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Review Article

Exploring the importance of kynurenine pathway (KP) approaches in colorectal cancer (CRC)

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ABSTRACT

One of the main causes of cancer-related fatalities is colorectal cancer (CRC). The majority of patients frequently receive a late diagnosis of colorectal cancer (CRC) due to the absence of accurate prognostic and predictive biomarkers. Furthermore, greater metastasis and shorter survival rates were seen in colorectal cancer (CRC) patients. Recent advances in cancer treatment have been made possible by therapeutic immune system potentiation. The immune system and the kynurenine pathway (KP) are closely related. As a result of kynurenine's promotion of T Reg (regulatory) differentiation, more anti-inflammatory cytokines are produced and the cytotoxic activity of T cells is suppressed. In malignancies, the overactivation of the kynurenine pathway (KP) creates a micro environment where mutant cells can survive and invade neighboring tissues.

The poor prognosis of several cancers, including gastrointestinal cancers, gynecological cancers, hematologic malignancies, breast cancer, lung cancer, glioma, melanoma, prostate cancer, and pancreatic cancer, is predicted by overactivation of the kynurenine pathway (KP), particularly the overactivation of indoleamine 2,3-dioxygenase (IDO). Additionally, kynurenine promotes cancer cell invasion, metastasis, and chemoresistance. The evolving understanding of the kynurenine pathway (KP) and its use in colorectal cancer (CRC) is covered in this review.

An essential amino acid called tryptophan can be processed by several different pathways, with the kynurenine pathway (KP) being one of the more important ones. Kynurenine (KYN) is recognized as an oncometabolite in colon cancer, and colorectal cancer (CRC) that results from its subsequent metabolites. For several physiological activities, indoleamine 2,3-dioxygenase (IDO), a crucial enzyme that catalyzes kynurenine metabolism, is required.

We talked about IDO's role in colorectal cancer (CRC) in this review. IDO knockdown decreased the expression of cancer stem cell markers as well as the ability of colorectal cancer (CRC) cells to migrate and invade. The application of an inhibitor to restrict the enzymatic activity of IDO also prevented the formation of spheres and hindered cell motility in colorectal cancer (CRC) cells. These findings demonstrate the clinical significance of IDO in the growth and tumorigenicity of colorectal cancer (CRC) tumors.

1. Introduction

Cancer has a major social influence on a global scale. According to distinct diseased sites, colorectal cancer (CRC) can be separated into colon cancer and rectal cancer, which are both frequent gastrointestinal tumor diseases. The third most frequent cause of cancer is colorectal cancer (CRC). And the second most frequent reason for death.[1,2] Therefore, it is imperative that we increase our knowledge of novel cancer chemotherapy

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techniques. Cancer treatments have changed significantly in recent years. However, new ideas are required to improve the survival and quality of life of cancer patients. One of the novel techniques for treating cancer is cancer immunotherapy, often known as immuno-oncology. In Immuno-oncology the patient's immune system will get stimulated. That will result in improving the immune system's natural ability to fight against the disease.[1]

2. Literature Review

The immunogenicity of cancer cells serves as the foundation for the operation of immune oncology. Due to their immunogenicity, cancer cells require means of escape from the immune system to advance from local invasion to metastasis.[3] Additionally, a higher risk of cancer is associated with immune system dysfunction in chronic inflammatory disorders.[4] Competent immune cells may not exist when the immune system is working abnormally. Mutant cells can therefore quickly proliferate.[5] This shows that more lymphocytes that infiltrate the tumor predict a favorable outcome for solid tumors.[5] Additionally, it was shown that cancer cells use specific ways to avoid immune monitoring. For instance, the release of numerous anti-inflammatory mediators is induced by cancer cells, which also stimulate the T Reg response.[6] The alteration in the tumor immune microenvironment, particularly immunosuppression, helps to modulate one of the key modifications linked to cancer growth, metastasis, recurrence, and chemoresistance. Cancer immunosuppression can take many different forms, including the stimulation of immunosuppressive cells while upregulating immunosuppressive mediators or the inhibition of immuno-stimulant cells while downregulating immuno-stimulant mediators. Indoleamine 2,3-dioxygenase and its converted form kynurenine are both of the most common immunosuppressive mediators that have been proven to be effective in the development of colorectal cancer.[5,6]

The kynurenine pathway (KP) is well known for its association with inflammatory diseases and is also recognized as part of cancer immunoregulatory mechanisms.[7] However, many of its metabolites, collectively referred to as "kynurenine", are physiologically active and not only play important immunomodulatory roles but also disrupt various physiological systems.[8–10] The tryptophan-kynurenine pathway (KP) is a key mechanism in controlling the epithelial-mesenchymal transition (EMT) and helping cancers evade immune surveillance. In addition, the kynurenine pathway (KP) is involved in key signaling pathways involved in cancer pathophysiology.[8–10]

In the current review study, the relationship between colon tumors and the kynurenine pathway (KP) is attempted to be explained. Separate discussions will be held regarding the potential role of the kynurenine pathway (KP) in colon cancer as well as its involvement in the pathogenesis of that malignancy.

