Research Progress of CD73 in Cancer

Shuang Guo[1], Hongli Liu[1,2*]

1. School of Medical Technology, Shaanxi University of Chinese Medicine, Xianyang 712000, China.

2. Clinical Laboratory Center of Xi'an People's Hospital (Xi'an Fourth Hospital), Xi'an 710000, China.

Abstract: CD73 (NT5E, extracellular 5' nucleotidase) is a multifunctional glycoprotein encoded by the NT5E gene with a relative molecular weight of 70 kD that can be anchored to the outer surface of cell membranes by glycosyl phosphatidylinositol (GPI).CD73 expression levels are aberrant in breast, colorectal, head and neck squamous cell carcinomas, gastric and hepatocellular carcinomas. However, the possible role and mechanism of CD73 in gastric carcinogenesis and development has not been clarified. In this paper, we will review the multiple roles of CD73 in tumour development, including the clinical significance of CD73, the promotion of tumour growth, metastasis and angiogenesis by CD73, the suppression of immune response by CD73, the regulatory mechanisms of CD73 expression, and the current status of CD73 anti-tumour therapy, with a view to providing a reference for subsequent studies.

Keywords*:* CD73; Cancer; Antitumor Therapy; Regulatory Mechanism

Introduction

The development, progression and metastasis of malignant tumours in vivo are intricate and complex, involving rapid proliferation of mutant cells in an uncontrollable manner, inhibition of programmed cell death, massive angiogenesis, escape from immune surveillance, invasion and colonisation to distant organs. In addition, many signalling pathways have been identified in relation to cancer progression[1].It is now clear that adenosine is one of the most important immunosuppressive regulatory molecules in the tumour microenvironment[2].

CD73 is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein with a molecular weight of 70 kD, encoded by the NT5E gene, also known as extracellular 5'-nucleotidase (Ecto-5'-nucleotidase), which plays a crucial role in the switching of adenosinergic signalling. A growing body of evidence confirms that CD73 is a key regulatory molecule in cancer development. It has a promising role in the study of rheumatoid mouse models, and although it has not yet been studied in clinical patients, ANTICD73 therapy has emerged as a promising approach for the future treatment of cancer patients[3-4] . This article provides a review of the role of CD73 in cancer development, including the clinical significance of CD73 in cancer patients, the role of CD73 in promoting tumour growth, metastasis and angiogenesis , the suppressive effect of CD73 on the immune system in the tumour microenvironment, the regulatory mechanisms of CD73 expression, and the prospects for antiCD73 therapy.

1. Clinical significance of CD73 in cancer patients

There is increasing evidence that NT5E is highly expressed in tumor tissues such as lung[5] , breast[6] , colorectal[7] , pancreatic[8] , gallbladder[9] , prostate[10] , thyroid[11] , and head and neck[12] . In addition, Inoue et al. found that CD73

overexpression was associated with gender, smoking and histological classification in patients with non-small cell lung cancer[5].in breast cancer patients, Turcotte et al.found that CD73 overexpression predicted trastuzumab resistance in breast cancer patients[13].Cushman et al. also found It has been shown that high CD73 expression was observed in gastric cancer tissues and serum compared to normal human gastric mucosal tissues and healthy human serum[14], respectively, and that high CD73 expression was positively associated with poor differentiation, depth of tumour infiltration, more lymph node metastases, number of distant metastases and clinical advanced stage in gastric cancer patients. However, its molecular mechanism is not clear.

