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Insights for the Inhibition of Cancer Progression: Revisiting Ca^{2+} and Camp Signalling Pathways

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Abstract

This editorial article gives insights for the inhibition of cancer progression. The pharmacological modulation of Ca^{2+}/cAMP signalling interaction is also cited.

Keywords: Cancer progression; Ca^{2+}/cAMP signalling interaction

Introduction

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

In fact, the release of Ca^{2+} 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 (PIP_2) of plasma membrane, so producing inositol-1,4,5-triphosphate (IP_3). The diffusion of IP_3 into the cells release intracellular Ca^{2+} of their stocks by the activation of specific receptors (IP_3R), which are localized in the cytoplasmic side of ER membrane [3]. The increase of expression, or activity, of Ca^{2+} channels in the plasma membrane leads to increase of Ca^{2+} influx, promoting Ca^{2+}-dependent cell proliferation, and differentiation [4]. In contrast, the nucleoplasmic reticulum can release Ca^{2+} independently of signals generated by cytosolic Ca^{2+} [5], microdomain where Ca^{2+} is able to bind to specific DNA promoter regions, modulating the activity of transcription factors, gene expression and cellular activity [6].

In addition, Ca^{2+} 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 antineoplasic 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 Ca^{2+} channels, Ca^{2+} transporters or Ca^{2+}-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]; Ca^{2+} channel blockers (CCBs), such as amlodipine and mibefradil used in anti-hypertensive therapy [8,9]; and also a mibefradil 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 Ca^{2+} 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 Ca^{2+}, 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 Ca^{2+}/cAMP Signalling in Cancer Progression

Considering that Ca^{2+} and cAMP signalling pathways can interact in a universally-operated manner, in our studies [16-18] we proposed that the pharmacological handling of the Ca^{2+}/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 adenylyl cyclase (AC) is regulated by Ca^{2+}, the reduction of $[Ca^{2+}]c$ 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 Ca^{2+} 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^{2+}/cAMP signalling interaction could be a more efficient therapeutic approach to inhibit cancer tumor progression.

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