Insights for the Inhibition of Cancer Progression: Revisiting Ca2+/ and Camp Signalling Pathways

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Abstract

This editorial article gives insights for the inhibition of cancer progression. The pharmacological modulation of Ca2+/cAMP signalling interaction is also cited.

Keywords: Cancer progression; Ca2+/cAMP signalling interaction

Introduction

Classically, Ca2+ is accepted as an intracellular second messenger that controls gene transcription, cell cycle regulation, mobility and apoptosis. Usually, Ca2+ is stored in specific organelles, such as endoplasmic reticulum (ER) and mitochondria [1]. Indeed, intracellular Ca2+ homeostasis is regulated by numerous channels and transporters of Ca2+, for example: by the receptor of inositol-1,4,5-triphosphate (IP3R) and Ca2+-ATPase pump. In addition, the Ca2+ influx across plasma membrane occurs through voltage-activated Ca2+ channels (VACCs) and transient receptor potential channels (TRPs). Intracellular Ca2+ homeostasis is also regulated by the Ca2+-induced Ca2+ release (CICR) mechanism, Na+/Ca2+ exchanger (NCX) and mitochondrial Ca2+ uniporter (MCU) [2].

In fact, the release of Ca2+ from the ER to the cytoplasm is performed through classical signalling pathways, activated by specific agonists and receptors, located in the surface of plasma membrane, for example: by activating phospholipase C, it hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) of plasma membrane, so producing inositol-1,4,5-triphosphate (IP3). The diffusion of IP3 into the cells release intracellular Ca2+ of their stocks by the activation of specific receptors (IP3R), which are localized in the cytoplasmic side of ER membrane [3]. The increase of expression, or activity, of Ca2+ channels in the plasma membrane lead to increase of Ca2+ influx, promoting Ca2+-dependent cell proliferation, and differentiation [4]. In contrast, the nucleoplasmic reticulum can release Ca2+ independently of signals generated by cytosolic Ca2+ [5], microdomain where Ca2+ is able to bind to specific DNA promoter regions, modulating the activity of transcription factors, gene expression and cellular activity [6].

In addition, Ca2+ is crucial for the cancer progression. Carcinogenesis is a process of non-lethal genetic injury that can be acquired by the action of environmental agents, such as chemical substances, radiation or viruses, or can be inherited in the germ line. This implies in alteration in proto-oncogenes, genes that regulate apoptosis, and genes involved in DNA repair. Most antineoplastic chemotherapeutic agents act in cell division, affecting both normal and neoplastic cells. Indeed, there is a consensus that carcinogenesis process is associated with an increased expression, or abnormal activation, of Ca2+ channels, Ca2+ transporters or Ca2+-ATPases [2], making these structures therapeutic targets for inhibiting cancer growth. For example, this issue can be observed by the use of selective SERCA pump inhibitor, thapsigargin [7]; Ca2+ channel blockers (CCBs), such as amiodpine and mibeferidul used in anti-hypertensive therapy [8,9]; and also a mibeferidul derived novel compound, named NNC-55-0396 [10]; CICRs and TRP channel regulators; the imidazole compound, named SKF 96365; and related antimycotic compounds, including econazole, miconazole and clotrimazole [11].

Also, non-pharmacological strategies that buffer nucleoplasmic Ca2+ have been described to reduce the rate of cancer tumor proliferation [12], and in combination with existing antitumor therapies, may be able to reduce the doses and adverse effects generated by radiotherapy and chemotherapy, conferring better quality of life to patients, and increase of global survival rate of patients with cancer. This therapy could be used to control growth of cancer tumors with high rates of resistance to conventional radiotherapy and chemotherapy treatments [13]; or in combination with immunotherapy to decrease dose of monoclonal antibodies intravenously infused, and their adverse effects [14].

In addition to Ca2+, cAMP has been implicated in the regulation of cancer progression [15]. From this concept in mind, phosphodiesterase IV inhibitors like rolipram, which increase cAMP have been proposed as potential adjuvant, chemotherapeutic or chemopreventive agents in hepatocellular carcinoma [15].

Role of Ca2+/cAMP Signalling in Cancer Progression

Considering that Ca2+ and cAMP signalling pathways can interact in a universally-operated manner, in our studies [16-18] we proposed that the pharmacological handling of the Ca2+/cAMP signalling interaction could be a more efficient therapeutic approach for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases. As the activity of adenylly cyclase (AC) is regulated by Ca2+, the reduction of [Ca2+]c produced by L-type CCBs results in increase of activity of ACs, and elevation of [cAMP][c] [16-18]. Thus, whether this interaction may be a novel therapeutic target to alter cancer tumor growth, angiogenesis and metastasis, without affecting normal cell physiology deserves special attention. Then, it would not be a surprise the suggestion of using CCBs in combination with pharmaceuticals which increase cAMP to inhibit cancer progression [8,9,15].

Therefore, the current knowledge about regulation of intracellular Ca2+ and cAMP homeostasis in cancer tumor cells, and the search for...
new pharmacological strategies to control these intracellular messengers may be able to lead the development of new pharmacological and non-pharmacological strategies that specifically alter tumor growth, angiogenesis and metastasis, without affecting normal cell physiology. Finally, the pharmacological handling of the Ca\textsuperscript{2+}/cAMP signalling interaction could be a more efficient therapeutic approach to inhibit cancer tumor progression.

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