Review Article

Therapeutic Value of CD73 as a Biomarker in Human Cancer

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Abstract

Context: Over the past several years, biomarkers have emerged as a diagnostic and therapeutic tool for cancer therapy. CD73 (ecto-5'-nucleotidase) which is a cell surface ectonucleotidase, mediates the conversion of extracellular Adenosine monophosphate (AMP) into adenosine through the purinergic signaling pathway. In this study the role of CD73 in different human cancers was investigated.

Evidence Acquisition: The present study reviewed the articles related to the importance of CD73 as a therapeutic tool in human cancers which were published from 1990 to 2019. The publications were found by searching the valid databases for instance PubMed, Google Scholar, ProQuest, Scopus and Science Direct using keywords CD73, ectonucleotidase, therapy, cancer, etc. During the review process 90 articles were selected.

Results: Different studies about the effect of CD73 on human malignancies show that CD73 is overexpressed in various types of cancer. Recent findings demonstrate that the extracellular adenosine can promote tumor growth and invasion. The significant regulatory role of CD73 has made it a suitable biomarker for cancer treatment.

Conclusion: This study outlines the impact of CD73 on tumor growth, metastasis and angiogenesis. The findings are promising and can highlight the efficacy of this protein as a therapeutic tool in the context of anti-CD73 cancer therapy.

Keywords: CD73, Ectonucleotidase, Therapy, Cancer

1. Context

It has been observed that a series of events such as the rapid proliferation of abnormal cells, immune escape, angiogenesis, inhibition of apoptosis, invasion and metastasis can lead to tumor malignancy [1, 2].

Over the past few years, the considerable progress in cancer immunotherapy has boosted our knowledge about tumor biology. Previous investigations have confirmed the efficacy of CD73 as a promising target for cancer therapy [3]. CD73 is encoded by NT5E gene, which is linked to the cell surface via a glycolipid molecule named glycosylphosphatidylinositol (GPI) and carries out essential roles in tumor processes. CD73 is one of the vital enzymes for adenosine production [4].

Purinergic signaling represents a pathway in which purine nucleotides including Adenosine triphosphate (ATP) and Adenosine diphosphate (ADP) and nucleosides like adenosine are the fundamental elements [5]. In this pathway, P2 receptors can become active and metabolize the conversion of nucleotide to adenosine through releasing ATP/ADP. Afterwards, these nucleosides might bind to one other and initiate events that cause progression of tumor processes [6, 7]. Furthermore, CD73 is also a cell adhesion molecule (CAM) which mediates lymphocyte adhesion to endothelium and adjusts the interplay of cells with extracellular matrix ingredients to intervene in cancer invasive attributes [8-10]. Generally, the dual functions of CD73 including enzymatic and non-enzymatic roles are contributed to tumor malignancies [11].

CD73 has been discovered to be overexpressed in a multitude of diverse types of cancers including breast cancer, leukemia and melanoma [11-13]. Considering such a key role, CD73 has become an appropriate target for research with potential applications in cancer treatment [14]. The aim of this study was to investigate the significant roles of CD73 in promoting tumor growth, metastasis and angiogenesis which could explain the importance of this appealing biomarker in order to cure the malignancies in the future.

2. Evidence Acquisition

In this study a search for articles that were related to the value of CD73 molecule in order to treatment human malignancies was performed in Pub Med, Google Scholar, ProQuest, Scopus and Science Direct databases. The search keywords including but not limited to, CD73, ectonucleotidase, therapy and cancer. 210 articles were collected, the retrieved publications were published from 1990 to 2019. The title and abstract of the acquired articles were checked and irrelevant papers and those which were not in English or their full text were not attainable excluded from the review. Afterwards the content of the publications was investigated and 90 articles were included for the present review.

3. Results

The acquired results from the investigated articles considering the aim of the study are presented into six categories.

1. Molecular Biology and Function of CD73
2. Expression of CD73 in Cancer Cells
3. The Effect of CD73 on Tumor Growth
4. The Effect of CD73 on Metastasis
5. The Effect of CD73 on Angiogenesis
6. Targeting CD73 for Cancer Treatment

3.1 Molecular Biology and Function of CD73

NT5E gene is located on chromosome 6 and is translated into CD73 which is a GPI anchored nucleotidase [15]. Studies on the structure of this enzyme has demonstrated that it has three domains, including the C-terminal which contains the substrate binding site and fragments that play a role in dimerization, the N-terminal consisting of two metal ion binding sites and finally, the joint region that allows the vast movement of this protein by connecting the N and C- terminal domains (Figure 1). Substitution of a specific part of the C-terminal for GPI anchor allows CD73 to bind to the cell surface [16, 17].

