde et al., 2016). Nevertheless, these pathways are critical regulators of cellular metabolism and cannot be considered as therapeutic targets that once normalized would automatically restore CD8⁺ T-cell function. Their contribution to the response to treatment in the context of breast cancer remains to be established.

Therapeutic efforts targeting this network should also draw a difference between IDO1, TDO, and downstream pathways that include kynurenine and AhR. Both IDO1 and TDO participate in tryptophan catabolism, but they probably differ significantly in their pattern of expression and relevance across breast-cancer subtypes. Targeting the production of kynurenine or its downstream signaling through AhR is a downstream therapeutic strategy that might have immunoregulatory consequences on the tumor microenvironment without directly targeting IDO1 or TDO. Because these pathways probably

function differently across tumors it may be necessary to identify patients whose tumors are enriched in tryptophan catabolism before targeting any of these molecules. However, the usefulness of measuring IDO1 and TDO, and of downstream kynurenine and AhR or mTOR and GCN2 pathways as predictive biomarkers is currently unclear.

Challenges and Current Knowledge Gaps

Although IDO1-mediated tryptophan metabolism has been linked to immunological suppression, the exact role of tryptophan depletion is still contested. Much of the molecular evidence for GCN2 activation has been established under experimentally limited tryptophan circumstances, but the extent to which tryptophan concentrations within tumors reach low enough levels to trigger amino-acid deprivation responses is unknown. The gap between experimental systems and the tumor microenvironment challenges understanding of the IDO1-GCN2 connection in cancer.

Another significant drawback is that GCN2 and mTOR should not be regarded as a single sequential signaling pathway. GCN2 responds to amino-acid deficiency through uncharged tRNA and eIF2 α -associated stress signaling, whereas mTOR acts as a wider nutrient-sensitive regulator (Zhang et al., 2026). Experimental data suggests that GCN2 is not required for all CD8⁺ T-cell responses to tryptophan restriction, indicating the presence of GCN2-independent pathways. As a result, the proportional contribution of GCN2 activation and mTOR inhibition to IDO1-associated T-cell dysfunction is context-dependent and not fully understood (Metz, Rust, DuHadaway, et al., 2012). While IDO1 expression and its relationship with the immunological microenvironment have been established, there is scant evidence linking IDO1-mediated tryptophan depletion, GCN2/mTOR regulation, and typical CD8⁺ T-cell dysfunction in breast cancers. To assess if these processes work together in vivo, research should directly measure IDO1 activity, local tryptophan availability, GCN2 and mTOR signaling, and CD8⁺ T-cell functional status within a breast cancer model or patient cohort (Wang et al., 2026).

Another problem is the variability of tryptophan metabolism in the breast tumor microenvironment. IDO1 expression varies among breast cancer subtypes and between tumor and immune-cell populations, and other tryptophan catabolic enzymes may also contribute to local metabolic alterations. Because of this diversity, it is impossible to say whether IDO1 activity alone can predict tryptophan deprivation or subsequent immunological dysfunction. As a result, analysis of IDO1 expression, as well as metabolic and immunological characteristics across several breast cancer subtypes, may be required to identify cancers in which IDO1-associated metabolic regulation has the greatest biological and therapeutic value (G. Li et al., 2026).

Future Perspectives

Future research should focus on investigating the relationship between IDO1-tryptophan-GCN2/mTOR in the context of the breast cancer microenvironment. Simultaneous assessment of IDO1 activity, levels

of local tryptophan and kynurenine, GCN2/eIF2 α , mTOR activity, and CD8⁺ T cell functional markers could determine if these metabolic processes are occurring simultaneously in breast cancers. It could shed light on whether activation of GCN2 and suppression of mTOR are parallel effects of IDO1-mediated metabolic stress or if they contribute differently to the metabolic environment of individual breast tumors (Sarangi, 2023).

Another key goal is to account for metabolic and spatial variability in breast cancers. Recent research suggests that tryptophan-metabolizing enzymes might provide spatially different metabolic environments, implying that measuring IDO1 expression in bulk may not correctly reflect local tryptophan availability or immune-cell exposure to metabolic stress. Integrating geographic profiling with metabolomic and immune-cell analysis should increase knowledge of how IDO1-associated metabolic niches impact CD8⁺ T-cell activity (Yan et al., 2026).

The future of treatment strategies may require a biomarker guided approach to patient selection rather than universal application of IDO1 targeted approaches. Breast cancer research suggests that it is critical to identify those tumors with active tryptophan metabolism and associated immunological alterations prior to considering metabolic immunotherapies. Further investigation is needed to assess if alterations in GCN2/eIF2 α and mTOR are associated with IDO1 activity and CD8⁺ T-cell dysfunction and if such measurements have value as biomarkers of response to treatment. However, their predictive or therapeutic value in the context of breast cancer has not yet been experimentally established (Ding et al., 2024) (G. Li et al., 2026).

Conclusion

IDO1-mediated tryptophan metabolism provides a potential metabolic link between the breast tumor microenvironment and impaired antitumor immunity. Increased IDO1 activity can reduce local tryptophan availability and increase kynurenine metabolites, while tryptophan restriction can activate GCN2-eIF2 α -associated stress signaling and suppress mTOR-dependent anabolic activity. These distinct nutrient-responsive mechanisms, which can operate in parallel after tryptophan restriction and whose cross-talk is context-dependent, may compromise the proliferation, metabolic fitness, protein synthesis, activation, and cytotoxic function of CD8⁺ T cells, thereby reducing effective tumor-cell killing and contributing to immune escape. However, an integrated IDO1-tryptophan-GCN2/mTOR-CD8⁺ T-cell dysfunction mechanism has not yet been conclusively demonstrated in breast cancer. Future studies should therefore evaluate IDO1 activity, local tryptophan and kynurenine levels, GCN2/eIF2 α and mTOR signaling, and functional CD8⁺ T-cell markers together within breast cancer models or patient cohorts to determine the biological and therapeutic relevance of this metabolic network.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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