3. Discussion

Due to the high prevalence of metastasis, recurrence, and medication resistance, colorectal cancer (CRC) still has a dismal prognosis. Therefore, it's crucial to uncover the prognostic markers and create cutting-edge therapeutic approaches for the treatment of colorectal cancer (CRC).[11] The term "cancer stem cells" (CSCs) refers to cells that can initiate tumors and have the capacity for self-renewal and differentiation. More and more evidence points to the involvement of cancer stem cells (CSCs) in the development, spread, and recurrence of tumors. In colorectal cancer (CRC), targeting cancer stem cells (CSCs) is seen as an effective anti-tumor therapy.[12] The role of the immune system in the etiology of various malignancies has recently received more attention. Additionally, immunomodulation has become increasingly important in the management of metastatic colorectal cancer (CRC).[13] Cancer cells have been shown to thrive in immune-suppressive environments. Host stromal cells, tumor cells, and immune cells, such as leukocytes and macrophages, make up the tumor microenvironment. Immune response, especially T cell-dependent immunity, guards against tumor development and stops metastasis. A higher percentage of T cells that infiltrate tumors indicates a better prognosis for cancer. Particularly in the early stages of cancer, natural killer (NK) cells and cytotoxic T cells can recognize and eliminate immunogenic cancer cells. To stop competent immune cells from engaging in cytotoxic activities, tumor cells encourage T regulatory cell differentiation. This suggests that the tumor microenvironment is an important factor in the development of the tumor and could be a therapeutic target.[14]

In a recent study, it was found that compared to healthy colonic cells and tissues, colon cancer cells exhibit higher uptake and processing of tryptophan. The tryptophan metabolizing enzyme and the oncogenic transcription factor mediate this process.[15] In colon cancer cells, tryptophan is converted to kynurenine, a physiologically active molecule required for ongoing cell growth. The findings suggest that kynurenine, at least in part, exerts its oncometabolite activity by triggering the aryl hydrocarbon receptor, which in turn controls the growth-promoting genes in cancer cells. According to the study, inhibiting kynurenine synthesis or activity is an effective way to selectively slow the proliferation of colon cancer cells.[15]

Cancer has been demonstrated to cause inflammation. Chronic inflammation is closely linked to the deregulation of proliferation and the development of malignant lesions, and proinflammatory circumstances speed up the progression and metastasis of colorectal cancer (CRC).[16] IDO expression is elevated by inflammation, which activates

the kynurenine pathway (KP).[17] A potential technique for the therapy of cancer is to target these amino acid-metabolizing enzymes, which are implicated in the control of immunosuppression.[18] Kynurenine encourages the development of cytokines and immune cells that fight inflammation.[19] The kynurenine pathway's (KP) immunosuppressive qualities may aid in the management of autoimmune illnesses, but they can also promote the growth of cancer and aid tumor cells in evading the immune system.[20] Therefore, blocking the kynurenine pathway (KP) has been suggested as a potential cancer chemotherapeutic target. An essential negative feedback loop that cuts down the inflammatory response is kynurenine pathway (KP) activation.[21]

It is well recognized that tryptophan (TRP) metabolism in mammals through the kynurenine pathway (KP) constitutes a significant avenue to produce a variety of bioactive metabolites and is also involved in immunological control. Numerous important kynurenine pathway (KP) enzymes have been investigated for their crucial involvement in human illnesses such as neurodegeneration, schizophrenia, depression, autoimmunity, and cancer as a result of the increased interest in the functional consequences of the kynurenine pathway (KP) pathway on the body.[22]

One essential amino acid that the human body cannot produce on its own, tryptophan (TRP), must be obtained from diet.[23] After being absorbed by the body, tryptophan (TRP) circulates in the peripheral circulation either bound to albumin or free, with the former accounting for up to 90% of the total.[24] Nevertheless, the non-specific, competitive L-type amino acid transporter is the only one capable of delivering tryptophan (TRP) in its free form across the blood–brain barrier.[25] Tryptophan functions as a precursor for several metabolic pathways as soon as it enters the central nervous system (CNS). Due to its versatility, tryptophan (TRP) is converted into a variety of bioactive compounds, including protein, serotonin, and kynurenines. Serotonin is the most well-known of them, yet only a very small percentage of tryptophan (TRP) gets converted into serotonin. The conversion of tryptophan (TRP) into kynurenine (KYN) and its breakdown products occurs at a rate of more than 95%.[26]