CD73 along with CD39 can play a vital role in the purinergic signaling pathway in order to catalyze the hydrolysis of ATP to adenosine (Figure 2).

ATP and ADP are dephosphorylated into AMP via CD39. Afterwards, CD73 catabolizes the conversion of AMP into adenosine [18-20]. Recently, the significant effect of adenosine on immune escape and tumor proliferation has been observed [21]. CD73 is found in many cells including endothelial cells, epithelial cells and lymphocytes; this protein has many functions in inflammation, hypoxia, ischemia, etc [22-24].

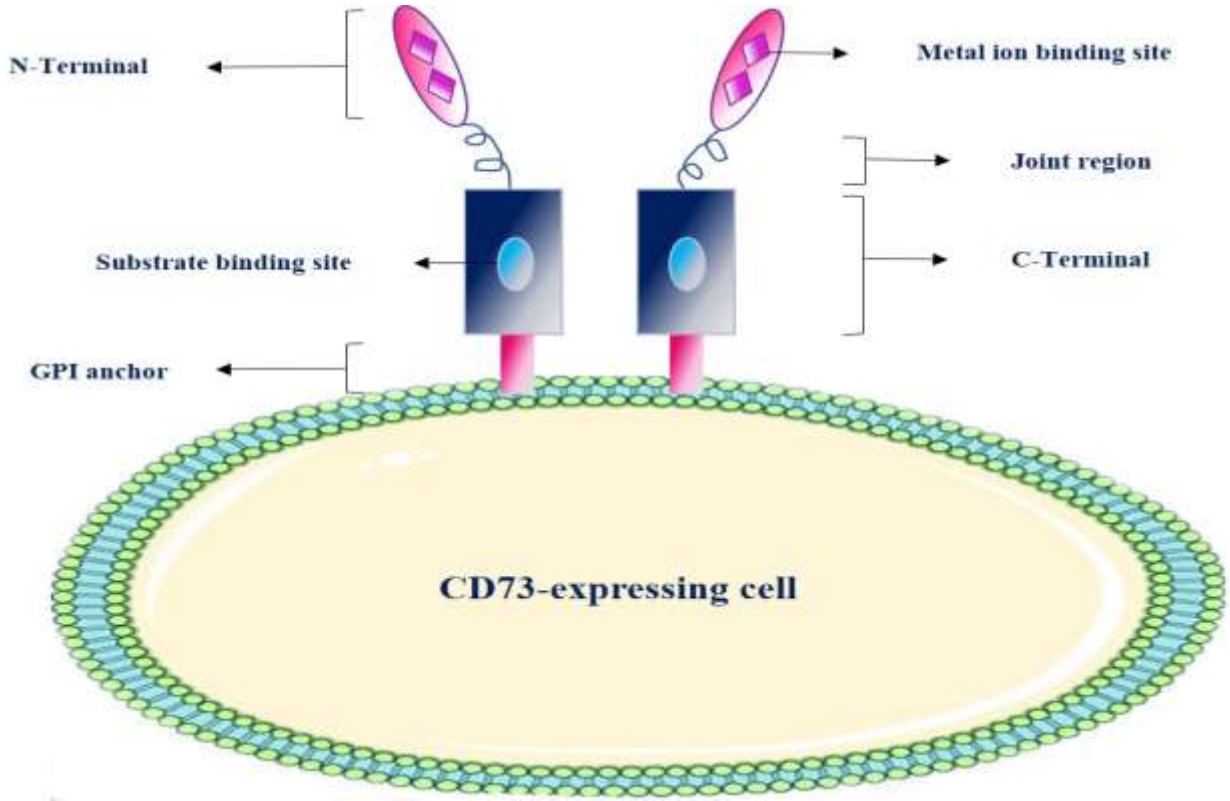

Figure 1. CD73 consists of three domains, including the N- terminal that contains two metal ion binding sites, the C - terminal which has a substrate binding site, and a α- helix that forms a flexible joint region. CD73 is connected to the cell membrane via a GPI- anchor

3.2 Expression of CD73 in Cancer Cells

CD73 is highly expressed in a broad spectrum of cancer cells. A number of studies demonstrated the elevated levels of CD73 are associated with invasion and metastatic properties in cancer cells [25].

