

# CD73

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Regulatory networks controlling cellular plasticity, important during early development, can re-emerge after tissue injury and premalignant transformation. One such regulatory molecule is the cell surface ectoenzyme ecto-5'-nucleotidase that hydrolyzes the conversion of extracellular adenosine monophosphate to adenosine (eADO). Ecto-5'-nucleotidase (NT5E) or cluster of differentiation 73 (CD73), is an enzyme that is encoded by *NT5E* in humans. In normal tissue, CD73-mediated generation of eADO has important pleiotropic functions ranging from the promotion of cell growth and survival, to potent immunosuppression mediated through purinergic G protein-coupled adenosine receptors. Importantly, tumors also utilize several mechanisms mediated by CD73 to resist therapeutics and in particular, evade the host immune system, leading to undesired resistance to targeted therapy and immunotherapy. Tumor cell CD73 upregulation is associated with worse clinical outcomes in a variety of cancers. Emerging evidence indicates a link between tumor cell stemness with a limited host anti-tumor immune response.

Keywords: CD73 ; cancer stemness ; treatment resistance ; tumor plasticity ; tumor differentiation ; metastasis ; targeted therapy ; immunotherapy ; drug repurposing

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## 1. Introduction

Cellular plasticity represents a broad phenomenon whereby cells change their identity or state representing an important event in early development enabling proper tissue morphogenesis <sup>[1]</sup>. One of the best-studied examples of cellular plasticity is the epithelial-to-mesenchymal transition (EMT) whereby epithelial cells take on characteristics of mesenchymal cells while becoming more motile <sup>[2]</sup>, which is essential during gastrulation and neural crest formation <sup>[3]</sup>. Under homeostatic conditions in adult tissues, cellular identity was originally believed to be hard-wired and non-malleable. However, it is now apparent that during periods of chronic perturbation, cellular identity is more pliant whereby cells within stressed tissues transition between cellular states, which is part of a natural adaptive process during wound repair and tissue regeneration <sup>[4]</sup>.

Cellular plasticity is also recognized as a hallmark of cancer <sup>[5]</sup>. Importantly, poorly differentiated tumors reflected in the histological grade and a product of an EMT program are more prone to metastatic spread and poor prognosis, also are enriched in gene signatures associated with dedifferentiation and stemness <sup>[6][7]</sup>. Our understanding of the drivers of cellular plasticity in cancer is not well understood. While wide-scale cell-autonomous genomic alterations (e.g., coding mutations, chromosomal alterations) have long been recognized as a basis for tumor initiation <sup>[8]</sup>, there is emerging evidence suggesting that non-cell-autonomous processes involving adaptive properties of the microenvironment also are critical features that contribute to tumor plasticity <sup>[9]</sup>.

Cluster of differentiation 73 (CD73; encoded by *NT5E* [ecto-5'-nucleotidase]) molecule is a membrane-bound ecto-5'-nucleotidase ubiquitously expressed throughout the body <sup>[10]</sup> and is the major enzyme responsible for the generation of extracellular adenosine (eADO) via enzymatic dephosphorylation of nucleotide adenosine 5'-monophosphate (AMP) <sup>[11]</sup>. Other AMP-hydrolyzing enzymes can also be involved in the generation of eADO such as CD39 and ectonucleotide phosphodiesterase 1 (ENPP1), which have been covered by other excellent reviews <sup>[12][13]</sup>. CD73 has been shown to impart particularly important cell-type-specific functions involved in regulating tissue homeostasis. The physiological functions regulated by CD73-mediated generation of eADO are coupled to the interaction with seven-transmembrane domain, G-protein-coupled receptors adenosine receptor A1 (ADORA1), ADORA2A, ADORA2B, and ADORA3, each possessing a unique binding affinity and signal transduction mechanism (for a review see Olah and Stiles <sup>[14]</sup>). Under normal physiological conditions, eADO is present at low concentrations in tissues, including the brain. During periods of heightened metabolic stress such as that occurs during prolonged inflammation, eADO levels are greatly increased by enhanced 5'-nucleotidase CD73 to regulate immunity and inflammation, which is a necessary response to ensure tissue repair following injury <sup>[15]</sup>.

