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New Antitumoral Pharmacological Strategies Involving Ca^{2+}/Camp Signaling Pathways

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Abstract

Cell signaling is a crucial event for the survival and progress of normal cellular functions. However, mutations of certain genes can lead to the emerging of cancer cells, which can use these signaling mechanisms for their survival, growth and dissemination. Among these mechanisms, we highlight the role of cyclic nucleotides such as cAMP, and Ca^{2+} and its Ca^{2+} channels, which are functionally altered, or amplified, in different types of cancer cells. Understanding these mechanisms is crucial for knowledge of process of tumor progression, and for the creation of new pharmacological strategies to control the growth and spread of tumor cells. In this review, we address the relevance of cyclic nucleotides such as cAMP, and Ca^{2+} channels in tumor cells, emphasizing the possibility of combined pharmacological interventions which interfere with these intracellular signaling pathways.

Keywords: Cancer; Ca^{2+} channels; Ca^{2+} signaling; Cyclic adenosine monophosphate; cAMP signaling

Introduction

Cell signaling is part of a communication process that governs basic activity of cell, and the ability of cell to respond to the microenvironment. This mechanism is fundamental to the homeostasis, tissue repair and control of malignance [1]. Errors in signaling interaction, and cellular information process between cells, are responsible for different pathologies, such as cancer. The development of cancer cells is associated with the mutation of four distinct groups of genes: the proto-oncogenes growth promoters [2]; tumor suppressor genes [3]; genes that regulate genetically programmed cell death (apoptosis) and genes involved in DNA repair [4]. The abnormal cell division causes cancer, also called as carcinogenesis, and may be associated with exposure to chemicals, radiation [5] or microbial agents, especially viruses [6].

Carcinogenesis is a multi-step process resulting from the accumulation of multiple mutations that accumulate independently in different cell types, generating subclones with different characteristics. These characteristics make the tumors have capacity for invasion and metastasis, rapid growth speed, hormone response and resistance to antineoplastic drugs [7,8]. Numerous normal biochemical mechanisms may be altered, leading to the emergence of these distinct characteristics of cancer cells. Among these several altered biochemical characteristics, the change in the behavior of influx, and efflux, of intracellular Ca^{2+}, and the signaling mediated by cyclic nucleotides i.e., cAMP can be verified. Since intracellular signaling measured by calcium and cyclic nucleotides is a canonical event, changes in this signaling pathway are crucial for the survival and growth of cancer cells [9]. In this way, the knowledge of cancer physiology is crucial to the development of new strategies to control the growth, dissemination and metastasis. In this article, the involvement of Ca^{2+} channels, and cyclical nucleotides like cAMP in cancer development and progression, and the use of new pharmacological strategies with potential capacity of control the cancer growth, and progression are discussed.

Cyclical nucleotides in cancer cells

The nucleotides are composed by a nitrogenous base, a pentose and one or more phosphate groups, and participate of numerous intracellular biochemical processes. They act as precursors of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), energy source (adenosine triphosphate and guanosine triphosphate), coenzymes (flavin adenine dinucleotide, nicotinamide adenine dinucleotide and coenzyme A) and physiological regulators (cyclic adenosine monophosphate and cyclic guanosine monophosphate) [10]. The cyclic adenosine monophosphate (cAMP) is a second messenger that acts as intracellular signal transduction leading to a cAMP-dependent pathway. The cAMP is synthesized from ATP by the adenylyl cyclase located on the inner side of the plasma membrane.

