A_3 adenosine receptors reduce bone-residing breast cancer

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Increasing evidence demonstrates that adenosine is a key endogenous molecule modulating numerous pathophysiological processes through G-protein coupled receptors named A_1, A_{2A}, A_{2B} and A_3 adenosine receptors (ARs) [1,2]. Several papers have reported that A_3ARs are highly expressed in tumor cells both in *in vitro* and *in vivo* models, showing a pivotal role in cancer and suggesting the utilization of this receptor to combat growth and development of malignant cells [3-5]. Among cancers with poor prognosis those originating from breast commonly metastasize to the skeleton for the high affinity of breast cancer cells to bone. In literature A_3 adenosine receptor (A_3AR) agonists were found to be potent anti-tumor agents even if their effect on bone-residing breast cancer has not yet been investigated.

An animal model of surgery-induced metastasis was used to mimic the human condition in an attempt to develop a novel effective treatment strategy. Sprague-Dawley rats receiving intra-tibial injections of syngeneic MRMT-1 rat mammary gland carcinoma cells developed cancer-associated osteolytic lesions and structural damage that were monitored by microcomputed tomography imaging and histological analysis. To address the involvement of A_3ARs in tumor-related signaling pathway, A_3AR expression and functional role were analyzed in MRMT-1 cells. The effect of chronic treatment with an A_3AR agonist, 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA) in comparison with cisplatin, was evaluated on rat tumor growth and bone cancer pain.

A_3ARs were expressed in MRMT-1 cells and their activation reduced NF-kB, increased p53 expression and apoptosis, inhibited tumor cell proliferation and migration. *In vivo* Cl-IB-MECA administration, started on day 1 after tumor cell injection, produced a significant reduction in tumor growth and cancer pain. Cl-IB-MECA treatment, performed on days 5 and 10 after the tumor cell inoculation, revealed the capability of A_3AR stimulation to partially reduce tumor progression. The microtomographic analysis reveals that Cl-IB-MECA treatment prevents the bone degradation depending on the treatment start. Histological analysis demonstrates a lower presence of tumor cells in rats treated with Cl-IB-MECA in comparison with tumor rats.

Our findings highlighted the effectiveness of A_3AR stimulation in the inhibition of breast tumor-derived bone metastasis growth strongly suggesting that targeting A_3ARs may have promising therapeutic value in the treatment of bone-residing breast cancer.

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