Tryptophan is oxidized by breakage of the indole ring following the kynurenine pathway (KP). The transformation of tryptophan (TRP) into N-formyl kynurenine is the major rate-limiting step in the kynurenine pathway (KP).[26] This results in a rise in kynurenine and is catalyzed by three separate heme-enzymes, indoleamine 2,3 dioxygenase 1 (IDO1).[27], indoleamine 2,3 dioxygenase 2 (IDO2)[28], and tryptophan 2,3 dioxygenase (TDO). A group of kynurenine pathway (KP) enzymes can then convert kynurenine into a variety of bioactive metabolites. Among them, kynurenine 3-monooxygenase (KMO) performs an important role in the primary branch of the enzymatic cascade because it produces several hazardous byproducts, such as 3-hydroxykynurenine and quinolinic acid, which are in charge of inflammatory and neurological diseases.[29] The enzyme Tryptophan 2, 3-dioxygenase (TDO) and cells of the immune system and brain, where indoleamine 2, 3-dioxygenase (IDO) catalyze the conversion of tryptophan to kynurenine, is the main tissues where the kynurenines are generated.[30] The kynurenine pathway (KP) denotes a significant pathway for the metabolism of tryptophan in both the peripheral and central systems.[26] Tryptophan or corticosteroids are the two main sources of tryptophan2,3-dioxygenase (TDO), which is primarily found in the liver. On the other hand, IDO1, which is present in many different cells such as macrophages, microglia, neurons, and astrocytes, is the primary enzyme extra-hepatically. Both tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenases (IDOs) are essential in regulating adaptive immune responses and are expressed in a variety of inflammatory and malignant diseases. They are the enzymes responsible for the initial and rate-limiting steps of tryptophan catabolism to kynurenine.[27]

When it comes to infection, inflammation, and maintaining the immunosuppressive microenvironment in different forms of cancer, kynurenine's metabolites play a significant role.[23,31] Heme-enzymes' indoleamine 2,3 dioxygenase (IDO) is the primary rate-limiting enzyme in the kynurenine pathway (KP), while kynurenine 3-monooxygenase (KMO) is IDO's downstream enzyme.[32–34] In the early stages of colorectal cancer (CRC), IDO may act as a signal for distant metastases. High IDO expression encourages the formation of tryptophan catabolite, which inhibits T cell invasion and immunological evasion and speeds the development of colorectal cancer (CRC).[35] On the other hand, certain research reported in the literature suggested that the IDO inhibitor 1-L-methyltryptophan (1-L-MT) inhibited the growth of colorectal cancer (CRC) linked to colitis through cell cycle arrest in a way independent of modulation of adaptive immunity.[36] IDO-2, an enzyme related to IDO, was recently discovered.[28] IDO-1 and IDO-2 have neighboring encoding genes, and IDO-2 shares many of IDO-1's structural and enzymatic functions. IDO-2, however, has a distinct expression pattern and signaling route, and D-1-methyl-tryptophan inhibits it preferentially.[27,37]

Leukocytes and activated T cells that generate IFN-throughout an immune response cause tryptophan to be further and continuously degraded. It was first thought that this implication was a defense mechanism that deprived parasites, viruses, and cancer cells of tryptophan.[38] IDO1 improves T regulatory cell differentiation, which therefore promotes the recruitment of immunosuppressive myeloid-derived suppressor cells. The two IDO isoforms and TDO2 all have different inducers and patterns of tissue expression

despite having the same substrate. TDO-2 is stimulated by its substrate tryptophan and glucocorticoids, whereas IDO1 is strongly induced by pro-inflammatory cytokines like IFN-γ.[39] IDO2 induction, on the other hand, is less clear. IDO2 is expressed by hepatocytes, in the bile duct, neuronal cells of the cerebral cortex, and dendritic cells, whereas IDO1 is often found in all major organs as well as immunological T and B cells.[40] TDO-2 is mainly expressed in the liver, but it is also found in the placenta, in tissues from pregnant women and developing babies, and in the brain.[30]

Researchers are interested in the diagnostic or therapeutic potential of kynurenine pathway (KP) enzymes for the treatment of cancer due to their participation in the progression of the disease. Even though IDO hasn't been studied in cancer as much as other important kynurenine pathway (KP) enzymes like TDO, this work offers a new line of inquiry by speculating on a potential mechanism that fosters colon cancer malignancy.[28,41] To completely comprehend the biological role of IDO, additional research is required to ascertain if IDO-mediated metabolic alteration might affect the tumorigenic process given that other kynurenine pathway (KP) enzymes promote carcinogenesis through their bioactive metabolites.[42]

