

## The Second Messengers Ca<sup>2+</sup> and cAMP as Potential Therapeutic Targets for the Control of Cancer Progression

Paolo Ruggero Errante, Francisco Sandro Menezes-Rodrigues, Alberto Andrade Leite, Afonso Caricati-Neto and Leandro Bueno Bergantini\*

Department of Pharmacology, Federal University of São Paulo-Paulista School of Medicine, Laboratory of Autonomic and Cardiovascular Pharmacology, Rua Pedro de Toledo 669 - Vila Clementino, São Paulo-SP, Brazil

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\*Corresponding author: Leandro Bueno Bergantini, Department of Pharmacology, Federal University of São Paulo-Paulista School of Medicine, Laboratory of Autonomic and Cardiovascular Pharmacology, Rua Pedro de Toledo 669 - Vila Clementino, São Paulo - SP, Brazil, Tel: 55 11 5576-4973; E-mail: leanbio39@yahoo.com.br

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### Abstract

This editorial highlights the relevance of interfering in cancer cell progression through the pharmacological manipulation on the cell metabolism of cyclic nucleotides such as cAMP, and on the intracellular Ca<sup>2+</sup> signaling, which may avail the reduction of toxic effects promoted by chemotherapy, radiotherapy and immunotherapy, thus decreasing the incidence of interruption in antitumoral treatment.

### Keywords:

Cancer progression; Ca<sup>2+</sup> channels blockers; Second messenger; Cyclic adenosine monophosphate, Ca<sup>2+</sup>/cAMP interaction

### Introduction

Cancer is an important cause of morbidity and mortality worldwide, leading to the rise of great economic costs in the diagnosis and treatment [1]. Despite the great scientific advances regarding the tracking of tumor cells by liquid biopsy [2], interventions on tumors are still limited to surgery, chemotherapy, radiotherapy and immunotherapy [3]. Many patients discontinue the treatment because of the great number of toxic and adverse effects promoted by antitumor therapy. This interruption, or discontinuation, of treatment may lead to cancer progression beyond the development of new mutations, limiting therapeutic success, decreasing the overall quality of life, or leading to early death of patients [4]. Our proposal consists in the use of Ca<sup>2+</sup> channel blockers and/or enhancers of cAMP synthesis for the control of tumor growth to reduce the adverse effects and the abandonment rate in different antitumor protocols.

Ca<sup>2+</sup>/cAMP intracellular signaling interaction Calcium (Ca<sup>2+</sup>) is an intracellular second messenger stored inside the endoplasmic reticulum and mitochondria [5,6]. The intracellular Ca<sup>2+</sup> flow is regulated by different channels and transporters, such as the receptor of inositol-1,4,5-triphosphate (IP3R) and Ca<sup>2+</sup>-ATPase pump [7]. The passage of Ca<sup>2+</sup> by the plasma membrane can occur through voltage-activated Ca<sup>2+</sup> channels (Cav family) and through transient receptor potential channels (TRPs). Intracellular Ca<sup>2+</sup> flow is regulated by mitochondrial Ca<sup>2+</sup> uniporter (MCU), Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX) and Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release (CICR) mechanism [8].

The process of cell proliferation depends on the control of intracellular levels of Ca<sup>2+</sup>, regulated by membrane transporters and regulators of intracellular flow. A greater amount of Ca<sup>2+</sup> is required by tumor cells in relation to healthy cells for progression in the cell cycle, which ultimately depends on signaling molecules, such as cyclins [9].

The transition from G1 phase to S phase (mitosis) is a Ca<sup>2+</sup>-signaling-dependent process, such as dependent on Ca<sup>2+</sup> calmodulin (CaM) and CaMkinase II (CaMK). The CaM and CaMK regulate cyclins A, D1 and E [10], and active proteins of nuclear factor of activated T-cells (NFAT) family, leading to activation of Ca<sup>2+</sup> channels. The NFAT transcription factor was described as relevant in the process of tumor invasion and metastasis in breast cancer [11]. Numerous transporters of Ca<sup>2+</sup>, like members of Ca<sup>2+</sup>-ATPases family such as SERCA, present altered expression of isoforms in different tumors cells [12]. A change in the expression of TRP channels [13], L-type calcium channel [14], and T-type Ca<sup>2+</sup> channels [15] were observed in tumors cells [16].

During the process of tumor dissemination, Ca<sup>2+</sup> participates in the invasion of healthy tissues by tumor cells with involvement of Ca<sup>2+</sup> channels. Thus, intracellular signals mediated by abnormal concentrations of cytosolic Ca<sup>2+</sup> are important in the maintenance of the growth, invasion and tumor metastasis. Inhibition of T-type calcium channels by mibefradil [17] or NecroX-5 [18] can prevent the process of metastasis in breast tumors.

In addition to Ca<sup>2+</sup>, cyclic adenosine cyclic nucleoside monophosphate (cAMP) acts as an intracellular signal transducer mediating extracellular signaling to the cytoplasm. The cAMP can directly regulate the activation of ion channels, and indirectly the gene expression, differentiation and cellular growth [7].

The cAMP can interact with Ras-mediated MAP kinase and, upon binding to cAMP-dependent kinases (PKA), is able to modulate cell growth. This mechanism of intracellular signaling has been implicated in different types of tumors [19], and the pharmacological manipulation of cAMP may lead to the decrease of tumor progression [20].

Thus, the pharmacology manipulation leading to decreased of intracellular Ca<sup>2+</sup> levels, and increasing of cAMP, can help to reduce the development of the intrinsic resistance of the tumors by different conventional antitumor protocols. Then, we suggest that the pharmacological control of the intracellular levels of Ca<sup>2+</sup> and cAMP may decrease the rate of tumor growth, invasion and metastasis. This strategy, combined with conventional antitumor treatments, may help reduce the dose of existing drugs in the treatment of tumors, reducing the adverse effects and the rate of abandoned therapy.

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