INHIBITION OF THE PURINE BIOSYNTHESIS GENES, CD73 AND MTAP, AS A THERAPEUTIC STRATEGY IN PROSTATE CANCER

Vandriel P. da Rosa[1]; Michelli Fontana[2]; Margarete D. Bagatini[1]; Sarah F. V. O. Maciel[1]

[1]Federal University of Fronteira Sul, Graduate Program in Biomedical Sciences, Chapecó (SC)
[2]Federal University of Fronteira Sul, Medicina Course, Chapecó (SC)

INTRODUCTION

Prostate cancer is the second leading cause of male cancer mortality (Siegel. R. L. *et al*., 2022). Purinergic signaling is involved in the progression of this tumor, linked to the formation of extracellular adenosine by the action of the CD73 enzyme (Vijayan D. *et al*., 2017). The methylthioadenosine phosphorylase (MTAP) pathway forms intracellular adenosine as a product of methionine recovery, which is converted to adenosine (Affronti HC. *et al*., 2020). Intracellular and extracellular adenosine promote immunosuppressive conditions in prostate cancer, allowing the inefficiency of antitumor immune cells (Gardani CFF. *et al*., 2019; Li Y. *et al*., 2019). Inhibition of CD73 and MTAP genes is a promising therapeutic mechanism by reducing immunosuppressive conditions and activating the antitumor capacity of immune cells against prostate cancer cells.

METHODOLOGY

Research on studies relating the adenosine-generating purinergic pathway to the MTAP pathway in prostate cancer was conducted by searching the PubMed scientific articles database. The parameters used were: Prostate cancer, Purinergic system, Methylthioadenosine phosphorylase. Studies that included molecules and/or drugs that were undergoing clinical trials or that were already being used as a treatment strategy, as inhibitors of the purinergic pathway targeting CD73 and MTAP, were selected.

RESULTS

Table 1: CD73 and MTAP inhibitors

CD73 inhibitors	Clinical response	Study	Author and year of publication
LY3475070 (Nib)	Restoration of ADO mediated inhibition of immune responses	An Exceptionally potent inhibitor of human CD73	Jeffrey, J. *et al*., 2019
Sodium polyoxo-tungstate (Nib)	Blockade of adenosine and activation of immune cells	Conversion of ATP to adenosine by CD39 and CD73 in multiple myeloma can be sucessfully targeted together with adenosine receptor tor A2A blockade	Yang R. *et al*., 2020
Oleclumab - Monoclonal Antibody	Increase NK cell activity and CD4+ and CD8+ T cell function. Increased levels of pro-inflammatory cytokines, such as IFN- γ	Pharmacology, Pharmacokinetics, and Toxicity Characterization of a Novel Anti-CD73 Therapeutic Antibody IBI325 for Cancer Immunotherapy	Zhou Y. *et al*., 2023
MTAP inhibitors	**Clinical response**	**Study**	**Author and year of publication**
MTDIA combined BENSpm	Synergistic blockade of proliferation and increase in PCa cell death	Pharmacological polyamine catabolism upregulation with methionine salvage pathway inhibition as an effective prostate cancer therapy	Affronti, H. *et al*., 2017
6'-thioguanine or 2'-fluoroadenine (2FA)	Inhibition of tumor growth	Specific targeting of MTAP-deleted tumors with a combination of 2'-fluoroadenine and 5'-methylthioadenosine	Tang B. *et al*., 2018
GSK3368715	Antiproliferative effect on tumors	Anti-tumor activity of the type I PRMT inhibitor, GSK3368715, synergizes with PRMT5 inhibition through MTAP loss	Fedoriw A. *et al*., 2019
2-methylthioadenosine associated with GSK3368715	DNA damage and mitotic defects	MAT2A inhibition blocks the growth of MTAP-deleted cancer cells by reducing PRMT5-dependent mRNA splicing and inducing DNA damage	Kalev P. *et al*., 2021

Subtitles: Nib - Small molecule inhibitor, **ADO -** Adenosine, **ATP -** Adenosine triphosphate, **CD73 -** ecto-5'-nucleotidase, **CD39 -** Ectonucleoside triphosphate diphosphohydrolase, **A2A -** adenosine receptor, **MTDIA -** MTAP inhibitor, **BENSpm -** N11-bis(ethyl) norspermine, **PRMT and PRMT5 -** protein arginine methyltransferase - 5, **MAT2A -** methionine adenosyltransferase 2A.

CONCLUSION

Inhibitory mechanisms involving the formation of adenosine related to the MTAP pathway, purine and pyrimidine analogues, such as 6-thioguanine and 5-fluorouracil, respectively, are interesting because they act by competing with methionine, causing its concentration to be reduce, making adenosine formation unfeasible. Correlating CD73 inhibitors, such as monoclonal antibodies that interfere with the ligand-receptor interaction associated with MTAP inhibition, are therapeutic strategies in tumor immunosuppression. When associated with chemotherapy and immunotherapy, the restoration of the immune response allows a greater possibility of antitumor treatment linked to then inhibition of the CD73 and MTAP genes.

References:
Affronti HC, Rowsam AM, Pellerite AJ, et al. Pharmacological polyamine catabolism upregulation with methionine salvage pathway inhibition as an effective prostate cancer therapy. Nat Commun 2020; 11: 52.
Gardani, C.F.F.; Cappellari, A.R.; de Souza, J.B.; da Silva, B.T.; Engroff, P.; Moritz, C.E.J.; Scholl, J.N.; Battastini, A.M.O.; Figueiró, F.; Morrone, F.B. Hydrolysis of ATP, ADP, and AMP is increased in blood plasma of prostate cancer patients. Purinergic Signal. 2019, 15, 95–105
Li Y, Wang Y, Wu P. 5'-methylthioadenosine and cancer: old molecules, new understanding. J Cancer 2019; 10: 927–36.
Siegel, R.L.; Miller, K.D.; Fuchs, H.E. Cancer Statistics, 2022. CA Cancer J. Clin. 2022, 72, 7–33.
Vijayan, D.; Young, A.; Teng, M.W.L.; Smyth, M.J. Targeting immunosuppressive adenosine in cancer. Nat. Rev. Cancer 2017, 22, 765, Erratum in Nat. Rev. Cancer 2017, 17, 709–724.

fapesc
Edital 18/2024