A short review of CD73 Role in Cancer

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Abstract
The purinergic signaling pathway has been introduced as the main way in the progression of cancer and is regulated by producing a series of nucleotides. CD73 is a surface protein encoded by the NT5E gene and plays a crucial role in cell signaling. CD73 has both enzymatic and non-enzymatic functions, independent of its enzymatic activity in cells; it has been detected to be over-expressed and plays an important role in many types of cancer. However, the non-enzymatic function of CD73 has not been well studied yet. Findings from recent research show that CD73 activities are exploited as ectoenzyme to produce extracellular adenosine; in other words, there is a tumor-induced immunosuppressive mechanism for CD73. It can increase tumor proliferation and development by restricting antitumor T immunity through adenosine receptor signaling. Several factors and mechanisms have been used to control CD73 expression.

Studies in various models have shown that CD73 plays a key role in the growth of tumors; it has also become an attractive therapeutic goal for scientists in many studies related to cancer. They include identifying different cancer subsets, the anticipation of drug response in patients, precipitation of purine escape pathway activity etc. Collective studies have proved that CD73 is a substantial molecule that formulates proliferation, colonialism and invasion in vitro, angiogenesis and immune escape in vivo in cancer and tumor cells. The data has shown that the potential of CD73 distinguished it as a recognizable biological marker in the next generation of treatment and research studies on cancer.

Keywords: Cancer, Tumorigenesis, Purinergic signaling, Ecto-5′-nucleotidase (CD73).

Introduction
Cancer cells use a variety of mechanisms to enforce and enhance immune evasion. The treatment of cancer includes surgery, radiotherapy, chemotherapy and using a complex network of factors to modulate and control the immune response in the microenvironment of tumors; inadequacies of these methods are the reasons for the failure of cancer therapy.9,24 The body exploits the immune system to recognize and suppress the development of malignant cells (40). During the progressive development of cancer or in tumorigenesis, these cells enhance the tolerant microenvironments that activate several immune suppression mechanisms in the patient.

These mechanisms can work effectively to neutralize the body’s immune response.19,53 Complex cell malignancy processes have been simulated in vivo and in vitro, ex vivo or in silico situations including tumor genesis, progression and metastasis by cancers or tumors which are very complex. It must be mentioned that they involve a chain of reactions including primarily dedifferentiation, preventing programmed cell death (apoptosis, autophagy etc.); it brings about rapid proliferation in mutated cells with the uncontrollable mechanism, deregulated metabolism, epigenetic, numerous angiogenesis, evasion from immune surveillance and incursion as well as colonization into distant organs etc.5,65

Many signaling pathways contributing to cancer and tumor progression have been elucidated; one of the most important pathways is the purinergic signaling pathway which plays an important and key role in tumorigenesis. Recent studies have indicated the extracellular adenosine triphosphate (ATP) mechanism to adenosine monophosphate (AMP) through the purinergic signaling pathway involving CD39 (ATP). This is followed by AMP transformation to adenosine (ADO) by involving CD73 as a leading signaling molecule.

The relations between extra-cellular nucleotides include ATP/ADP with CD39, AMP and CD73, the corresponding receptors on cancer and tumor cells were illustrated by figure 1.10,25,54

Investigating biopsies from patients has recently illustrated that CD73 could be over-expressed in a multitude of cancer types such as breast cancer, colorectal cancer (CRC), ovarian cancer, gastric cancer and gall bladder cancer associated with clinical features; these properties can be used as prognostics and diagnostics methods in cancer patients.3,14,42
This study focuses on previous research that has provided new empirical evidence. This evidence suggests that CD73 interferes with the mechanisms of T-cell anti-tumor activities. These studies strongly support and extend the fact that extracellular adenosine and A2A adenosine receptors (A2AR) play a fundamental role in tumor immune escape. It has been confirmed that CD73 is a major regulatory molecule in cancer formation. It was found that controlling CD73 can be considered a promising approach to treat cancer patients in the future (Figure 1).