There is emerging evidence suggesting that the CD73-adenosinergic signaling pathway is hijacked by tumors that arise because of prolonged periods of inflammation, resulting in suppression of immune-mediated disease control of tumors or limitations for resources and cell competitions due to a limited supply of oxygen [16]. Hypoxia and transforming growth factor-beta 1 (TGF- $\beta$ 1) represent two of the most prominent extrinsic features of the microenvironment in solid tumors that are responsible for initiating a transcriptional program triggering cellular plasticity in carcinoma cells in the form of developmental differentiation programs EMT and stemness [17]. Importantly, these changes in the tumor microenvironment (TME) also serve as drivers of CD73 expression, so it is not surprising that there is a possible link between tumorigenesis and increased CD73 expression. In this review, we will focus on the functional role of CD73 in solid tumors and its correlation with signatures of cellular plasticity (mRNA and epigenetic signatures together with an EMT signature) and host immune response, with a particular focus on solid tumors. In addition, we will touch upon the association between CD73 and metastasis, which is responsible for over 90% of cancer deaths. Finally, we will discuss the current state of drug discovery and drug development efforts focusing on CD73 and the potential of targeting the CD73-adenosinergic signaling pathway by drug repurposing.

## 2. CD73 and Human Cancer

Several recent studies have provided evidence that overexpression of CD73 is associated with poor patient outcomes across diverse cancer cohorts [18][19][20][21]. Gene expression analysis of the pan-cancer cohort from the public The Cancer Genome Atlas (TCGA) reveals that mRNA expression of *NT5E* is highly heterogeneous across different cancer types. For example, the most abundant expression of *NT5E* was observed in thyroid carcinoma (THCA), glioblastoma (GBM), sarcoma (SARC), and minimal in blood cancer (LAML, acute myeloid leukemia) (Figure 1A). Compared to matched normal tissue, *NT5E* is highly upregulated in the majority of solid cancer types (Figure 1B). Interestingly, this is not the case for tumors of the genitourinary system, e.g., cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), ovarian serous cystadenocarcinoma (OV), testicular germ cell tumors (TGCT), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), bladder urothelial carcinoma (BLCA), kidney chromophobe (KICH) and prostate adenocarcinoma (PRAD). These observations may be due to the common embryological origin (the intermediate mesoderm) of the reproductive and urinary systems. Consistent with previous reports demonstrating the relationship between CD73 and patient survival, we demonstrate that high expression of *NT5E* predicts poor patient survival in the majority of TCGA solid tumors that have overexpressed *NT5E*/CD73 relative to paired normal tissue (Figure 1C). Collectively, the evidence provided here suggests the critical role of CD73 in a subset of non-genitourinary system-derived solid cancers and prioritizes CD73 as a potential therapeutic target in cancer.



**Figure 1.** CD73 in human cancers. (A) *NT5E* (encoding CD73) gene expression across human solid tumors. Data were downloaded and reanalyzed from TCGA (The Cancer Genome Atlas Program) pan-cancer cohort. (B) Bar plot showing the *NT5E* gene expression in tumor compared with the matched normal tissue. The height of the bar represents the

median expression of the indicated tumor type (red) or normal tissue (blue). (C) Forest plots showing the Cox proportional-hazards model-based survival analysis of cancer patients stratified by the gene expression of *NT5E* across the TCGA pan-solid cancer cohort. Only significant ( $p < 0.05$ ) results were presented. The “high” and “low” expression groups were stratified by the optimal cutoff value using “survminer” and “survival” packages in R software. N, the total number in each group. Scale line indicates the 95% confidence interval for effect estimate for each survival-influencing factor with the hazard ratio showing to the right. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; UCS, uterine carcinosarcoma; UCEC, uterine corpus endometrial carcinoma; UVM, uveal melanoma. Ca., carcinoma; Ad., adenocarcinoma; Sq., squamous; Sa., sarcoma. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . The detailed information about the bioinformatic analysis can be found in [Appendix A](#).