High-grade adenomas induce a considerable decrease in plasma tryptophan concentration and an increase in the kynurenine/tryptophan ratio, similar to colorectal cancer.[43] It has been demonstrated in the past that patients with colorectal cancer may benefit from colorectal cancer screening due to greater plasma concentrations of kynurenine.[44]

According to the study, when using 1.83 M as the cut-off point, plasma kynurenine had a sensitivity of 82.5% and a specificity of 100% for screening colorectal cancer. It's interesting to note that a decline in tryptophan independently predicts a lower quality of life in colorectal cancer patients.[43,44]

IDO is expressed in endothelial cells, metastases, tumor-draining nodes, and tumor cells. Another predictor of disease recurrence in colorectal cancer is endothelial expression of IDO. Lymph node metastasis is associated with colorectal cancer with elevated IDO expression.[45] Elevated IDO expression in colorectal cancer is positively correlated with the frequency of liver metastases and is associated with a significant reduction in CD3+ T-cell populations. In addition, increased IDO expression is thought to be a poor prognostic indicator for colorectal cancer. IDO activity modification has been proposed as a measure of colorectal cancer therapy response.[46]

Numerous investigations sought to understand how the kynurenine pathway (KP) and intracellular signaling pathways interacted in colorectal cancer. Similar to this, blocking the kynurenine pathway (KP) results in the death of colorectal cancer cells. In the azoxymethane (AOM)/dextran sodium sulfate (DSS) model of colitis-associated colorectal cancer, IDO deletion was linked to reduced carcinogenesis.[47] Additionally, it was discovered that IDO quickly activates the WNT/-catenin pathway, PI3K/serine/threonine kinase 1 (AKT), and cancer cell growth. Similar to this, a recent study found that in a model of inflammation-related colorectal cancer, IDO knockout mice have smaller and fewer tumors than wild-type mice.[48] Poor gastric cancer prognosis and a rise in immunological tolerance due to T Reg cell activation have been linked to high IDO expression. According to Liu et al., IDO expression can predict 3- and 5-year survival in gastric cancer and is an independent prognostic factor.[49]

Tryptophan can be used intracellularly in three different ways: it can be incorporated into newly created proteins, it can be converted into serotonin and melatonin by the serotonin pathway, and it can be converted into a variety of biologically active catabolites by the kynurenine pathway (KP). It was found in the literature that the activity of the oncogene MYC controls the abnormal activation of the kynurenine pathway (KP) in cancer cells. In the first step of the kynurenine pathway (KP), tryptophan is metabolized by one of the three functionally equivalent enzymes: indoleamine 2,3-dioxygenase1 (IDO1), indoleamine 2,3-dioxygenase2 (IDO2), or tryptophan 2,3- dioxygenase 2 (TDO2). After metabolism tryptophan produce N-formyl kynurenine. Then with the help of arylformamidase (AFMID) N-formyl kynurenine will be converted into kynurenine.[50–52]

According to the literature, colon cancer samples show higher kynurenine levels than the corresponding matched healthy colon samples.[43,44] The expression of the enzymes TDO2, IDO1, and AFMID in the same patient samples coincides with this elevation in kynurenine. The tryptophan transporters SLC1A5 (Solute Carrier Family 1 Member 5) and SLC7A5 (Solute Carrier Family 7 Member 5), as well as the enzyme AFMID, are interestingly expressed more frequently in colon cancer samples than in normal tissues from the same patients. Fewer patients had increased levels of TDO2 and IDO1.[43,44] Importantly, colon cancer samples do not show upregulation of the enzymes that break down kynurenine further into downstream catabolites, indicating that kynurenine is the main metabolite of this pathway in colon cancer cells. The findings demonstrate that tryptophan and kynurenine are found in colon cancer samples at equimolar quantities. The levels of all other catabolites are orders of magnitude lower. These findings supported the idea that colon cancer has kynurenine's biological activity.[43,44]