**Background studies**

**Molecular function**: Stress in biology is defined as any environmental or physical pressure (biotic or abiotic) that elicits reactions from an organism; in other words, any factor that seriously threatens homeostasis in the organism. Many biotic and abiotic stressors have been shown to induce cell responses such as injury, different pathogens, inflammatory agents, oxygen availability (hypoxia), oxidative and ER stress, chemotherapeutic agents, irradiation etc. Due to all these stressors, different types of cells release nucleotides in response to them. Subsequently, a lot of enzyme cascades hydrolyze nucleotides include ATP or ADP into AMP by NTPDases, AMP into adenosine by Ecto-5′-nucleotidase also known as CD73 and finally, Adenosine-to-inosine (A-to-I) by applying adenosine deaminase. CD73 is a glycosylphosphatidylinositol (GPI) and anchored cell surface protein that is encoded by the NT5E gene and plays multiple roles in tumor processes. Previous studies have presented a potential value of CD73 served as a detectable biomarker for the prognosis of several solid tumors, but the results were more controversial.

Purinergic signaling can be defined as a multistep adjusted cascade that induced secretion of ATP/ADP, enabling signaling activity via P2 receptors and nucleotide inactivation to adenosine; Furthermore, adenosine binds to its P1 receptors, which use biological pathways as well as regulation and maintenance of micro internal environment and homeostasis of cells and tissues, differentiation, proliferation, or finally the cell death.

Figure 1: One of the most important signaling pathways contributing to cancer and tumor progression is the purinergic signaling pathway, which plays an important and key role in tumorigenesis, extracellular adenosine triphosphate (ATP) mechanism to adenosine monophosphate (AMP) through the purinergic signaling pathway involving CD39. This is followed by AMP transformation to adenosine involving CD73 as a leading signaling molecule. CD73 could be over-expressed in a multitude of cancer types and interferes with mechanisms of anti-tumor activity of immune systems. Extracellular adenosine and A2A adenosine receptors (A2AR) play a fundamental role in tumor immune escape.
Hence, it is adjusted with a set of cell surface-located ectonucleotidases and coordination between ATP/ADP, AMP and adenosine that could be considered as an essential method for controlling tumor progression\textsuperscript{1,57}. Ectoenzymes CD39 and CD73 sequentially convert ATP or ADP to AMP and finally produce ADO by coordinated action. Extracellular adenosine (EADO) mediates the effect of antibodies, paracrine hormones and type I purine receptors.\textsuperscript{37,62} CD73 has been determined as Ecto-5'-nucleotidase (Ecto-5'-NT, EC 3.1.3.5) and is a glycosyl-phosphatidylinositol (GPI)-anchored cell surface protein; its enzymatic activity was detected in many tissue cell types\textsuperscript{52}. Adenosine has now been identified as one of the most important molecules for regulating the immune system in microenvironment tumors\textsuperscript{57}. CD73 genes have been reported to be overexpressed in a wide range of cancers.

Also, with clinical and statistical studies, its importance has been determined by correlation analysis\textsuperscript{16}. CD73 has both enzymatic and non-enzymatic functions in cells; CD73 acts as a nucleotidase that catalyzes AMP hydrolysis to adenosine and phosphate; adenosine is produced by CD73 which in particular plays an important role in immunogenesis in tumor cells.\textsuperscript{20,57,59} In addition, CD73 has a non-enzymatic function as a signaling and adhesive molecule which can suppress the interaction of the cell with Extracellular Matrix Components (ECM), laminin and fibronectin and affects metastatic characteristics of cancer\textsuperscript{27}.

Studies have indicated that both the enzymatic and non-enzymatic roles of CD73 are involved in cancer-related processes and are not independent of each other.\textsuperscript{2,37} It was demonstrated that Higher expression of CD73 was connected to metastasis, invasiveness and tumor revascularization.\textsuperscript{51,62} It was proved in patients who have breast cancer and the survival time was observed to be shorter than normal cells regarding encodes CD73\textsuperscript{54}.

