Store-Independent Calcium Entry

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Calcium is recognized as a universal intracellular second messenger involved in a plethora of physiological as well as physiopathological processes, such as cell proliferation, migration, invasion, apoptosis, and chemoresistance in a cancer situation. Store-independent calcium entry is a distinctive calcium entry in cells, which is not activated by calcium store depletion. This entry is supported by basal activated calcium channels, ligand-activated calcium channels, or voltage-gated calcium channels.

Keywords: calcium channels ; basal calcium entry ; Orai-K channel complex ; transient receptor potential channels ; voltage-gated calcium channels ; breast cancer

1. Introduction

Cancers are a major public health problem due to their incidence and, more particularly, their mortality. Among all cancers, breast cancer (BC) is one of the most diagnosed in the world. Despite significant discoveries in treatment, some BC are currently incurable. Thereby, we still need to identify targets to treat BC. In recent years, a research field has developed around the role of ion channels and their implication in tumor progression [1]. The involvement of ion transporters in tumor development could thus classify cancers as onco-channelopathies [2]. Furthermore, several studies reported the involvement of calcium (Ca 2+) channels in almost all hallmarks of cancer [3]. Research on BC has shown the involvement of a certain number of proteins related to its development and progression. It has also been found that Ca 2+ -regulating proteins are key effectors in BC. Indeed, Ca 2+ is recognized as a universal intracellular second messenger involved in a plethora of physiological as well as physiopathological processes, such as cell proliferation, migration, invasion, apoptosis, and chemoresistance in a cancer situation [4][5].

2. Orai Channels

Orai channels play distinct roles in different BC subtypes [6]. Two isoforms (Orai1 and Orai3) in particular have been found overexpressed in BC. Regarding Orai3, it was found overexpressed in 76.9% of 13 tested BC samples when compared to non-tumoral breast ones [7]. In addition, a positive correlation between Orai3 and the c-Myc proto-oncogene transcriptional expression in BC tissues has also been reported [8]. By analyzing Orai3 in clinical BC samples through the analysis of a public dataset, Hasna et al. proposed Orai3 as a predictive marker in the resistance to chemotherapeutic drugs [9]. Subsequently, a study conducted by Azimi et al. reported a sensitivity of Orai3 to hypoxia [10]. They observed an increase in Orai3 expression in response to hypoxia in both basal and luminal types of BC cells, and identified hypoxia and hypoxia-inducible factor 1 α (HIF1α) as critical regulators of Orai3 expression in these types of cell lines [10]. Finally, Orai3 transcriptional expression is regulated via the expression of micro-ribonucleic acid (miRNA). Indeed, it has been shown that miR34A and miR18A/B inhibit and activate Orai3 expression, respectively [11]. On the other hand, Orai1 was found expressed in the mammary gland and its expression increased during lactation assuming the trans-epithelial Ca 2+ transport [12]. Orai1 was also found up-regulated in BC cell lines and is particularly highly expressed in basal subtype cells where it regulates migration [10][12][13].

Orai1 is the most studied channel among the store-operated channels (SOC). Some studies have shown a modulation of the Ca 2+ entry through Orai1, which does not depend on the Ca 2+ store depletion. Indeed, in 2010, Feng et al. demonstrated another mode of activation of the Orai1 channels [14]. In luminal ER + cells, Orai1, which is activated independently from STIM1, regulates basal Ca 2+ entry and Ca 2+ homeostasis. This mechanism involves the SPCA2 pumps initially located in the Golgi apparatus [14]. It has been demonstrated by co-immunoprecipitation and pull-down techniques that SPCA2 via its amino-terminus (N-ter) physically interacts with Orai1 at the level of the plasma membrane, which results in the activation of Orai1 by SPCA2 carboxyl-terminus (C-ter) and thus in an increase in the basal Ca 2+ concentration [14]. Interestingly, the SCPA2/Orai1 coupling has also been shown in a cell model of lactation. Indeed, SPCA2 and Orai1 were found co-localized in mouse lactating glands and participate in a SICE to support lactation [15].

Therefore, it seems that BC cells redirect this SPCA2-dependent Orai1 activation to acquire cancer capacities. SICE induced by the Orai1/SPCA2 coupling has also been shown in the MCF-7 cell line, where it regulates cell proliferation [14]. Moreover, our team reported that SPCA2 also constitutes a complex with Kv10.1 potassium (K +) channels in ER + cell lines and allows its trafficking from the Golgi to the plasma membrane [16]. Both SPCA2 N-ter and C-ter are involved in this trafficking [17]. Indeed, in MCF-7 cells, SPCA2 regulates the localization and the activity of both Kv10.1 and Orai1 channels, mediating a SICE able to sustain channel membrane localization and Erk1/2 phosphorylation, and to promote cell survival in a collagen environment [16][18].

For both of these channels, it has been found that Orai1 was the main actor in the constitutive Ca 2+ entry in BC. In fact, both Kv10.1 and SK3 functionally regulate the Ca 2+ entry through Orai1 leading the cell migration regulation. Indeed, Kv10.1 was observed expressed alongside Orai1 in invasive breast tumors and lymph node metastasis, and regulates cell migration through an Orai1-dependent constitutive Ca 2+ entry [19]. On the other hand, it has been shown that SK3 knockdown inhibits BC bone metastasis [20]. This process is explained by the fact that, in the basal MDA-MB-435S cell line, Orai1 is recruited with SK3 to the lipid rafts, and following the SK3-dependent hyperpolarization, Orai1 is activated in a store-independent manner. Moreover, the same team showed an involvement of the SigmaR1 protein in the activity and localization of SK3 in lipid rafts [21]. The SICE through Orai1 activates the calpain leading to cell migration in the MDA-MB-435S cell line [20][21].