2. Promotion of tumour growth, metastasis and angiogenesis by CD73

Recently, Lu et al. evaluated the clinical significance and prognostic value of CD73 in human gastric cancer tissues in digestive system cancers:CD73 expression was analysed by immunohistochemistry (IHC) and CD73 overexpression was found to be positively correlated with tumour differentiation, depth of infiltration, lymph node morphology, metastasis and cancer stage, and overall survival was lower in patients with high CD73 expression[15] . In addition to gastric cancer, Serra et al. evaluated the clinical significance of CD73 in chronic lymphocytic leukaemia and found that high CD73 expression was associated with more aggressive clinical behaviour[16], while another study showed that CD73 expression had no prognostic value in children (aged 1-18 years) with acute lymphoblastic leukaemia In other cancers, Yang et al. reported that CD73 in prostate cancer Overexpression of CD73 in prostate cancer was associated with lymph node metastasis[17].Taken together, these results reveal that CD73 is an important clinical or prognostic biomarker in several types of cancer, suggesting its potential value in clinical diagnosis and prognosis.

3. Regulatory mechanisms of CD73 expression

CD73 plays an important role in the progression of malignancies and has been found to be overexpressed in many types of cancer. CD73 expression was found to be negatively regulated by the estrogen receptor (ER) in breast cancer, and ER deficiency significantly increased CD73 expression. Thus,CD73 is highly expressed in ER-negative breast cancer patients than in ER-positive breast cancer patients and may be a promising target for clinical treatment of ER-negative breast cancer patients[18].In contrast to ER, thyroid hormones are thought to synergistically promote CD73 expression in several cell types of the nervous and cardiovascular systems (glioma cells, vascular smooth muscle cells and ventricular myocytes)[19-20].It was found that CD73 expression was positively correlated with cell sphere-forming capacity and was highly expressed in hepatocellular carcinoma cells. downregulation of CD73 impeded cell clone formation, whereas overexpression of CD73 produced the opposite effect[21].

4. The future of CD73 anti-tumour therapy

The role of CD73 in tumour growth and metastasis, particularly as a key immunosuppressor in the tumour microenvironment, offers a potential opportunity for the development of anti-CD73 therapies for various human cancers.Cancer immunotherapy has become increasingly interesting in recent years. Drugs such as anti-pd1 monoclonal antibodies and anti-CTLA-4 monoclonal antibodies that block programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen (CTLA-4) receptors have shown very impressive objective responses in patients[22].Interestingly, Allard found that in mouse models, anti-cd73 monoclonal antibody significantly enhanced the activity of anti-ctla -4 and anti-PD-1 monoclonal antibodies against MC38-OV A (colon) tumours, RM-1 (prostate) subcutaneous tumours and metastatic 4T1.2 breast cancer[23].

5. Summary and perspectives

The relationship between CD73 overexpression and cancer subtype, prognosis, and patient response to drugs has been significantly correlated. CD73 is a potential target for cancer therapy. Some researchers have also shown good anti-tumour effects in mouse tumour models treated with inhibitors or monoclonal antibodies targeting CD73. It is believed that in the future, CD73 blockers and immunotherapeutic agents will be developed that are safe, effective and can be used in the treatment of clinical patients, providing a good opportunity to treat some cancer patients.

References

[1] Burnstock G, Di Virgilio F. Purinergic signalling and cancer. Purinergic Signal. 2013 Dec; 9(4): 491-540.

[2] Bours MJ, Swennen EL, Di Virgilio F, *et al*. Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther. 2006 Nov;112(2):358-404.

[3] Zhang B. Opportunities and challenges for anti-CD73 cancer therapy. Immunotherapy. 2012 Sep;4(9):861-5.

[4] Stagg J. The double-edge sword effect of anti-CD73 cancer therapy. Oncoimmunology. 2012 Mar 1;1(2):217-218.

[5] Inoue Y, Yoshimura K, Kurabe N, et al. Prognostic impact of CD73 and A2A adenosine receptor expression in non-small-cell lung cancer [J]. Oncotarget, 2017, 8(5): 8738-51.

[6] Yu J, Wang X, Lu Q, et al. Extracellular 5'-nucleotidase (CD73) promotes human breast cancer cells growth through AKT/GSK-3beta/beta-catenin/ cyclinD1 signaling pathway [J]. Int J Cancer, 2018, 142(5): 959-67.

