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Adenosine turnover in GtoPdb v.2023.1

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Abstract

A multifunctional, ubiquitous molecule, adenosine acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5'-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5'-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing L-homocysteine).

Contents

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Database links

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References

1. Agarwal RP, Spector T and Parks Jr RE. (1977) Tight-binding inhibitors--IV. Inhibition of adenosine deaminases by various inhibitors. *Biochem Pharmacol* **26**: 359-67 [PMID:849330]
2. Antonioli L, Blandizzi C, Pacher P and Haskó G. (2013) Immunity, inflammation and cancer: a leading role for adenosine. *Nat Rev Cancer* **13**: 842-57 [PMID:24226193]
3. Antonioli L, Pacher P, Vizi ES and Haskó G. (2013) CD39 and CD73 in immunity and inflammation. *Trends Mol Med* **19**: 355-67 [PMID:23601906]
4. Baqi Y, Lee SY, Iqbal J, Ripphausen P, Lehr A, Scheiff AB, Zimmermann H, Bajorath J and Müller CE. (2010) Development of potent and selective inhibitors of ecto-5'-nucleotidase based on an anthraquinone scaffold. *J Med Chem* **53**: 2076-86 [PMID:20146483]
5. Bastid J, Cottalorda-Regairaz A, Alberici G, Bonnefoy N, Eliaou JF and Bensussan A. (2013) ENTPD1/CD39 is a promising therapeutic target in oncology. *Oncogene* **32**: 1743-51 [PMID:22751118]
6. Beamer E, Gölöncsér F, Horváth G, Bekő K, Otrokocsi L, Koványi B and Sperlágh B. (2016) Purinergic mechanisms in neuroinflammation: An update from molecules to behavior. *Neuropharmacology* **104**: 94-104 [PMID:26384652]
7. Bhattarai S, Pippel J, Scaletti E, Idris R, Freundlieb M, Rolshoven G, Renn C, Lee SY, Abdelrahman A and Zimmermann H *et al.*. (2020) 2-Substituted α,β-Methylene-ADP Derivatives: Potent Competitive Ecto-5'-nucleotidase (CD73) Inhibitors with Variable Binding Modes. *J Med Chem* **63**: 2941-2957 [PMID:32045236]
8. Boison D. (2013) Adenosine kinase: exploitation for therapeutic gain. *Pharmacol Rev* **65**: 906-43 [PMID:23592612]
9. Borea PA, Gessi S, Merighi S and Varani K. (2016) Adenosine as a Multi-Signalling Guardian Angel in Human Diseases: When, Where and How Does it Exert its Protective Effects? *Trends Pharmacol Sci* **37**: 419-34 [PMID:26944097]
10. Borea PA, Gessi S, Merighi S, Vincenzi F and Varani K. (2017) Pathological overproduction: the bad side of adenosine. *Br J Pharmacol* **174**: 1945-1960 [PMID:28252203]
11. Bowman CE, da Silva RG, Pham A and Young SW. (2019) An Exceptionally Potent Inhibitor of Human CD73. *Biochemistry* **58**: 3331-3334 [PMID:31334635]
12. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
13. Burger RM and Lowenstein JM. (1975) 5'-Nucleotidase from smooth muscle of small intestine and from brain. Inhibition of nucleotides. *Biochemistry* **14**: 2362-6 [PMID:1169962]
14. Cortés A, Gracia E, Moreno E, Mallol J, Lluís C, Canela EI and Casadó V. (2015) Moonlighting adenosine deaminase: a target protein for drug development. *Med Res Rev* **35**: 85-125 [PMID:24933472]
15. Geoghegan JC, Diedrich G, Lu X, Rosenthal K, Sachsenmeier KF, Wu H, Dall'Acqua WF and Damschroder MM. (2016) Inhibition of CD73 AMP hydrolysis by a therapeutic antibody with a dual, non-competitive mechanism of action. *MAbs* **8**: 454-67 [PMID:26854859]
16. Glazer RI, Hartman KD, Knode MC, Richard MM, Chiang PK, Tseng CK and Marquez VE. (1986) 3-Deazaneplanocin: a new and potent inhibitor of S-adenosylhomocysteine hydrolase and its effects on