Research has shown that kynurenine generated by tumors is transferred into the tumor microenvironment and inactivates T cells there.[53] Cancer cells survive as a result of immunological evasion. A growing body of evidence from other sources demonstrated that kynurenine promotes the proliferation of cancer cells by cell-autonomous pathways

in addition to having a paracrine effect on T-cells.[53-54] [53] The role of kynurenine as a ligand for the transcription factor aryl hydrocarbon receptor (AHR) is its most well-understood molecular function. AHR stimulates the production of genes required for cell development in colon tumors, where literature has previously demonstrated that AHR expression is high. Recent research has shown that kynurenine and AHR are co-induced in the same tumors, proving that colon cancer cells actively use the kynurenine-AHR pathway.[55] According to published research, preventing the conversion of tryptophan into kynurenine is a useful way to particularly stop colon cancer cells and convert colonic organoids from proliferating. It's interesting to note that restricting kynurenine synthesis has a greater impact on reducing colon cancer cell proliferation than blocking kynurenine binding to AHR. Data from the literature also hints at the possibility of kynurenine having AHR-independent activities.[55]

IDO1 inhibitors were created in response to the finding that IDO1 levels are raised in a variety of tumor types.[56] These inhibitors work by preventing the formation of kynurenine, enabling the patient's T cells to remove cancerous cells from the body. However, more research is required to better understand the role of IDO in cellular proliferation and to ascertain whether this enzyme may be targeted to reduce kynurenine formation and stop the growth of cancer cells without compromising the health of normal tissues. Colon cancer and other disorders may be diagnosed or predicted using one or more tryptophan catabolites.[57]

Given the significance of the kynurenine pathway (KP) in a variety of disorders, research on therapeutic approaches that target this pathway may offer an alternate form of treatment or serve as a supplement to currently available therapies.[57] The body's immune system is weakened as a result of tryptophan's rapid breakdown and depletion. Another effect is the suppression of T-cell proliferation. The replacement of tryptophan might enhance immune response but unintentionally increase neurotoxins.[58]

In cancer research, IDO-1 activity suppression has been specifically targeted. IDO-1 inhibitors, 1-methyl-DL-tryptophan, and methyl-thiohydantoin tryptophan were able to enhance the effectiveness of chemotherapy medications by boosting tumor regression without increasing adverse effects in a transgenic mice model of breast cancer.[59] Understanding the mechanism underlying the antitumoral effects of 1-methyltryptophan and developing new IDO inhibitors may be made possible by the discovery of D-l-methyltryptophan's selective inhibition on IDO-2.[60-61]

Since then, more proof has appeared to support the idea that advanced colorectal cancer (CRC) patients have high IDO1 levels, which are linked to a bad prognosis. All of these findings indicate the crucial functions that kynurenine pathway (KP) activation plays in colorectal cancer (CRC). As a result, adding kynurenine pathway (KP) enzyme inhibitors to regular chemotherapy regimens may offer a promising therapeutic strategy.

4. Conclusion

This review, which provides an overview of how the kynurenine pathway (KP) may be implicated in the start of disease and the levels of tryptophan and kynurenines in cancer patients, compiles the majority of the studies. The kynurenine pathway (KP) is a successful method for managing the immune response and encouraging immunological tolerance. By accelerating the breakdown of tryptophan and the formation of kynurenines, this is achieved. The pathway's metabolites might interact with or compete with one another due to their diverse intrinsic properties to create different results. By comparing the levels of tryptophan, kynurenines, and the K/T ratio under various clinical conditions, it is possible to gauge the degree of immunological activation and the relationship between the kynurenine pathway (KP) and disease states. Since it was found that IDO1 is essential for controlling maternal-fetal tolerance, there has been a lot of interest in the possible roles that IDO1 and other kynurenine pathway (KP) enzymes may have in cancer immunology. Over the past ten years, there has been a significant accumulation of evidence indicating IDO1/TDO2 overexpression in tumors leads to tryptophan depletion in the microenvironment, which in turn suppresses the T-cell-driven immunological response. According to other research, kynurenine pathway (KP) activation promotes immune evasion. Due to their immunosuppressive properties, IDO and its Kyn metabolite become promising targets for cancer therapy. IDO/KYN also has carcinogenic potential and oncogenic impacts on angiogenesis, metastasis, oxidative stress, proliferation, and apoptosis. IDO, TDO, and the kynurenine/tryptophan ratio can be used to diagnose and treat several cancers, including colorectal cancer, esophageal cancer, gastric cancer, melanoma, HCC, RCC, non-small cell lung cancer (NSCLC), glioma, breast cancer, pancreatic cancer, osteosarcoma, thyroid carcinoma, uterine cancer, cervical cancer, prostate cancer, and hematologic malignancies. Invasion, metastasis, and angiogenesis of tumors are also associated with IDO activation. Additionally, kynurenine and IDO may help in cancer screening for particular tumors, such as non-small cell lung cancer (NSCLC), colorectal, prostate, and gastric cancer.

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None.

6. Conflict of Interest

None.

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