In the context of brain carcinoma, the role of CD73 is impressive. CD73 is upregulated in glioblastoma multiforme (GBM) cells [26, 27]. CD73 and adenosine cooperate with each other to enhance invasion and drug resistance in glioblastoma malignant cells [28]. CD73 also traced on glioma cells [26, 29].

Studies on triple-negative breast cancer (TNBC) indicate that overexpression of CD73 can lead to poor prognosis and inhibition of CD73 probably can be effective for treatment of these cells [30-33]. Another study shows that estrogen receptor signaling has a converse relation with CD73 expression in breast carcinoma cells [12]. Further studies on TNBC show that blocking of CD73 can decrease the formation of endothelial vessels in 4T1 murine cell lines [34]. The blocking of ER with tamoxifen as an estrogen receptor modulator stimulates CD73 expression in ER+ cells whereas in ER- cells, it decreases the expression of CD73 [31].

Colorectal carcinoma is considered to be a prevalent malignancy worldwide. Two comprehensive cohort studies indicate that upregulation of CD73 in colorectal cancer (CRC) patients is associated with low survival rate [35].

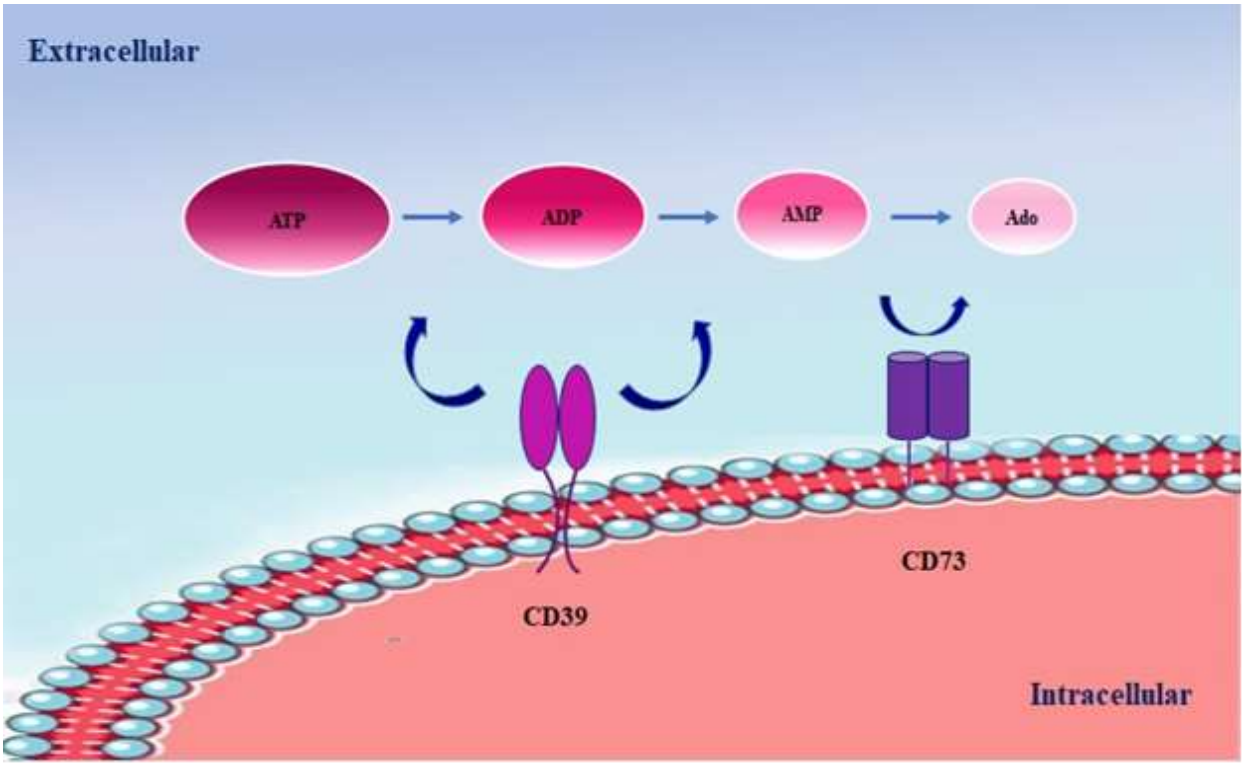

Figure 2. CD73 in tandem with CD39 generates extracellular adenosine (Ado). CD39 mediates the conversion of ATP into AMP, CD73 which is an ectonucleotidase catalyzes the hydrolysis of AMP to adenosine

