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Extracellular Cyclic AMP/Adenosine Signaling Pathway: A Potential Pharmacological Target for Therapeutic Intervention in Chronic Lymphocytic Leukemia

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Lymphocytic Leukemia

The chronic lymphocytic leukemia (CLL) is the most prevalent type of leukemia in adults of western countries with an estimated annual 15,000 new cases and 4,500 deaths in the USA [1,2]. CLL is a disorder characterized by a progressive accumulation of biologically and functionally incompetent lymphocytes. Clinically, CLL is a heterogeneous disease with variable prognosis depending on the age affected, being dependent on the presence of associated comorbidities, clinical stage and expression of molecular markers specific to the disease [3-6].

In tumor progression of CLL, numerous factors further the tumor growth, progression, invasiveness and dissemination. Among these factors, nucleosides (adenosine) and cyclic nucleotides (adenosine triphosphate) have capacity to bind in purinergic receptors and modulating not only tumor growth, and its capacity for dissemination, but also controlling the adaptive immune response [7-9].

Nucleotides like ATP can be converted to adenosine through the enzymes ectonucleotides, located on the surface of the plasma membrane [8-10]. The adenosine produced by the tumor cells, besides being used for the synthesis of nucleotides, can act as agonist of the purinergic receptor coupled to G protein (A1, A2a, A2b, A3), promoting the suppression of tumor infiltrating lymphocytes (immunosuppressive effect) and inflammatory activity (anti-inflammatory effect) [8-12].

In the intracellular medium, cyclic AMP (cAMP) can act as a second messenger, with a relevant antitumoral activity by regulating cell differentiation, proliferation and apoptosis, as seen in different types of leukemia. Since the intracellular concentrations of cAMP are regulated by phosphodiesterases (PDE), the most studied being type 4 PDE (PDE4) [13-15]. In addition, the intracellular cAMP concentration in tumor cells can be regulated by the multidrug resistance protein 4 (MRP4), which acts as an efflux pump for cAMP to the extracellular medium, and subsequently degraded in adenosine by enzyme EctoPDE, located in outsider portion of plasma membrane [16].

The increase of extracellular adenosine turnover in the tumor microenvironment, as well as the increase in the amount of enzymes involved in this sequence of chemical reactions favor tumor growth, accompanied by the detriment of the antitumor activity by the immune system [17]. Adenosine contributes to the survival of tumor cells by inhibiting the process of apoptosis-mediated tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and multiresistant drug phenotype of leukemic cells [18], with a high expression of catalytically active ectonucleotidases (such as CD73) being described in CLL [19]. In addition, considering the existence of a cAMP efflux system mediated by multiresistant protein transporters: the blockade of adenosine receptors reduces the negative inotropic effect promoted by extracellular adenosine due to cAMP efflux system, altering important intracellular signaling pathways [20,21]. Thus, we have proposed that the pharmacological modulation of the intra and extracellular signaling mediated by cAMP and adenosine could be a new antitumoral strategy in CLL therapy [22-26].

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