Adenylyl cyclase is activated by signaling molecules through the activation of receptors with the G-protein stimulatory (Gs) of adenylyl cyclase, and inhibited by inhibitory G (G) receptor agonists of adenylyl cyclase [11]. When cAMP concentration increases (activation of the adenylate cyclases by the Gs protein, and inhibition of cAMP-degrading phosphodiesterases), cAMP binds to the regulatory subunits, which leads to the release of the catalytic subunits. The free catalytic subunits catalyze the transfer of terminal phosphates from ATP [12]. The link between membrane surface of cell and cytoplasm is mediated by a family of enzymes called kinase proteins dependent of cAMP, or protein kinase A (PKA), by transformation of ATP in ADP with phosphorylation of protein substrates responsible by intracellular effects [13]. Mechanisms involving the control of cAMP over PKA can be divided into: direct protein phosphorylation and protein synthesis. In direct phosphorylation, PKA both increases and decreases the activity of a protein; and in protein synthesis PKA first activates the cAMP response element-binding protein (CREB), a cellular transcription factor, which binds to the cAMP response element, altering transcription and protein synthesis [14]. In the negative regulation of PKA, one of the substrates activated by kinase is a phosphodiesterase, which converts cAMP to AMP, reducing the amount of cAMP that can activate PKA. The catalytic function of PKA can be combined with A-kinase anchoring proteins (AKAP). AKAP are signal-organizing molecules that compartmentalize various enzymes that are regulated by second messengers. PKA binding with AKAP, and a phosphodiesterase, form a complex that hydrolyzes cAMP. Considering the phosphodiesterase contributes to the low concentration of cAMP in cells, PKA is responsible for the activation of phosphodiesterase, to lower the concentration of cAMP [11]. The cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), are important intracellular signal transduction molecules, acting as second messengers through an extracellular signal. Both cAMP and cGMP signaling have positive or negative effects on growth and survival, depending on the type cell. The cAMP can regulate a variety of cellular functions: metabolism of ion channel activation, cell growth and differentiation, gene expression and apoptosis [15]. The cAMP pathway acts with other intracellular signaling pathways such as those mediated by Ca^{2+} [16], and Jak/STAT [17]. The cAMP interacts with Ras-mediated MAP kinase, modulating cell growth [18] when binding to cAMP-dependent protein kinases (PKA) [19]. When activated, PKA phosphorylates macromolecular complexes responsible for the destruction of mitotic cyclins, and separation of sister chromatids in the anaphase-metaphase transition [20]. The involvement of cAMP, and the activation of PKA, has been associated with different types of cancer [21], where oncogenic activity of cAMP is due to the activation of PKA, and downstream effectors (exchange protein directly activated by cAMP (Epac) and CREB) [22].

The PKA-mediated cascade is required for the functional regulation of D-type cyclins, so defects in the cAMP/PKA pathway can induce tumors in cell lines [23], which can be reversed by modifying the PKA subunit type that is expressed by the cell. The circuity formed by PKA, and cAMP, can influence the growth of colorectal cancer cell by decreasing cAMP intracellular levels [24]. Any tumors present a predominant of determined forms of PKA, such as glioblastoma, with predomin of PKA type II [25]. In the same way, the increase of cAMP levels can diminish the tumor growth [26]. Other function, in which PKA may be dysregulated in cancer, is the cell migration that involves cytoskeleton remodeling [27].

Numerous mutations lead to the formation of oncogenes that encode different protein kinases. Changes in the activity of protein kinases alter numerous signaling pathways, such as those involved in the cytosolic concentration of Ca^{2+}. Intracellular signals mediated by abnormal cytosolic Ca^{2+} concentrations are important in maintenance, growth, inavasion and metastasis by cancer cells.

Ca^{2+} signaling and channels in cancer cells

The Ca^{2+} acts as an important intracellular messenger because it is a bivalent molecule that has strong and specific binding to it receptor, and has an atomic radius that gives it ideal geometry for protein binding [28]. Usually, Ca^{2+} is stored in specific organelles, such as endoplasmic reticulum and mitochondria [9]. Indeed, intracellular Ca^{2+} 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 [for example plasma membrane Ca^{2+}-ATPase (PMCA), ER/SR Ca^{2+}-ATPase (SERCA), and golgi vesicles secretory pathway Ca^{2+}-ATPase (SPCA)]. In addition, the Ca^{2+} influx across plasma membrane occurs through voltage-activated Ca^{2+} channels (VACCs, also known as Cav family) 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) [29].

The release of Ca^{2+} from the endoplasmic reticulum 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 cell releases intracellular Ca^{2+} of their stocks by the activation of specific receptors (IP3R), which are localized in the cytoplasmic side of endoplasmic reticulum membrane [30]. 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 [31]. These mechanisms of influx, and efflux, of intracellular Ca^{2+} are dependent on Ca^{2+} transporters located mostly in the plasma membrane. Several Ca^{2+} channels, like Ca^{2+}-dependent voltage channels, are involved in the Ca^{2+} influx. However, these channels require depolarization of the plasma membrane, being more common on the surface of excitable cells, as cardiomyocytes [32]. Some of these Ca^{2+} channels, are members of the Cav3 subfamily activated by low voltage, are expressed on the surface of different cancerous cells [33], and

Ca^{2+} entry in non-excitable cells mostly occurs through non-voltage gated channels.