Furthermore, CD73 causes migration and promotes the invasion of cancer cells in humans.\textsuperscript{39,65} Upregulated expression of CD73 has been discovered in extremely invasive human melanoma cell lines\textsuperscript{63}. The biological function of CD73 (Ecto-5'-NT) is broadly the consequence of the enzymatic activity of phosphate enzymes which adjusts extracellular nucleotides\textsuperscript{23}. This ecto-enzymatic cascade is associated with CD39 (ecto-ATPase) that generates adenosine from ATP which exploits adenosine receptors\textsuperscript{2}. Despite the intracellular production of adenosine, cytosolic repositories of adenine can be catalyzed by cytosolic 5' NTnucleotidase in the cell. Howbeit, the extracellular pathways and the amount of the availability of extracellular AMP play a major role in maintaining immune cell homeostasis.\textsuperscript{64,66}

**Clinical studies:** In research on CD73 expression regulation by proinflammatory cytokines, there has been disagreement whether these inflammatory cytokines affect CD73 in cancer cells or not. However, it has recently been revealed in epithelial cells that there is a case of hypoxia-inducible factor 1 (HIF-1) for regulating the CD73 pathway.\textsuperscript{26,62} The available evidence points to the role of HIF-1\textalpha and CD73 in the conversion of AMP to adenosine which results in an increased level of extracellular adenosine in the tumor.\textsuperscript{34,54} Loi et al\textsuperscript{55} showed that the expression of CD93 and CD73 was connected with prognosis in patients with triple-negative breast cancer (TNBC).

Lu et al\textsuperscript{38} measured the clinical significance and prognostic power of CD73 in \( n = 68 \) human gastric cancer patients. Analysis of CD73 expression by Immune Histochemistry (IHC) disclosed that overexpression of CD73 was positively correlated with differentiation of cells in the tumor\textsuperscript{40}. Zhao et al surveyed the expression of CD73 in miscellaneous leukemia subtypes in \( n = 86 \) patients with hematologic neoplasms and revealed that the expression of CD73 was correlated with leukemia subtype, differentiation and proliferation\textsuperscript{23}. In clinical practice, high expression of CD73 in papillary thyroid tumors of patients with thyroid carcinoma presents a base for the differential diagnosis test\textsuperscript{38}.

The unregulated ecto-enzymatic activity of CD73 was suggested to have diagnostic value for colon cancer patients\textsuperscript{1}. Researchers have discovered that epithelial tumor cells in mice and humans expressed CD39 and CD73. The presence of CD73 is accompanied by high enzymatic activity in cancer tissue cells and it can mediate the production of adenosine in the extracellular environment, this supports the hypothesis that the tumor cells contribute to the increase of adenosine in the microenvironment of the tumor through the enzymatic activity of CD73 levels.

In particular, it indicates the development of T-cell-based therapy by enhancing adaptive immune response processes in T lymphocytes which would infiltrate the tumor and subsequently improve survival in cancer patients\textsuperscript{23}. Cancer immunotherapy by endogenous or adoptively transferred antitumor T-cells could be complementary to routine therapies including chemotherapy, radiotherapy, surgery etc.\textsuperscript{13,51}

In another investigation performed by Grozio et al\textsuperscript{22}, it was proved that nicotinamide adenine dinucleotide (NAD+) can be chiefly synthesized in "salvage" pathways inside human cells beginning by nicotinamide, nicotinic acid, or nicotinamide riboside (NR). Initiation of the “salvage” pathway from nicotinamide is activated by FK866 inhibition\textsuperscript{44}. FK866 brings about apoptosis by very special non-competitive inhibition activity of nicotinamide phosphoribosyltransferase (NAPRT) and is a key enzyme for adjustment of the NAD+ production from natural nicotinamide.\textsuperscript{21,39} In addition, it displays a strong anti-tumor activity in multiple different clinical models of cancer\textsuperscript{25}. It was shown in this study that clinical experiments have been performed by FK866 and for patients who underwent this
treatment, there is no need for resection of their tumor, in other words, they do not need surgery to take out tumors.\textsuperscript{29,31}

Also, it was illustrated that extracellular micromolar concentrations of NAD\(^+\) or NAD\(^+\)-(low) and low concentrations of Nicotinamide Mononucleotide (NMN) and NR can invert the FK866-induced cell death. This can be a logical explanation for the failure of Nicotinamide phosphoribosyltransferase (NAMPT) inhibition as an antitumor therapy.\textsuperscript{59,61} NMN can be a substrate of both CD38 and CD73 ectoenzymes for producing NAM and NR respectively.\textsuperscript{32} The role of CD38 and CD73 was investigated in providing Ecto-cellular NAD\(^+\) precursors for NAD\(^+\) biosynthesis and modification of cell sensitivity to FK866. Exclusively silencing or over-expressing CD38 enhances endogenous production of CD73 whereas CD38 suppresses the extracellular alteration of NMN to NR (an intracellular precursor of NAD biosynthesis in cells). In addition, cell survival by FK866-treated cells with extracellular NMN in tumor cells is severely diminished after drug control (pharmacological inhibition) or special adjustment (down-regulation) of CD73.

