



The Pharmacological Modulation of Ca²⁺/Camp Intracellular Signaling Pathways and Traditional Antitumoral Pharmaceuticals: A Plausible Multitarget Combined Therapy?

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Introduction

Cancer is a major public health issue worldwide, affecting both developed and developing countries, thus leading to the rise of a large annual expenses every fiscal year [1]. Surgery, radiotherapy, chemotherapy, immunotherapy and multitarget pharmaceutical therapies are the current strategies for cancer treatment. Generally, cancer treatments are based on the clinical history of the patients, including histological type and the presence of molecular biomarkers [2]. Nonetheless, new options are clearly needed to increase survival and improve the patients' quality of life, especially for those in advanced stages of this disease. Thus, the increased knowledge of the mechanisms responsible for growth, invasion and metastasis of cancer, including development of intrinsic resistance, is critical.

Calcium (Ca²⁺) is an ion that acts as an important intracellular second messenger. Since tumor cells have a higher metabolic and mitotic rate (compared to healthy cells), different amounts of intracellular Ca²⁺ are required in the process of genomic stability and cell survival; including telomerase activity, genic transcription, control of cell cycle, oncogenes regulation, inhibition of apoptosis, cell motility, tumor invasion, metastasis and angiogenesis [3]. Thus, the developing of tumor cells may present a quantitative and functional alteration of channels that regulate Ca²⁺ influx through plasma membrane, such as transient receptor potential channels, TRPC, e.g. TRPC-1, TRPC-3, TRPC-6, TRPM-7, TRPM-8, TRPV-1, TRPV-6; voltage-gated Ca²⁺ channels, such as Cav, e.g. Cav1.2, Cav3.2; and store-operated Ca²⁺ channels, e.g. ORAI1, ORAI3; or regulators of Ca²⁺ efflux through the plasma membrane, such as Na⁺/Ca²⁺ and plasma membrane Ca²⁺-ATPases, PMCA, e.g. PMCA2, PMCA4 [4]. In addition, dysfunction of intracellular organelles may play a critical role in the regulation of cytosolic Ca²⁺, and Ca²⁺

regulatory proteins, such as store release channels, e.g. IP₃R1, IP₃R3; sarcoplasmic/endoplasmic reticulum Ca²⁺-ATPases, SERCA, e.g. SERCA2, SERCA3; and secretory pathways Ca²⁺-ATPases, SPCA, e.g. SPCA1, SPCA2 [5].

Besides Ca²⁺, cyclic adenosine monophosphate (cAMP) is a nucleotide that acts as a second messenger in several biological processes, such as in cell signal transduction pathways in response to an external, or internal, stimulus, including post-translational regulation [6]. Also, cAMP can be associated with activation of protein kinases [7]. The dysregulation of cAMP-mediated intracellular pathways may compromise modulation of cAMP-controlled transcriptional factors [8] and genes associated with the growth of different kinds of cancer [9-11].

Considering that Ca²⁺ and cAMP signaling pathways may interact in an inversely-operated manner in tumors (e.g. less Ca²⁺, more cAMP production), our proposal is to reduce Ca²⁺ levels and to increase cAMP levels within tumor cells, limiting the process of tumor progression and heterogeneity [12]. This strategy, combined with chemotherapy, radiotherapy and immunotherapy may decrease the toxicity, and deleterious effects, of current antitumoral therapies. In conclusion, this would lead to achieve lower treatment costs, increasing adherence rate, decreasing dropout rate and increasing overall survival of cancer patients.

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