The non-voltage gated channels of Ca^{2+} associated with different types of cancer cells include: ligand-gated channels; receptor-operated channels (ROC) or secondary messenger-operated channels linked to GPCR activation [SMOC: Orai family and members of TRP (Transient Receptor Potential) superfamily of channels]; store-operated channels (SOCE: Orai family and members of TRPC (TRP Canonical) subfamily of channels); and stretch-operated channels (members of TRP superfamily of channels); plasma membrane Ca^{2+}-ATPase (PMCA); and Na+/Ca^{2+} exchanger [34].

Cellular proliferation depends on the cell cycle, which is dependent on Ca^{2+}. Cell proliferation, and cell division, depend on extracellular Ca^{2+}, and the increase in intracellular Ca^{2+} is involved in cell cycle progression, and proliferation [35]. The Ca^{2+} is required at the beginning of the G1 phase of the cell cycle, where activation of transcription factors like activator protein 1 (AP1), a transcription factor that regulates gene expression, and cellular processes differentiation, proliferation, and apoptosis; cAMP-responsive element binding protein (CREB) and the nuclear factor of activated T-cell (NFAT) [36].

The Ca^{2+} plays a key role in the expression of cell cycle regulators like the D-type cyclins, required for the activation of cyclin-dependent kinase 4 complexes, responsible of phosphorylation and inactivation of retinoblastoma gene, involved in the entry into S phase of cell cycle. The start of G1/S phase is dependent of Ca^{2+} calmodulin (CaM), and CaMkinase II (CaMK) [37]. Calcineurin, a Ca^{2+}-dependent phosphatase, plays a major role in progression of G1 and S phases, regulating cyclins A, D1 and E [37,38] and active NFAT, favoring the cell proliferation, through the activation of Ca^{2+} channels. The IP3Rs are the major channels of intracellular Ca^{2+} release in non-excitable cells, being activated in different types of cancer, such as gastric and colorectal cancer [39,40]. Making part of the Ca^{2+}-ATPases family, SERCA presents an altered expression in diferents cancers cells such as colon, gastric, lung, myeloid leukaemia and choroid plexus [41]. Altered expression of SPCA isoforms are expressed in breast, colon and prostate cancer [42], and altered expression of PMCA isoforms are expressed in breast cancer cells [43].

The non-voltage gated channels of Ca^{2+}, Orai and stromal interaction molecule 1 (STIM1), a Ca^{2+} sensor in the endoplasmic reticulum, present higher expression in glioblastoma [44], pancreatic adenocarcinoma [45], prostate cancer [46] and hepatocellular carcinoma [47]. The MCU is overexpressed in breast cancer cells [48]. Changes in expression of TRP channels, like TRPV1, TRPV2, TRPV6, TRPM8, TRPM2, TRPC6 [34], L-type calcium channel [49], and T-type Ca^{2+} channels [50,51] were observed in prostate cancer cells. Also, the expression of TRP channels TRPC1, TRPC3, TRPC6, TRPM7, TRPM8, and TRPV6 is altered in breast cancer [52], thyroid, colon and ovary cancer, with emphasis of TRPV6 [53,54]. In lung cancer cells the expression of TRPC1, TRPC3, TRPC4, TRPC6, TRPM7, and TRPM8 is altered [55]. During the process of metastasis, Ca^{2+} participles of invasion of health tissues by cancer cells, with involvement of voltage independent Ca^{2+} channels [56-58] in breast [59,60] and lung cancer cell [61].

Potential use of modulators of cyclical nucleotides or inhibitors of Ca^{2+} channels

The growing understanding of cancer biology has led to the development of new drugs for the treatment of cancer. However, a total beneficial effect of these agents has not yet been verified by the presence of intrinsic cancer cell resistance, the result of compensatory signaling pathways, or the development of acquired resistance through the evolution of cell clones by selective treatment pressures.

Recognizing the toxicity induced by the treatment and the inability to use high effective pharmacological doses in the treatment of cancer, we are exploring the combination of Ca^{2+} channel blockers and/or enhancer agents of cAMP, associated with chemotherapy, radiotherapy or immunotherapy.

Variations in expression of Ca^{2+} channels in cell cancer suggest that a decrease in Ca^{2+} channel expression, or Ca^{2+} influx, will lead to cell cycle arrest, inhibiting the process of invasion, metastasis, and recurrence of cancer. We also believe that increasing the cytosolic concentration of cAMP produced by the drug combination could simultaneously generate activation of the RAS (antitumor) mediated signaling pathway, and inhibition of the PKA (pro-tumor) pathway, favoring the host.

