The Second Messengers Ca2+ 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 Bergantin

Department of Pharmacology, Federal University of São Paulo-Paulista School of Medicine, Laboratory of Autonomic and Cardiovascular Pharmacology, Rua Pedro de Toledo669 - Vila Clementino, São Paulo-SP, Brazil

Accepted date: July 5, 2017

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 Ca2+ 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; Ca2+ channels blockers; Second messenger; Cyclic adenosine monophosphate, Ca2+/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 Ca2+ 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.

Ca2+/cAMP intracellular signaling interaction Calcium (Ca2+) is an intracellular second messenger stored inside the endoplasmic reticulum and mitochondria [5,6]. The intracellular Ca2+ flow is regulated by different channels and transporters, such as the receptor of inositol-1,4,5-triphosphate (IP3R) and Ca2+-ATPase pump [7]. The passage of Ca2+ by the plasma membrane can occur through voltage-activated Ca2+ channels (Cav family) and through transient receptor potential channels (TRPs). Intracellular Ca2+ flow is regulated by mitochondrial Ca2+ uniporter (MCU), Na+/Ca2+ exchanger (NCX) and Ca2+-induced Ca2+ release (CICR) mechanism [8].

The process of cell proliferation depends on the control of intracellular levels of Ca2+, regulated by membrane transporters and regulators of intracellular flow. A greater amount of Ca2+ 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 Ca2+-signaling-dependent process, such as dependent on Ca2+calmodulin (CaM) and CaM kinase 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 Ca2+ channels. The NFAT transcription factor was described as relevant in the process of tumor invasion and metastasis in breast cancer [11]. Numerous transporters of Ca2+, like members of Ca2+-ATPases family such as SERCA, present altered expression of isofoms in different tumors [12]. A change in the expression of TRP channels [13], L-type calcium channel [14], and T-type Ca2+ channels [15] were observed in tumors cells [16].

During the process of tumor dissemination, Ca2+ participates in the invasion of healthy tissues by tumor cells with involvement of Ca2+ channels. Thus, intracellular signals mediated by abnormal concentrations of cytosolic Ca2+ are important in the maintenance of the growth, invasion and tumor metastasis. Inhibition of T-type calcium channels by mibebradil [17] or NecroX-5 [18] can prevent the process of metastasis in breast tumors.

In addition to Ca2+, 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\textsuperscript{2+} 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\textsuperscript{2+} 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.

References

1. Sagar B, Lin YS, Castel LD (2017) Cost drivers for breast, lung, and colorectal cancer care in a commercially insured population over a six-month episode: an economic analysis from the payer perspective. J Med Econ 21:1-15.
2. Hanjani JM, Wilson GA, McGranahan N, Birkbak NJ, Watkins TBK, et al. (2017) Tracking the evolution of non-small-cell lung cancer. N Engl J Med 376: 2109-21.
3. Mori C (2017) Highlights from the 15th Gallen International Breast Cancer Conference 15-18 march, 2017, Vienna: tailored treatments for patients with early breast cancer. Ecamericalscience. 11: 732.
4. Eagles JR, Jimeno A (2016) Comimetib: Inhibiting MEK1/2 in BRAF V600-mutant melanoma. Drugs Today (Barc) 52: 593-605.
5. Groenendyk J, Lynch J, Michaelak M (2004) Calrecticulin, Ca\textsuperscript{2+}, and calcineurin-signaling from the endoplasmatic reticulum. Mol Cells 17: 383-89.
6. Frieden M, Arnaudeau S, Castelbou C, Demaurex N (2005) Subplasmaleminal mitochondria modulate the activity of plasma membrane Ca\textsuperscript{2+} ATPases. J Biol Chem 280: 43198-208.
7. Errante PR, Menenes-Rodrigues FS, Leite AA, Caricati-Neto A, Bergantin LB (2017) New antitumoral pharmacological strategies involving Ca\textsuperscript{2+}/cAMP signaling pathways. J Cancer Epidemiol Prevent 2: 1-6.
8. Cui C, Merritt R, Fu L, Pan Z (2017) Targeting calcium signaling in cancer therapy. Acta Pharmaceutica Sinica B 7: 3-17.
9. Prakriya M, Lewis RS (2015) Store-operated calcium channels. Physiol Rev 95: 1383-436.
10. Kahl CR, Means AR (2003) Regulation of cell cycle progression by calcium/calmodulin dependent pathways. Endocr Rev 24: 719-36.
11. Yoeli-Lerner M, Yu G, Rabinovitz I, Erhardt P, Jauliac S, et al. (2005) Akt blocks breast cancer cell motility and invasion through the transcription factor NFAT. Molecular Cell 20: 539-50.
12. Dang D, Rao R (2016) Calcium-ATPases: gene disorders and dysregulation in cancer. Biochim Biophys Acta 1863: 1344-50.
13. Delli N, Constantin B (2015) Plasma membrane calcium channels in cancer: Alterations and consequences for cell proliferation and migration. Biochimica et Biophysica Acta 1848: 2512-22.
14. Chen R, Zeng X, Zhang R, Huang J, Kuang X, et al. (2014) Cav1.3 channel alpha1D protein is overexpressed and modulates androgen receptor transactivation in prostate cancers. Urol oncol 32: 524-36.
15. Mariot P, Vanoverberge K, Lallevee N, Rossier MF, Prevarskaya N (2002) Overexpression of an alpha 1H (Cav3.2) T-type calcium channel during neuroendocrine differentiation of human prostate cancer cells. J Biol Chem 277: 10824-833.
16. Chen J, Luan Y, Yu R, Zhang Z, Zhang J, et al. (2014) Transient receptor potential (TRP) channels, promising potential diagnostic and therapeutic tools for cancer. Biosci Trends 8: 1-10.
17. Zhang Y, Cruickshanks N, Yuan F, Wang B, Pashuski M, et al. (2017) Targetable T-type calcium channels drive glioblastoma. Cancer Res 3479-3490.
18. Park JH, Kim HK, Jung H, Kim KH, Kang MS, et al. (2017) NecroX-5 prevents breast cancer metastasis by AKT inhibition via reducing intracellular calcium levels. Int J Oncol 50: 185-92.
19. Caretta A, Muscignat-Caretta C (2011) Protein kinase A in cancer. Cancers 3: 913-926.
20. Ramezani S, Yousoughi N, Kapoorchali FR, Hadijghasem M, Hayat P, et al. (2017) Rolipram potentiates bevacizumab-induced cell death in human glioblastoma stem-like cells. Life Sci 173: 11-19.

Citation: Errante PR, Rodrigues FSM, Leite AA, Caricati-Neto A, Bergantin LB (2017) The Second Messengers Ca2+ and camp as Potential Therapeutic Targets for the Control of Cancer Progression. Adv Cancer Prev 2: e105. doi:10.4172/2472-0429.1000e105