In another study on CRC cells, overexpression of MIR30A led to the reduction of CD73 expression which inhibited the growth and apoptosis in mentioned cells [36].

Gastric carcinoma is the fourth most common cancer all over the world [37]. Hypoxia-inducible factor-1α (HIF-1α) is widely expressed on several types of carcinomas. There exists a relationship between CD73 and this factor in gastric cancer cells. Then, these two molecules might be the valuable prognostic indicators for this carcinoma [38].

Ovarian cancer is one of the primary causes of cancer mortality among women [39]. High-grade serous (HGS) ovarian cancer is the most dangerous type of this cancer. It has been found that high level of CD73 is correlated with less chance of survival in a large number of cases [40]. CD73 has been a desirable target for ovarian cancer therapy in some preclinical studies [41, 42].

In prostate cancer which is the second most frequent neoplasia in men, CD73 expression intensity is connected with biochemical recurrence-free survival [43, 44]. These findings comply with another research that shows a clear correlation between over-expression of CD73 and elevating the likelihood of lymph node metastasis in prostate cancer [45].

The significant regulatory role of CD73 is observed in many other cancerous cells including bladder cancer, leukemia, glioblastoma, long cancer, etc [28, 46-48].

3.3 The Effect of CD73 on Tumor Growth

Over the past several years, different kinds of research have revealed that overexpression of CD73 elevates the growth of cancerous cells.

CD73 has an important role in immune escape, growth boosting and proliferation of neoplastic cells [49, 50]. In a study in 2010, knockdown of CD73 using shRNA inhibited the growth of breast carcinoma cells through affecting the cell apoptosis [51]. Additionally, suppressing CD73 in

4T1.2 mouse cells reduced tumor growth. Knocking down of transforming growth factor beta (TGF-β) signaling could indirectly decline the level of CD73 in myeloid cells and consequently, the tube formation and tumor proliferation were diminished [52].
Later, some studies showed that CD73 could adjust the expression and phosphorylation of epidermal growth factor receptor (EGFR). EGFR is a leading factor in cell growth and ecto-5'-nucleotidase expression is significantly correlated with EGFR expression. Overexpression of CD73 induces the EGFR expression which can lead to the growth of breast cancer cells [53]. Wang et al. found that downregulation of CD73 elevates penetration of CD8+ T cells into the tumor tissue and inhibits tumor proliferation in mice [41]. In a clinical research on nude mice which was transfected by breast cancer cells and CD73, the rate of hypodermal tumor proliferation was more accelerated in models that were CD73 positive than negative ones. In addition, CD73 suppression by siRNA could reduce tumor progression in xenotransplant mice [9, 51]. Stagg et al. reported that the expression of CD73 could remarkably confine CD8 positive T-cell–mediated antitumor immunity in hematopoietic and non-hematopoietic cells. Most importantly, they represented that overexpression of CD73 on regulatory T cells (Tregs) had a significant impact on the development of colon cancer [54]. Furthermore, the non-enzymatic activity of CD73 also had promotive effects on tumor proliferation [55, 56].

3.4 The Effect of CD73 on Metastasis

Tumor metastasis is the most invasive and deadly feature of malignancies [57]. Therefore, understanding metastasis associated pathways seems to be of great importance. Different findings display that CD73 could enhance the tumor metastasis [58, 59].
Many studies have demonstrated that the generation of adenosine by CD73 activity mediates the spread of cancer cells [60, 61]. CD73 upregulates in lymphoid metastasis breast carcinoma cells in comparison with non-metastasizing cells which indicates the effect of this molecule in progression of metastasis [62]. CD73-generated adenosine increases metastasis using the A2B adenosine receptor [30].
High expression of CD73 on abnormal cells is related to metastasis of breast, cervical and ovarian cancer [63-65].
CD73 can induce aggressive features and activate epithelial-mesenchymal transition (EMT) in some cancer cells through its non-enzymatic function [66]. Zhi et al. found that the suppression of EGFR in CD73 transfected breast carcinoma cells can control the aggressive properties of the mentioned cells [53].