human promyelocytic leukemia cell line HL-60. *Biochem Biophys Res Commun* **135**: 688-94 [PMID:3457563]
17. Griffin EP, Miller RA, Frey GJ and Chang HW. (2017) Humanized anti-cd73 antibodies Patent number: WO2017100670A1. Assignee: Corvus Pharmaceuticals. Priority date: 09/12/2015. Publication date: 15/06/2017.
18. Guranowski A, Montgomery JA, Cantoni GL and Chiang PK. (1981) Adenosine analogues as substrates and inhibitors of S-adenosylhomocysteine hydrolase. *Biochemistry* **20**: 110-5 [PMID:7470463]
19. Haskó G, Linden J, Cronstein B and Pacher P. (2008) Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. *Nat Rev Drug Discov* **7**: 759-70 [PMID:18758473]
20. Häusler SF, Del Barrio IM, Diessner J, Stein RG, Strohschein J, Hönig A, Dietl J and Wischhusen J. (2014) Anti-CD39 and anti-CD73 antibodies A1 and 7G2 improve targeted therapy in ovarian cancer by blocking adenosine-dependent immune evasion. *Am J Transl Res* **6**: 129-39 [PMID:24489992]
21. Jarvis MF, Yu H, Kohlhaas K, Alexander K, Lee CH, Jiang M, Bhagwat SS, Williams M and Kowaluk EA. (2000) ABT-702 (4-amino-5-(3-bromophenyl)-7-(6-morpholinopyridin-3-yl)pyrido[2, 3-d]pyrimidine), a novel orally effective adenosine kinase inhibitor with analgesic and anti-inflammatory properties: I. In vitro characterization and acute antinociceptive effects in the mouse. *J Pharmacol Exp Ther* **295**: 1156-64 [PMID:11082453]
22. Kameoka J, Tanaka T, Nojima Y, Schlossman SF and Morimoto C. (1993) Direct association of adenosine deaminase with a T cell activation antigen, CD26. *Science* **261**: 466-9 [PMID:8101391]
23. Leclerc BG, Charlebois R, Chouinard G, Allard B, Pommey S, Saad F and Stagg J. (2016) CD73 Expression Is an Independent Prognostic Factor in Prostate Cancer. *Clin Cancer Res* **22**: 158-66 [PMID:26253870]
24. Li J, Chen L, Billedeau RJ, Stanton TF, Chiang JTP, Lee CC, Li W, Steggerda S, Emberley E and Gross M *et al.*. (2023) Discovery of a Series of Potent, Selective, and Orally Bioavailable Nucleoside Inhibitors of CD73 That Demonstrates *In Vivo* Antitumor Activity. *J Med Chem* **66**: 345-370 [PMID:36529947]
25. Loi S, Pommey S, Haibe-Kains B, Beavis PA, Darcy PK, Smyth MJ and Stagg J. (2013) CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer. *Proc Natl Acad Sci USA* **110**: 11091-6 [PMID:23776241]
26. Lu XX, Chen YT, Feng B, Mao XB, Yu B and Chu XY. (2013) Expression and clinical significance of CD73 and hypoxia-inducible factor-1α in gastric carcinoma. *World J Gastroenterol* **19**: 1912-8 [PMID:23569336]
27. Maier SA, Galellis JR and McDermid HE. (2005) Phylogenetic analysis reveals a novel protein family closely related to adenosine deaminase. *J Mol Evol* **61**: 776-94 [PMID:16245011]
28. McGaraughty S, Chu KL, Wismer CT, Mikusa J, Zhu CZ, Cowart M, Kowaluk EA and Jarvis MF. (2001) Effects of A-134974, a novel adenosine kinase inhibitor, on carrageenan-induced inflammatory hyperalgesia and locomotor activity in rats: evaluation of the sites of action. *J Pharmacol Exp Ther* **296**: 501-9 [PMID:11160637]
29. Ren ZH, Lin CZ, Cao W, Yang R, Lu W, Liu ZQ, Chen YM, Yang X, Tian Z and Wang LZ *et al.*. (2016) CD73 is associated with poor prognosis in HNSCC. *Oncotarget* **7**: 61690-61702 [PMID:27557512]
30. Roifman CM, Zhang J, Atkinson A, Grunebaum E and Mandel K. (2008) Adenosine deaminase deficiency can present with features of Omenn syndrome. *J Allergy Clin Immunol* **121**: 1056-8 [PMID:18243287]
31. Stagg J. (2012) The double-edge sword effect of anti-CD73 cancer therapy. *Oncoimmunology* **1**: 217-218 [PMID:22720247]
32. Villa A, Notarangelo LD and Roifman CM. (2008) Omenn syndrome: inflammation in leaky severe combined immunodeficiency. *J Allergy Clin Immunol* **122**: 1082-6 [PMID:18992930]
33. Wang H, Lee S, Nigro CL, Lattanzio L, Merlano M, Monteverde M, Matin R, Purdie K, Mladkova N and Bergamaschi D *et al.*. (2012) NT5E (CD73) is epigenetically regulated in malignant melanoma and associated with metastatic site specificity. *Br J Cancer* **106**: 1446-52 [PMID:22454080]
34. Wang L, Fan J, Thompson LF, Zhang Y, Shin T, Curiel TJ and Zhang B. (2011) CD73 has distinct roles in nonhematopoietic and hematopoietic cells to promote tumor growth in mice. *J Clin Invest* **121**: 2371-82 [PMID:21537079]
35. Williams-Karnesky RL, Sandau US, Lusardi TA, Lytle NK, Farrell JM, Pritchard EM, Kaplan DL and Boison D. (2013) Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. *J Clin Invest* **123**: 3552-63 [PMID:23863710]
36. Wilson NS, Waight JD, Jennings SM, Ignatovich O, Briend ECP, Morin BM, Schon O and Campbell S. (2019) Anti-cd73 antibodies and methods of use thereof Patent number: WO2019173692A2. Assignee:

Agenus Inc.. Priority date: 09/03/2018. Publication date: 12/09/2019.
37. Wu XR, He XS, Chen YF, Yuan RX, Zeng Y, Lian L, Zou YF, Lan N, Wu XJ and Lan P. (2012) High expression of CD73 as a poor prognostic biomarker in human colorectal cancer. *J Surg Oncol* **106**: 130-7 [PMID:22287455]
38. Zavialov AV, Yu X, Spillmann D, Lauvau G and Zavialov AV. (2010) Structural basis for the growth factor activity of human adenosine deaminase ADA2. *J Biol Chem* **285**: 12367-77 [PMID:20147294]