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Abstract

Adenosine Overcomes Triple-Negative Breast Cancer Resistance to Platinum-Derived Chemotherapeutic Drugs †

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Abstract: Triple-negative breast cancer (TNBC), a poor survival cancer has high resistance to therapy, with low-drug efficacy. Adenosine is present in high concentrations in the tumor microenvironment. Recently, adenosine was found to sensitize ovarian cisplatin-resistant cancer. This work aims at addressing if adenosine can sensitize TNBC resistance to platinum drugs. Concomitant or preincubation of adenosine with cisplatin or carboplatin induced cell proliferation in TNBC cisplatin-sensitive (MDA) and -resistant (MDA/R) cells (using Lionheart-FX microscope). Phosphorylation of the ERK or NF-κB pathways and cAMP production were evaluated (AlphaScreen assays). Data were analyzed with a one-way ANOVA *t*-test. Results: concomitant or preincubation of adenosine (300, 600, 700 μM) with cisplatin reduced resistance in MDA/R cells, with proliferation levels approaching those observed in MDA cells. In MDA cells, endogenous and exogenous adenosine have no effect over ERK phosphorylation; in MDA/R cells, exogenous adenosine lowers ERK phosphorylation. NF-κB phosphorylation was induced by A_3R and A_{2B}R tonic activation in MDA and MDA/R cells, respectively, increasing survival—exogenous adenosine inactivates this. Tonic cAMP production was altered in MDA and MDA/R cells, revealing inhibitory and stimulatory effects in cAMP production by A_1R and A_{2B}R, respectively, in MDA/R cells. In contrast, exogenous adenosine revealed that adenosine receptors in MDA cells contribute differently while in MDA/R cells all receptor subtypes have a similar contribution to cAMP production. Thus, adenosine contributes to overcome platinum-derived resistance in TNBC, involving the inactivation of the NF-κB pathway and decrease in ERK phosphorylation (partially mediated by A_3R).

Keywords: adenosine; P1-receptors; carboplatin; cisplatin; TNBC; cancer resistance; A2B receptor

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