3.5 The Effect of CD73 on Angiogenesis

Angiogenesis is an essential process for distant invasion of tumor cells. Cancer cells are able to infiltrate into immature vessels in order to transfer into other organs [67]. Many investigations have proved the role of CD73 in tumor angiogenesis [68, 69].
Studies on mouse melanoma cells showed that CD73 takes part in the development of new blood vessels and suppression of CD73 diminishes the angiogenesis in these cells [68]. In a research on pulmonary microvascular endothelial cells (PMECs), researchers demonstrated that development of structures which was similar to microvessels in CD73 negative cells was less than CD73 positive cells. The enzymatic and non-enzymatic activities of CD73 increased the invasion of capillary endothelial cells and angiogenesis. CD73 overexpression can upregulate cyclin D1 that is a checkpoint protein and lead to tumor growth and angiogenesis in PMECs. Moreover, CD73-generated adenosine can elevate the level of an angiogenic protein called vascular endothelial growth factor

(VEGF) and consequently, enhances angiogenesis [69]. Researchers also showed that inhibition of NT5E gene can reduce the blood vessel development in human umbilical vein endothelial cells (HUVEC) [34].

3.6 Targeting CD73 for Cancer Treatment

Cancer is a significant public health issue worldwide, accordingly finding the most effective therapeutic methods seems undeniably crucial [70]. Targeted therapy and immunotherapies possess advantages in comparison with conventional cytotoxic cancer treatments [14].

Over the past years, investigation of CD73 in many disorders demonstrated the clinical significance of this protein. Findings imply that CD73 overexpression leads to the drug and chemotherapy resistance in some tumor cells [71, 72]. With regard to targeted therapy, it can be pointed out that the treatment efficacy of CD73 as an appealing therapeutic biomarker is quite noteworthy [25, 34, 73].

Targeting cancer biomarkers by monoclonal antibodies (mAbs) in the process of development [74]. Some of these mAbs have entered clinical trials; since 2017, many patients had been treated with anti-CD73 mAb named BMS-986179 [75, 76]. In one study, anti-CD73 mAb therapy could postpone the tumor growth in some mice. The progression of lung metastases was also inhibited in these mice [30].

α, β-methylene adenosine-5'-disphosphate (APCP) is approximately a structural analog of ADP molecule which can suppress CD73 enzymatic functions [51, 77]. The efficacy of APCP has been proved in various murine models including ovarian and lung tumors [41, 42, 54].

Additionally, using small interfering RNA (siRNA) can be effective for down-regulation of CD73 on cancer cells which leads to tumor free survival in mice [42]. Ghalamfarsa et al. points that knockdown of CD73 with siRNA can control tumor growth in 4T1 cells and be associated with suppression of angiogenesis-inducer factors such as (VEGF)-A and VEGF-R2 [78].

Using checkpoint inhibitors including anti-PD-1, anti-PD-L1, anti-CTLA4 is a growing approach in cancer treatment. Adenosine can increase PD-1 expression in some T lymphocytes such as CD8 positive cells [79]. In fact, inhibition of adenosine A2A receptors and PD-1 can lead to promoting the antitumor function of these lymphocytes and consequently, reduce tumor proliferation [80].

4. Conclusion

CD73 through its enzymatic and non-enzymatic activities plays a crucial role in the progression of cancer processes. A considerable body of evidence implies that CD73 is overexpressed in a broad spectrum of cancer cells. It is now obvious that CD73 has an impressive effect in immune suppression, metastasis, tumor growth and angiogenesis. On the whole, findings propose CD73 could be an appropriate target for treatment of diverse cancers. Several clinical trials that targeted CD73 therapy using mAbs anti-CD73 and small molecule inhibitors have presented eligible antitumor results in malignant murine cells. These outcomes could open the field for more research and offer a valuable anticancer tool which appears to be promising for translating anti-CD73 therapeutic approaches into clinical cancer patients.

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Conflict of Interest

The authors declare no conflict of interest.

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