3. TRP Channels

In addition, it has also been shown that the TRPC1 channel expression is regulated via activation of the calcium-sensing receptor (CaR) [22]. Indeed, the activation of CaR by extracellular Ca 2+ (up to 10 mM) increases TRPC1 expression, via the phospholipase C (PLC) and Erk1/2 pathway in MCF-7 cells [22][23][24]. Furthermore, TRPC1 is required for Erk1/2 phosphorylation and Ca 2+ entry, and also for the proliferative effect induced by the activation of CaR. Moreover, the involvement of TRPC1 in the CaR-induced proliferation has been suggested [22].

The melastatin family of TRP channels is also a well-known regulator of carcinogenesis processes. For example, our team showed that TRPM7 is a key regulator in BC progression. It participates in cell proliferation as well as cell migration and invasion [25][26][27]. First, it has been found that TRPM7 silencing decreases the constitutive Ca 2+ entry and hence the cell viability [25]. Guilbert et al. established that TRPM7 basal activity regulates ER + BC cell line progression. In addition, they demonstrated that TRPM7 silencing decreased both Ca 2+ entry and MCF-7 cell line proliferation [25]. However, it has been shown that TRPM7 regulates MDA-MB-231 cell line migration via its catalytic kinase domain, and not through its channel activity, by regulating the myosin II-based cytoskeletal tension and thereby SRY-Box transcription factor 4 (SOX4) [26][28][29]. Furthermore, research work on the MDA-MB-435S cell line showed that TRPM7 knockdown decreases both cell migration and invasion following a decrease in the MAPK protein phosphorylation [27]. However, this study does not show a direct channel activation of TRPM7, particularly when TRPM7 presents a kinase-type catalytic domain [27].

Another TRPM family member, the Ca 2+ -permeable TRPM8 channel, was found as a regulator of BC processes. This channel was shown to be activated in BC cells and associated with an elevation of cytosolic Ca 2+ concentration following the application of icilin (TRPM8 agonist) [30]. However, the estrogen status does not seem to be involved in the TRPM8 activation state since 17β-estradiol increased TRPM8 mRNA expression but failed to affect the Ca 2+ entry [30]. Moreover, it has been shown that TRPM8, following menthol or icilin activation, regulates BC cell proliferation and migration via activation of AMP-activated protein kinase–Unc-51 like autophagy activating the kinase 1 (AMPK-ULK1) signaling pathway, suggesting that TRPM8, by regulating the autophagy, leads the proliferative and migratory processes [31].

4. Voltage-Gated Calcium Channels

A number of studies have focused on the role of VGCC, which could be activated under normal cell culture conditions. Indeed, the resting membrane potential, measured by whole-cell patch-clamp technique, varies from −40 to −20 mV in BC cell lines [32][33][34]. The opening of VGCC at rest allows, therefore, a basal Ca 2+ entry. Some VGCC see their expression and activity being altered in BC. This is the case in T-type Ca 2+ channels, such as Cav3.1, Cav3.2, which are overexpressed in BC tissue [35][36]. Indeed, through an experimental and informatic study using microarray analysis, it has been found that certain L-type channels, such as Cav1.2 and Cav1.3, seem to be overexpressed in different types of cancer, including BC, and participate in inward Ca 2+ entry following melatonin and 5α-dihydrotestosterone perfusion [37][38][39].

L-type VGCC were found to be active at a basal level and regulated by the L-type voltage-gated calcium channel γ 4 subunit (CACNG4) [40]. CACNG4 modulates L-type VGCC basal activation, and thereby the downstream processes. This subunit has been found to be involved in BC cell proliferation, motility, and adhesion. Its silencing reduced these cellular

processes and its overexpression increased the metastasis to the lungs in vivo. Treatment with L-type channels antagonists Verapamil and Amlodipine decreased the MCF-7 and MDA-MB-231 cell proliferation. It has also been shown that CACNG4 silencing led to an increase in Ca 2+ entry. However, the application of L-type channel antagonists decreased Ca 2+ entry. These results suggested that CACNG4 subunit regulates the channel in an active state resulting in the higher intracellular Ca 2+ concentration leading in fine to the inhibition of processes such as cell proliferation, motility, and adhesion [40]. Moreover, L-type VGCC are involved in BC cell invasion [41]. The activation of the L-type Ca 2+ channel with a specific agonist BAY K8644 leads to an increase in the intracellular Ca 2+ concentration responsible for filopodia stability. Indeed, treated cells with L-type channels pharmacological blockers, such as amlodipine besylate, felopidine, manidipine dichloride, and cilnipidine, lose their stable filopodia. Furthermore, it has been shown in the same study that integrin activation promotes filopodia formation through the proto-oncogene tyrosine-protein kinase Src signaling pathway, calpain activity, as well as a Ca 2+ entry at the filopodia level. In addition, the L-type Ca 2+ channel seems to be colocalized with myosin X (MYO10) within filopodia [41].

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