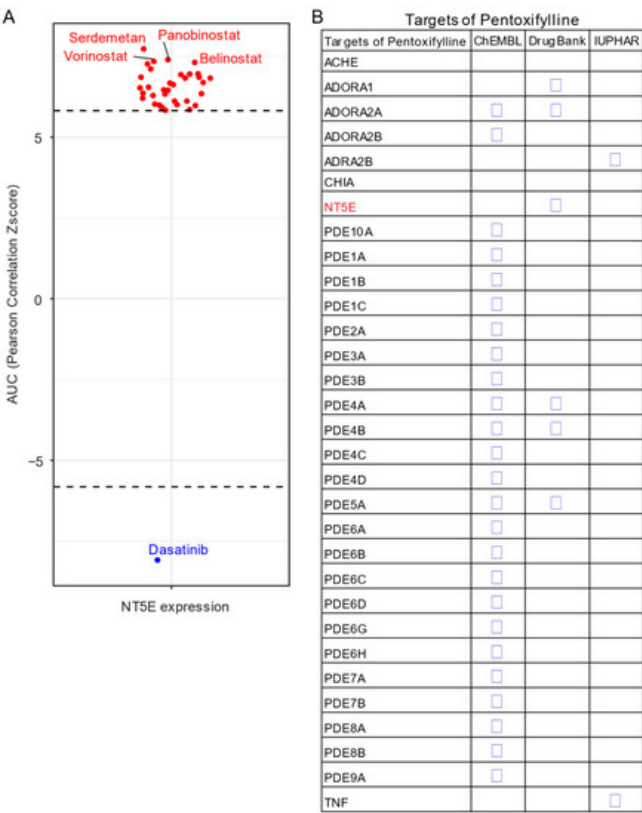
### **3. CD73 and Tumor Immune Microenvironment**

Although cancer has primarily been studied as a cell-intrinsic disease, it is widely accepted that the tumor microenvironment (TME) plays an essential role in regulating plasticity. Along these lines, Malta et al. demonstrated that tumor types with higher stemness indices are correlated with reduced immune infiltration and PD-L1 expression at the protein level [22]. CD73 is an emerging immune checkpoint in modulating cancer progression via conversion of immunostimulatory eATP into immunosuppressive eADO [23][24]. As described above, CD73 nucleotidase activity promoting an immunosuppressive TME represents an ideal target to enhance immunotherapies in cancer, which to date are underwhelming in the majority of patients [25][26][27].

Comprehensive profiling of over 10,000 tumors across 33 diverse cancer types from TCGA pan-solid cancer cohort using a multi-omics approach uncovered six (C1–C6) immune subtypes [28]. This work provides a key resource for understanding tumor-immune interactions. The lymphocyte-depleted (immune C4) and TGF- $\beta$  dominant (immune C6) subtypes were marked by the worst prognosis and their immune makeup was consistent with an immunosuppressed TME. Accumulating evidence points towards CD73 shaping the TME [15][16]. Further exploration revealed that the Immunologically Quiet (Immune C5) and TGF- $\beta$  dominant (immune C6) immune subtypes are highly enriched in tumors with high *NT5E* expression compared with low *NT5E* expression (Figure 4A). To gain a clearer picture of the immune infiltrates across the tumor subtypes which may be of potential relevance to cancer immunology, we utilized TIMER, an algorithm that provides information regarding proportions of immune cell types by multiple immune deconvolution methods [29]. Focusing primarily on T cells, we demonstrate that T cell regulatory (Tregs)\_QUANTISEQ fraction is positively correlated with CD73 gene expression across a wide number of tumor types including BRCA and THCA. In addition, CD73 gene expression displays a broadly positive correlation with the T cell CD8+\_TIMER and multiple CD4+ fractions (Figure 4B). This pan-cancer dataset suggests a mixture of suppressive and activated immune infiltrates together with high CD73 gene expression. For example, in HNSC a negative correlation between CD73 and CD8+ T cell infiltration, including HPV-positive patients was observed (Figure 4B). This observation supports a recent study from Watermann et al. [30] demonstrating that recurrent HNSC has an immunosuppressive tumor microenvironment with significant depletion of CD8 tumor-infiltrating lymphocytes (TILs), which was more pronounced following adjuvant chemo-radiotherapy. Therefore, these tumors might be less susceptible to respond to ICIs due to the lack of infiltrating CD8+ CTLs. Whether anti-CD73 treatment can turn an immunosuppressive cold tumor-like HNSC into a hot tumor awaits further investigation. It is important to note that CD73-mediated production of immunosuppressive adenosine has also been described for tumor-infiltrating B cells [31] and NK cells [32] whereby tumors can hijack both B cell- and NK cell-mediated suppression of activated T cells to escape immunity.



