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The Pharmacological Interference on the Ca^{2+}/cAMP Intracellular Signalling Pathways: Advances for the Antitumoral Immunotherapy Research

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Cancer is considered a worldwide public health problem, with a large annual number of deaths, and treatment public spending [1]. Conventional treatments such as chemotherapy and radiotherapy have limitations since they are not selective and specific, affecting both: tumor and healthy cells [2]. In recent years, new therapies have been emerged, such as: target therapies and immunotherapy both used as monotherapy or in combination with conventional therapies [3-5].

Immunotherapy for the treatment of cancer, using monoclonal antibodies, is considered selective, such as antibodies against Vascular Endothelial Growth Factor (VEGF) [6]. This therapeutic approach has significant efficacy in the treatment of different types of tumors, but its cost and toxic effects limit its application [7]. Thus, one of the greatest challenges is the development of combined therapies capable of inducing an antitumor response, availing the control of tumor growth, angiogenesis and dissemination [8].

In the early stages of tumor development, when the tumor is less than 2 mm of diameter, the nutrition of the tumor mass is performed through the diffusion from neighboring tissues. Exceeding this size, tumor growth depends on the process of angiogenesis and the new formed blood vessels serve as routes for dissemination of the neoplasia to other places (colonization) [9]. For tumor-induced angiogenesis occurring, αvβ3 integrins play a relevant role in the physical interaction with the extracellular matrix necessary for cell adhesion, migration and positioning, in addition to inducing signs for cell survival and proliferation [10]. Integrins are adapted for the transmission of information from the extracellular medium into the cells by cytoskeleton proteins, with activation of GTPases, activation of Mitogen Activated Protein-Kinase (MAPK), alteration of intracellular levels of Ca^{2+} and increase of levels of substrates for activation of phospholipase C [11,12]. Activation of phospholipase C causes increased hydrolysis of membrane phospholipids, generating inositol-1-4-5-triphosphate and diacylglycerol. Inositol-1-4-5-triphosphate activates Ca^{2+} channels located in the membrane of the endoplasmic reticulum, releasing Ca^{2+} into the cytosol; and thus diacylglycerol activates the plasma membrane voltage sensitive Ca^{2+} channels, with passage of Ca^{2+} from extracellular into intracellular compartment [13]. Thus, this signaling system - with increased levels of intracellular Ca^{2+} - may contribute to the process of tumor growth and dissemination, exemplified by sarcoplasmic/endoplasmic reticulum calcium ATPases channels (SERCA, specifically SERCA2, SERCA3) and voltage-gated Ca^{2+} channels (CaV, specifically CaV1.2, CaV3.2) [14-16].

In addition, the blockade of Ca^{2+} channels is able to decrease vascularization in breast and kidney tumors; and the drug NNC 55-0396, a T-type Ca^{2+} channel inhibitor, is capable of inhibiting angiogenesis of tumor by suppression of hypoxia-inducible factor-1alpha signal transduction via both proteasome degradation, and protein synthesis pathways [17,18].

Besides Ca^{2+} the cyclic adenosine monophosphate (cAMP) is a nucleotide responsible for intracellular signalling transduction from different stimuli, associated with activation of protein

kinases [19,20]. The decrease of intracellular levels of cAMP stimuli may modulate transcriptional factors, and gene activation, making cells start DNA synthesis, and entry to cell cycle [21]. In contrast, increasing intracellular levels of cAMP through the action of phosphodiesterase inhibitors (that hydrolyze cAMP) may inhibit Endothelial Extracellular Matrix (ECM) remodeling, thus suppressing PI3K/AKT signals to down-modulate Vascular Endothelial Growth Factor (VEGF) secretion and vessel formation in vitro, and stimuling the lower synthesis of VEGF and diminishing the micro vessel density in animal model of diffuse large B-cell lymphoma (DLBCL) [22,23]. Also, the association of curcumin with phosphodiesterase 2, and phosphodiesterase 4 inhibitors, inhibits the production of VEGF, angiogenesis and tumor growth [24]. Thus, the combination of anti-VEGF monoclonal antibodies with Ca^{2+} channel blockers or phosphodiesterase inhibitors, may decrease the toxic effects of antitumor immunotherapy.

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