For example, new treatments of cancer involving the use of monoclonal antibodies against programmed death 1 (PD-1) receptor, and its PD-L1 ligand [62], presented promising results. PD-L1 is expressed in different types of cancer cells, such melanoma, lung, breast, ovaries, pancreas, esophagus, bladder and haematological tumors [63]. However, in spite of the positive results observed with the use of monoclonal antibodies against PD-L1/PD-1, recent studies have revealed an aggressive growth of tumors in a small portion of patients [64,65]. This process of tumor progression after immunotherapy has been described as being associated with amplification of MDM2/MDM4 genes [65]. The MDM2/MDM4 genes inhibit the p53 tumor suppressor gene [66]. Normally p53 is activated in response to DNA damage, or oncogene activation, which in turn starts mechanisms of apoptosis, cell-cycle arrest or modulation of autophagy.

Monoclonal antibodies against PD-1 can induce the increase synthesis of interferon gamma (IFN-γ) by T lymphocytes [67], which in turn activates JAK-STAT signaling [68] resulting in increase of interferon regulatory fator-8 (IRF8) expression [69]. Finally, the IRF8 binds to the MDM2 promoter inducing MDM2 higher expression [70] shown in **Figure 1A**.

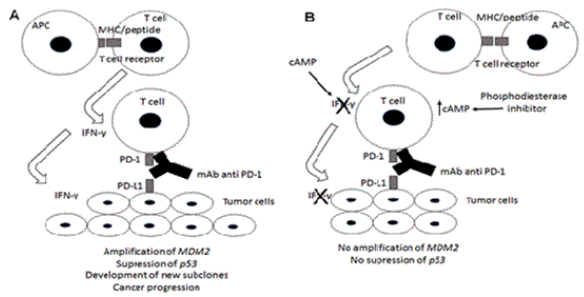

Figure 1 A. Monoclonal antibodies against PD-1 can induce the increase synthesis of IFN-γ by T lymphocytes, with increase of interferon regulatory fator-8 (IRF8) that binds to the MDM2 promoter inducing MDM2 amplification in tumor cells. This results in suppression of p53, with tumor growth and progression. B. The use of phosphodiesterase inhibitors promotes increase levels of cAMP, diminishing the production of IFN-γ, expression of IRF8 and MDM2 amplification. In turn, not occurring suppression of p53, or tumor growth and progression. APC=Antigen presenting cell; MHC=Major histocompatibility complex; mAB=Monoclonal antibody. **B.** Increase in the expression of MDM2.

Because the elevation of intracellular cAMP creates an oxidative environment that oxidizes and inactivates p56(lck) in lymphocytes by an H_2O_2 dependent, PKA-independent mechanism, and inhibits the production of IFN-γ by nitric oxide, PKA-dependent mechanism [71], the use of phosphodiesterase inhibitors can promote the increase levels of cAMP [72], hindering the production of IFN-γ, which would make difficult to increase the expression of IRF8, and increase in the expression of MDM2 shown in **Figure 1B**.

Thus, the combination of a phosphodiesterase inhibitor with anti-PD-1 monoclonal antibodies could prevent the emerging of new more aggressive tumor subclones.

This new pharmacological strategy could be extended not only for the use of modulators of cAMP, but also for inhibitors of Ca^{2+} channels. For example, it was described that the use of inhibitor of Ca^{2+}-dependent K^+ channels (TRAM-34) is able to block the growth of hepatocellular carcinoma [73]. Thus, the use of TRAM-34 may be associated with hepatic intra-arterial chemotherapy, allowing a minor concentration of the chemotherapeutic floxuridine [74] in the liver with a lower systemic toxic effect to the treatment of hepatic adenocarcinoma, primary or metastatic. Because the relevance of Orai1 and TRP channels in tumor neovascularization [75], blockers of these channels can diminish the adverses effects of treatment with ramucirumab, a monoclonal antibodies against vascular endotelial growth factor receptor 2 (VEGFR2), with anti-angiogenic effect used to the treatment of advanced gastric, gastro-oesophageal junction adenocarcinoma and non-small cell lung cancer (NSCLC), with the possibility of decreased toxicity, and adverses effects like neutropenia, febrile neutropenia and hypertension [76].

Conclusion

Thus, the use of modifiers of cAMP production may decrease the chance of developing intrinsic anti-tumor resistance, and the use of Ca^{2+} channel blockers may modify tumor growth, and also by reducing the adverse effects of chemotherapy, or immunotherapy.

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