significantly negatively correlates with the expression of CD73. Conversely, several pan-HDAC inhibitors appear as the top whose AUC significantly positively correlated drug compounds. Therefore, cancer cells with enhanced CD73 activity might be sensitive to dasatinib treatment, but resistant to pan-HDAC inhibitors. Regarding this, we and others have previously shown that dasatinib not only inhibits cancer cells but also modulates the tumor immune microenvironment and enhances the efficacy of ICIs [37][38][39]. Others have shown that dasatinib effectively blocks TGFβ-induced expression of transcription factors promoting EMT and may be a novel therapeutic option in pancreatic and prostate cancer [40] and pulmonary sarcomatoid carcinoma, a rare and deadly form of NSCLC [41].



**Figure 5.** Drug repurposing for CD73 targeted therapy. **(A)** Integrated correlation analysis of *NT5E* gene expression with drug ( $n = 481$ ) response profiles (reflected by Z-score normalized area under the curve [AUC] value) across solid cancer cell lines ( $n = 659$ ). Red dots indicate drugs whose AUC value significantly (adj.  $p < 0.05$ ) positively correlates with *NT5E* gene expression, while the blue represent the significantly negatively correlated ones. The drug response data were downloaded from a previously published study (see the methods in [Appendix A](#)). **(B)** Drug repurposing identifying *NT5E* as one target of Pentoxifylline. Data were downloaded from ReframeDB database (<https://reframedb.org/>). The detailed information about the bioinformatic analysis can be found in [Appendix A](#).

Based on a public drug repurposing database ReframeDB (<https://reframedb.org/>), we have found that the synthetic dimethylxanthine derivative pentoxifylline (PTX), clinically approved for the treatment of peripheral vascular diseases and osteoradionecrosis, as well as the management of cerebrovascular insufficiency [42][43] also targets the CD73-adenosinergic signaling pathway (Figure 5B). Originally identified as a nonselective phosphodiesterase inhibitor (PDE4B, PDE4A, PDE5A), PTX also has additional anti-inflammatory, immunomodulatory and bronchodilatory effects due to its ability to act as a non-selective adenosine receptor antagonist (A1, ADORA1 and A2a, ADORA2A) and *NT5E*/CD73 inhibitor [44]. CD73 is upregulated following radiotherapy and is linked to radiation-induced tissue injury [45] and PTX shows protective effects against radiotherapy-induced lung toxicity in both breast and lung cancer [46]. Blocking radiotherapy-induced CD73 upregulation promotes host-mediated immune rejection of tumors [47]. Collectively, repurposing of well-known clinically approved drugs targeting CD73-adenosine together in combination with dasatinib and/or PTX with ICIs may represent an ideal combination therapy in solid tumors with an extensive desmoplastic stroma, which warrants further investigation.

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