[7] Xie M, Qin H, Luo Q, et al. MicroRNA-30a regulates cell proliferation and tumor growth of colorectal cancer by targeting CD73 [J]. BMC Cancer, 2017, 17(1): 305.

[8] Wu R, Chen Y, Li F, et al. Effects of CD73 on human colorectal cancer cell growth in vivo and in vitro [J]. Oncol Rep, 2016, 35(3): 1750-6.

[9] Haun RS, Quick CM, Siegel ER, et al. Bioorthogonal labeling cell-surface proteins expressed in pancreatic cancer cells to identify potential diagnostic/ therapeutic biomarkers [J]. Cancer Biol Ther, 2015, 16(10): 1557-65.

[10] Yang Q, Du J, Zu L. Overexpression of CD73 in prostate cancer is associated with lymph node metastasis [J]. Pathol Oncol Res, 2013, 19(4): 811-4.

[11] Bertoni APS, Bracco PA, De Campos RP, et al. Activity of ecto-5'-nucleotidase (NT5E/CD73) is increased in papillary thyroid carcinoma and its expression is associated with metastatic lymph nodes [J]. Mol Cell Endocrinol, 2019, 479(54-60.

[12] Song Y, Song C, Yang S. Tumor-Suppressive Function of miR-30d-5p in Prostate Cancer Cell Proliferation and Migration by Targeting NT5E [J]. Cancer Biother Radiopharm, 2018, 33(5): 203-11.

[13] Turcotte M, Allard D, Mittal D, et al. CD73 Promotes Resistance to HER2/ErbB2 Antibody Therapy [J]. Cancer Res, 2017, 77(20): 5652-63.

[14] Cushman SM, Jiang C, Hatch AJ, et al. Gene expression markers of efficacy and resistance to cetuximab treatment in metastatic colorectal cancer: results from CALGB 80203 (Alliance) [J]. Clin Cancer Res, 2015, 21(5): 1078-86.

[15] Zhao J, Soto LMS, Wang H, Katz MH, Prakas. *et al*. Overexpression of CD73 in pancreatic ductal adenocarcinoma is associated with immunosuppressive tumor microenvironment and poor survival. Pancreatology. 2021 Aug;21(5):942-949.

[16] Serra S, Horenstein AL, Vaisitti T, *et al*. CD73-generated extracellular adenosine in chronic lymphocytic leukemia creates local conditions counteracting drug-induced cell death. Blood. 2011 Dec

1;118(23):6141-52.

[17] Yang Q, Du J, Zu L. Overexpression of CD73 in prostate cancer is associated with lymph node metastasis. Pathol Oncol Res. 2013 Oct;19(4):811-4.

[18] Loi S, Pommey S, Haibe-Kains B, *et al*. CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer. Proc Natl Acad Sci U S A. 2013 Jul 2;110(27):11091-6.

[19] Wink MR, Tamajusuku AS, Braganhol E, *et al*. Thyroid hormone upregulates ecto-5'-nucleotidase/CD73 in C6 rat glioma cells. Mol Cell Endocrinol. 2003 Jul 31; 205(1-2):107-14.

[20] Tamajusuku AS, Carrillo-Sepúlveda MA, Braganhol E, *et al*. Activity and expression of ecto-5'-nucleotidase/CD73 are increased by thyroid Activity and expression of ecto-5'-nucleotidase/CD73 are increased by thyroid hormones in vascular smooth muscle cells. Mol Cell Biochem. 2006 Sep; 289(1-2): 65-72.

[21] Ma XL, Hu B, Tang WG, *et al*. CD73 sustained cancer-stem-cell traits by promoting SOX9 expression and stability in hepatocellular carcinoma. j Hematol Oncol. 2020 Feb 5;13(1):11.

[22] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252-64.

[23] Allard B, Pommey S, Smyth MJ, *et al*. Targeting CD73 enhances the antitumor activity of anti-PD-1 and anti-CTLA-4 mAbs. Clin Cancer Res. 2013 Oct 15;19 (20):5626-35.