This study, therefore, mentioned genetic or pharmacological interventions by CD73 activity indicating that it could be useful to increase the sensitivity of cancer cells to NAMPT inhibitors\textsuperscript{32}. The possibility of expression of CD39 and CD73 by chronic lymphocytic leukemia cells (cells) for measuring activators of adenosinergic factors which affected cell proliferation and survival, has been investigated by Serra et al.\textsuperscript{34} It was shown by immune-histochemistry methods that CD39 is highly expressed in the CLL lymph nodes. CD73 was found to be confined to proliferation centers and expression of CD73 may be numerous in the Ki67 cells and the vicinity of T lymphocytes; also it was found in vascular areas in which T lymphocytes are likely found and in perivascular areas\textsuperscript{46}. CD39/CD73 CLL (Chronic lymphocytic leukemia) cells produce ADO from ADP in a time-dependent way\textsuperscript{2}. CD73 expression takes place in CLL\textsuperscript{97/299 (32\%)} and is connected with CD38 and ZAP-70 expression in peripheral blood of patients\textsuperscript{54}. The extracellular CD73/CD39 induced A2A purinergic type1 of A1 receptors in CLL cells and increased the proliferation of neoplastic cells\textsuperscript{4}. Activation of the ADO receptors enhanced cytoplasmic cAMP amounts and limited chemotaxis and restricted spontaneous drug-induced apoptosis in CLL cells\textsuperscript{54}. The results from Serra et al\textsuperscript{34} are following the presence of an autocrine adenosinergic loop in which leukemia cells dwell in optimal growth niches where they are protected from the function of chemotherapeutic agents\textsuperscript{37}.

Antonioli et al\textsuperscript{1} investigated the role of immunotherapy by anti-CD73 in cancer treatment; they emphasized that new methods that complement routine chemotherapy and targeted therapy could prove effective in treatment\textsuperscript{1,15} such as restraining of CD152, CTLA4 (CD152) is a B7/CD28 family member\textsuperscript{44} that inhibits T cell functions and alternatively acts as immune checkpoint receptor so Anti- CTLA-4 antibodies can promote cancer immunity in cancer therapies.\textsuperscript{4,56} CD279 also named programmed cell death protein-1 (PD-1)\textsuperscript{51} or CD274 Kwon as the programmed death 1 receptor (PD-1) and its ligand (PD-L1)\textsuperscript{13,60} are successfully used in clinical immunotherapy experiments.

Checkpoints between the respective pathways were also considered; Ecto-5'-nucleotidase (CD73) was found to have a greater effect on escaping from the immune system’s invasion than other previously studied substances\textsuperscript{43} which implied a goal for the development of exquisite anticancer immunotherapy practices\textsuperscript{1}.

The expression of CD73 and hypoxia-inducible factor-1α (HIF-1α) in human gastric carcinoma was investigated by Lu et al\textsuperscript{28} who discovered the clinical importance and credibility of their prognosis by applying immune-histochemistry in sequential sections of 68 specimens from gastric carcinoma patients’ tissue. It was demonstrated that CD73 and HIF-1α expressions were higher in gastric carcinoma than in gastric mucosal tissues. In gastric carcinoma, the expression of CD73 could be related to the expression of HIF-1α (28). CD73 could be an independent diagnosis marker for gastric carcinoma. The findings of Lu et al\textsuperscript{28} confirm the results of previous studies that indicate the key role of CD73 in cancer development.

