A Novel Potential Therapeutic Target as Adjuvant Treatment for Cancer: The Pharmacological Interference on the Ca\(^{2+}\)/Camp Cellular Signaling Pathways

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Cancer is one of the leading causes of death worldwide: about 12.7 million people worldwide are diagnosed with cancer every year, and 7.6 million of the diagnosed patients die because of this disease. It is estimated that in 2030, there will be 26 million new cases, and 17 million deaths per year worldwide [1]. This number of deaths is two and a half times higher than the number of deaths worldwide caused by complications from HIV/AIDS, tuberculosis and malaria (all combined) [2]. The costs of cancer in global economy, including disability of patients, deaths and medical costs, are estimated at one trillion dollars [3], and approximately 57% of all types of cancer occur in developing countries and 43% in developed countries (excluding skin cancer) [4].

Nowadays, cancer treatment is performed through surgery, radiotherapy, chemotherapy or immunotherapy, and in many cases, it requires the combination of more than one modality of treatment [5]. Another important issue is the large number of untreated deaths, and also the pain affecting cancer patients, where most occur in developing countries [6,7]. A reduction in the annual worldwide incidence of cancer, and suffering from the disease, can be achieved by adopting: new therapeutic strategies, easy access to the treatment and lower costs. Thus, it is fundamental to understand the molecular, and cellular, mechanisms that govern the pathophysiology of cancer.

The calcium ion (Ca\(^{2+}\)) participates in numerous biological processes, and acts as an intracellular signalling messenger, controlling gene transcription, proliferation, differentiation and cell death. Intracellular levels of Ca\(^{2+}\) are regulated by plasma membrane transporters that control the influx, and efflux of Ca\(^{2+}\). Organelles, such as endo/sarcoplasmic reticulum, and Golgi complex, also regulate the intracellular levels of Ca\(^{2+}\) [8]. Since tumor cells preferentially produce energy by anaerobic glycolysis in detrimental of mitochondrial oxidative phosphorylation process, it is necessary to pump larger amounts of Ca\(^{2+}\) into the intracellular compartment [9]. This can occur through the quantitative, and qualitative, alteration of Ca\(^{2+}\) channels and pumps in tumor cells, as transient receptor potential channels in tumors of breast, lung, liver, prostate, pancreas, colon and ovary; voltage-gated calcium channels in colon and prostate tumors; store-operated Ca\(^{2+}\) channels in breast tumors; plasma membrane Ca\(^{2+}\)- ATPases in breast and colon tumors; and store release channels in tumors of central nervous system and colorectal [10].

Another important molecule in the transduction of intracellular signals is cyclic adenosine 3', 5'-monophosphate (cAMP), which it is formed from the adenosine triphosphate (ATP), catalyzed by the enzyme adenyl cyclase. The intracellular cAMP can activate the cAMP-dependent protein kinase, capable of phosphorylating numerous proteins, directly or indirectly controlling different cellular processes [11]. The cAMP activates protein kinase A (PKA), which alters the activity of target proteins by phosphorylating specific groups of serine and threonine. The PKA can recruit Ras protein, capable of hydrolyzing a GTP molecule in GDP [12]. The Ras-GTP combination becomes active, and propagates a cascade signal that leads to cell proliferation. Mutations of RAS gene can lead to inhibition of GTP hydrolysis by Ras proteins, causing the mutated Ras proteins reaming continuously in the active form bound to GTP, leading to disordered proliferation of tumor cells, even in the absence of stimulation by growth factors [13], such as epidermal growth factor (EGF), neuronal growth factor (NGF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) [14]. Activation of the mutated RAS gene...
may be associated with alterations in the regulation of the Ca\(^{2+}\) and cAMP signaling pathways [15], and different tumors are associated with the Ras mediated signaling pathway [16,17]. Once the use of Ca\(^{2+}\) channels blockers [18] and phosphodiesterase inhibitors (alone or in combination with other drugs) [19,20] for the treatment of cancer presents significant pre-clinical results, our proposal is to pharmacologically modulate the intracellular levels of Ca\(^{2+}\) and cAMP signaling pathways in tumor cells [8], pathways that are altered in relation to healthy cells. Thus, we believe that combining this new strategy of treatment with existing antitumoral therapies may lead to reduce tumor progression, toxicity and costs of treatment.

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