Gene-expression information from over 6,000 breast cancer patients has been gathered by Loi et al.\textsuperscript{37} It was reported that high CD73 expression could be associated with a little anticipation in triple-negative breast cancer (TNBC). Also, anthracycline-based chemotherapy regimens were commenced treatment by applying mouse models of breast cancer. They illustrated that CD73 overexpression in tumor cells conferred chemo-resistance to doxorubicin, routine consumption of anthracycline. Suppression of compatible antitumor immune targeted blockade of CD73 and elevated doxorubicin-mediated antitumor immune responses and increased survival significantly in mice suffering from metastatic breast cancer. Overall, these data suggest that CD73 would be a therapeutic target in TNBC.\textsuperscript{37,44}

**Drug studies:** In the course of cancer immunotherapy, studies on ecto-nucleotidases and adenosine receptors have been introduced as novel clinical targets to enhance antitumor immune response therapies and early clinical attempts have presented hopeful results to discover different mechanisms of action. Thus, adenosine target agents are becoming important for research related to cancer. Excessive CD73 expression can be related to resistance to antitumor factors\textsuperscript{55}.

Quezada et al\textsuperscript{47} indicated that knocking down or/and deterrence activity of CD73 gene expression by siRNA reverses the vincristine resistance phenotype in glioblastoma multiform (GBM) cells.\textsuperscript{3,21}
Small molecule suppressors or monoclonal antibodies which target CD73 showed in the mice model that targeted CD73 therapy was an alternative and realistic method to effectively control tumor growth. In particular, increasing the response of the adaptive immune system helps T-cell-based therapy which enhances the function of T-penetrating lymphocytes into tumor cells and subsequently leads to improved survival in cancer patients.\textsuperscript{36,38}

The relationship between CD73 expression level and pathologic complete responses (PCR) rate in \(n = 59\) triple-negative breast cancer (TNBC) patients treated with preoperative chemotherapy anthracycline was evaluated by Loi et al.\textsuperscript{37} Their investigation showed that low-level expression of CD73 was related to enhancing PCR rate. In addition, they used breast cancer mouse models to show that in tumor cells, CD73 overexpression might give chemoresistance to doxorubicin interdependent on the activity of the A2A adenosine receptor. In mice models, targeted blockage of A2A adenosine receptors could release doxorubicin sensitivity of CD73-overexpressing tumors.\textsuperscript{37,47}

Therewith, despite the great interest in cancer immunotherapy, clinical advantages must be further studied to better understand the mechanisms of immune escape. As an important immune escape monitoring molecule in the body, CD73 can inevitably be involved in immunotherapy resistance\textsuperscript{37}. Therefore, treatment of patients with high CD73 expression should be considered by linking CD73 and resistance to some anti-tumor therapies; in other words, anti-CD73 chemotherapy could be combined with immunotherapy. In the future, with the next generation of cancer treatment, CD73 expression in cancer patients could also be an indicator of gene identification in the selection and use of drugs that can be used to treat cancer.\textsuperscript{12,23}

Geoff et al\textsuperscript{18} experimented for testing interferon-beta-1a (IFN-beta-1a) in ex-vivo for CD73 activity and illustrated that IFN-beta-1a induced up-regulation of CD73 in cultured human lung tissue specimens of patients with Acute Respiratory Distress Syndrome (ARDS). FP-1201 up-regulates CD73 expression in human lung and it is correlated with a 28-day decline in mortality in patients with ARDS. These findings, in general, needed to be proven and are needed to be prospective in randomized trials; however, this suggests that FP-1201 may be an effective drug with a particular target for patients having ARDS\textsuperscript{18}.

**Conclusion**

Briefly, CD73 plays a key role in various studies in the field of cancer.\textsuperscript{66} Early-phase clinical trials showed promising results to decipher the distinct mechanisms of agents targeting the A2a receptor for cancer immunotherapy\textsuperscript{69}. The association between overexpression of CD73 and clinical approaches such as the identification of different subtypes of cancer, the patient's prognosis and response to medication, has shown that CD73 can be considered as a biologically detectable marker in the next generation of cancer therapies and studies\textsuperscript{28}. In addition, the early effects of CD73 on tumor formation and metastasis have shown that CD73 could be a potential target for cancer treatment. These findings suggest that CD73 is a key factor in controlling tumor growth and proliferation.\textsuperscript{12,36} Subsequently, increased CD73 expression during tumor development could be a physiological attempt by tumor cells to provide more substrate for the initiation of purine escape pathway activity; it reveals that CD73 would be a leading agent for controlling tumor proliferation\textsuperscript{11}.

Recently, evidence in rat models suggests that targeted CD73 blockade may be an appropriate treatment for future cancer patients\textsuperscript{23}. Discoveries with small molecule receptors or monoclonal antibodies that target CD73 in mouse tumor cells for cancer model analysis suggest that targeted CD73 therapy is an effective and realistic alternative to controlling tumor growth. These observations provide a useful opportunity to expand anti-CD73 therapy for patients with specified cancers\textsuperscript{2}.

However, based on these findings, there is still a long way to go to achieve this goal. Further studies are expected to translate anti-CD73 therapy into clinical approaches. In particular, due to the high performance of the CD73 range \textit{in vivo}, there are still no side effects with anti-CD73 therapy in rat models. In this case, it is necessary to measure the potential for harmful risk before using this treatment for cancer patients and there should be a detailed discussion of anti-CD73 therapy during treatment\textsuperscript{1}. However, based on previous studies, the exact function of CD73 in cancer progression has not yet been fully elucidated.

CD73 contributes to cell-cell and cell-matrix interactions and is involved in drug resistance in tumor progression. In general agreement, genetic data illustrates that CD73 is expressed in disparate human cancers as well as ovary, lung, colon, carcinomas, pancreas etc.\textsuperscript{38} The body exploits the immune system to recognize and suppress malignant cells but as has been mentioned already, previous studies have shown that CD73 is a significant molecule to regulate the proliferation of cancer cells, colonization and incursion \textit{in vivo} as well as tumor and cancer angiogenesis and immune evasion \textit{in vivo} situations.\textsuperscript{23,38}

It is now acknowledged that extracellular adenosine is produced by CD39 and CD73 enzymatic consecutive activity in tumors that represent a major pathway for the regulation of extracellular adenosine in the tumor microenvironmment (Figure 1). It was suggested that this activity can down-regulate antitumor immunity by affecting extracellular adenosine metabolism in tumor-induced tolerance and immune suppression.\textsuperscript{16} The action of CD39 and CD73 is caused by tumor hypoxia that results in degrading ATP and the generation of ADO in the tumor microenvironment\textsuperscript{6}. It is most likely when consonant expression and activity of CD39-CD73 increase, it causes decreasing ecto-Adenosine Deaminase (ADA) in human
cells that might be connected to CD26 in the cell surface and contribute to high levels of extracellular adenosine.

Because adenosine acts as an anti-inflammatory mediator on the immune system and regulatory suppression mediator for T cells (Treg), in the absence of adenosine deaminase (ADA), adenosine and other purine metabolites accumulate and leading to Adenosine deaminase deficiency - severe combined immunodeficiency (ADA-SCID) during tumor progression. Precise effects of CD39-CD73 on the nonmalignant host cells (e.g. Treg) in the tumor microenvironment have not been specified yet.

In figure 2, the effects of high concentrations of adenosine suppressor on antitumor T-cell activation, survival and effectors function through A2 adenosine receptor (A2aR) are being considered; in addition, it was shown that adenosine interacts with adenosine receptors (AR) on cancer cells to expand the cell chemotaxis and tumor progression. Also, adenosine may adversely affect the differentiation and function of Dendritic cells (DC) and may further inhibit natural killer cell proliferation and cytolytic function.

Successful use of first-generation immunotherapy against various types of tumors has been around for decades, but the use of these treatments in many therapeutic and clinical cases leads to side effects. Over time, it is possible to better understand the complex interactions between the immune system and tumors by identifying key molecules, for instance, programmed death-ligand 1 (PD-L1). CTLA-4 is also known as CD152 that governs such relationships. Further research is needed to overcome the mechanisms used in tumors to prevent the destruction of immune mediators.

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Figure 2: In order to expand the cell chemotaxis and tumor progression, released adenosine may also adversely affect the differentiation and function of T Cells, dendritic cells (DC) and further inhibit NK cell proliferation and cytolytic function.
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References


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