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Mini-review

Cell proliferation, calcium influx and calcium channels

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ABSTRACT

Both increases in the basal cytosolic calcium concentration ($[Ca^{2+}]_{cyt}$) and $[Ca^{2+}]_{cyt}$ transients play major roles in cell cycle progression, cell proliferation and division. Calcium transients are observed at various stages of cell cycle and more specifically during late G_1 phase, before and during mitosis. These calcium transients are mainly due to calcium release and reuptake by the endoplasmic reticulum (ER) and are observed over periods of hours in oocytes and mammalian cells. Calcium entry sustains the ER Ca^{2+} load and thereby helps to maintain these calcium transients for such a long period. Calcium influx also controls cell growth and proliferation in several cell types. Various calcium channels are involved in this process and the tight relation between the expression and activity of cyclins and calcium channels also suggests that calcium entry may be needed only at particular stages of the cell cycle. Consistent with this idea, the expression of L-type and T-type calcium channels and SOCE amplitude fluctuate along the cell cycle. But, as calcium influx regulates several other transduction pathways, the presence of a specific connection to trigger activation of proliferation and cell division in mammalian cells will be discussed in this review.

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1. Introduction

About 40 years ago, several scientists have established that external calcium controls cell division and proliferation [1,2]. Since then, the involvement of calcium channels in normal and pathological proliferation has been investigated [3] but there are two important points which can be emphasized in these early studies. First, they showed that low concentrations of external calcium, well below physiological levels, can trigger cell proliferation [2,4]. Cells proliferate maximally in the presence of as little as 50–100 μM free calcium. Second, transformed cells have a much lower sensitivity to external calcium [3,5,6] and proliferate even in the presence of 20 μM external calcium. Therefore, the role of calcium channels and calcium influx in cell proliferation can be questioned. Although voltage-dependent calcium channels are mentioned throughout, this review is mainly focused on calcium channels, such as Orai1, Orai3 and TRPC, involved in capacitative (SOCE) and non capacitative (NCCE) calcium entries as described previously [7–9].

2. Calcium channels blockers and cell proliferation inhibition

One of the major arguments in favour of a role of calcium influx in cell proliferation comes from the use of calcium channels blockers. Drugs used to block L- and T-type voltage-dependent, SOCE or NCCE channels have potential antiproliferative effects in several tissues. The list of blockers includes verapamil, diltiazem, nifedipine, amlodipine, mibefradil, TH-1177, 2-APB, SK&F 96365 and carboxyamidotriazole (CAI) [10–16]. None of these drugs are clearly specific to one type of channel but they all emphasize the role of calcium channels in the control of cell proliferation. There are found on almost all cell types and therefore may have to adapt their modes of activation when expressed in different cell types. For example, lymphocytes, prostate and breast cancer cells are not known to spontaneously depolarize but nevertheless they express functioning voltage-dependent calcium channels [15,17,18]. Alternative activation mechanisms are therefore needed in some cells to account for the sustained calcium entry regulating cell proliferation.

Abbreviations: 2-APB, 2-Aminoethoxydiphenyl borate; CAI, carboxyamidotriazole; ER, endoplasmic reticulum; DMEM, Dulbecco's modified Eagle's medium; RPMI, Roswell Park Memorial Institute medium; TRPC, Transient Receptor Potential Canonical; SOCE, Store-Operated Calcium Entry; NCCE, Non Capacitative Calcium Entry; Icrac, calcium release activated current; STIM, Stromal Interaction Molecule; SERCA, sarco-endoplasmique reticulum Ca^{2+}–Mg^{2+}–ATPase.

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3. Constitutive calcium influx and cell proliferation

SOCE activation is a complex sequence of events involving Orai1 and Orai3 on the plasma membrane and STIM1 and STIM2 on the ER membrane. This sequence described elsewhere is triggered by ER Ca^{2+} depletion [9,19]. In physiological conditions, calcium store depletion mainly results from InsP3 or RyR receptors stimulation [20] and ER Ca^{2+} content decrease below threshold triggering STIM1 oligomerization, the first event of the sequence leading to SOCE activation [21]. However, constitutive activation of Icrac could occur through several mechanisms. Mutations in the EF hand domain that abrogate Ca^{2+} binding ability render STIM1 constitutively active, behaving as if ER stores were constantly depleted [22,23]. Biophysical studies have shown that STIM2 has a slightly lower affinity for Ca^{2+} than does STIM1 (400 μM for STIM2 versus 200 μM for STIM1), and STIM2 EF-SAM domain monomers are more stable than the equivalent STIM1 monomers in the absence of Ca^{2+}, with a lower tendency for aggregation, particularly at low protein concentrations [24,25]. Cells overexpressing STIM2 have increased resting intracellular Ca^{2+} levels, which can be blocked by SOC channel inhibitors [26], and STIM2 knockdown, but not STIM1 knockdown, significantly lowered basal cytosolic Ca^{2+} in HeLa, HUVEC, and HEK293T cells [27]. This is indeed consistent with STIM2 mediating the persistent signalling of SOC channels at a low level of ER Ca^{2+} depletion. STIM2 functional role remains unclear but some studies showed that STIM2 functions as STIM1 to activate SOCE [28–30] and others reported that STIM2 inhibits SOCE [31]. Both constitutive Ca^{2+} entry and SOCE mediated by STIM2 appear to occur through ORAI channels because STIM2 interacts with ORAI1, 2 and 3 [26]. Finally, any physiopathological conditions resulting in a decreased ER Ca^{2+} content [32] could activate constitutive SOCE, unless compensating mechanisms are present to counteract this Ca^{2+} depletion. Evidence for ER Ca^{2+} depletion during cell cycle is sparse. Calcium transients have been measured in eggs and oocytes during cell cycle [33] but in mammalian cells, studies are often restricted to mitosis [34,35]. Hence, it is not clearly known whether cytosolic free calcium increase and ER Ca^{2+} depletion are happening during the different cell cycle phases when cells are free to cycle and not released from any kind of cell cycle block.

Another mean to record constitutive calcium influx in cancer cells comes from the relative wide expression of voltage-dependent T-type channels in these cells [36]. The unique low voltage dependent activation/inactivation and slow deactivation of T-type Ca^{2+} channels indicate that these channels may play a physiological role in carrying depolarizing current at low membrane potentials. Therefore, these channels may play a direct role in regulating $[Ca^{2+}]_i$, especially in non-excitable tissues, including some cancerous cells. At low voltages, T-type Ca^{2+} channels are known to mediate a phenomenon known as “window current” [37]. The term “window” refers to the voltage overlap between the activation and steady state inactivation at low or resting membrane potentials. As a result, there is a sustained inward calcium current carried by a small portion of channels that are not completely inactivated. Window current allows T-type Ca^{2+} channels to regulate Ca^{2+} homeostasis under non-stimulated or resting membrane conditions [38].

4. Cell cycle, calcium influx and membrane potential

This window current is either active at resting membrane potential or can be activated when membrane potential is shifted to the right range of potential, by means of activating other ionic channels (Fig. 1A). Briefly, K^+, Na^+ and Cl^- channels expression and membrane potential are modified in cancer cells [39,40]. Interestingly, plasma membrane is hyperpolarized in G1 and S phases and depolarized in G2/M phase. Hyperpolarization is mainly resulting

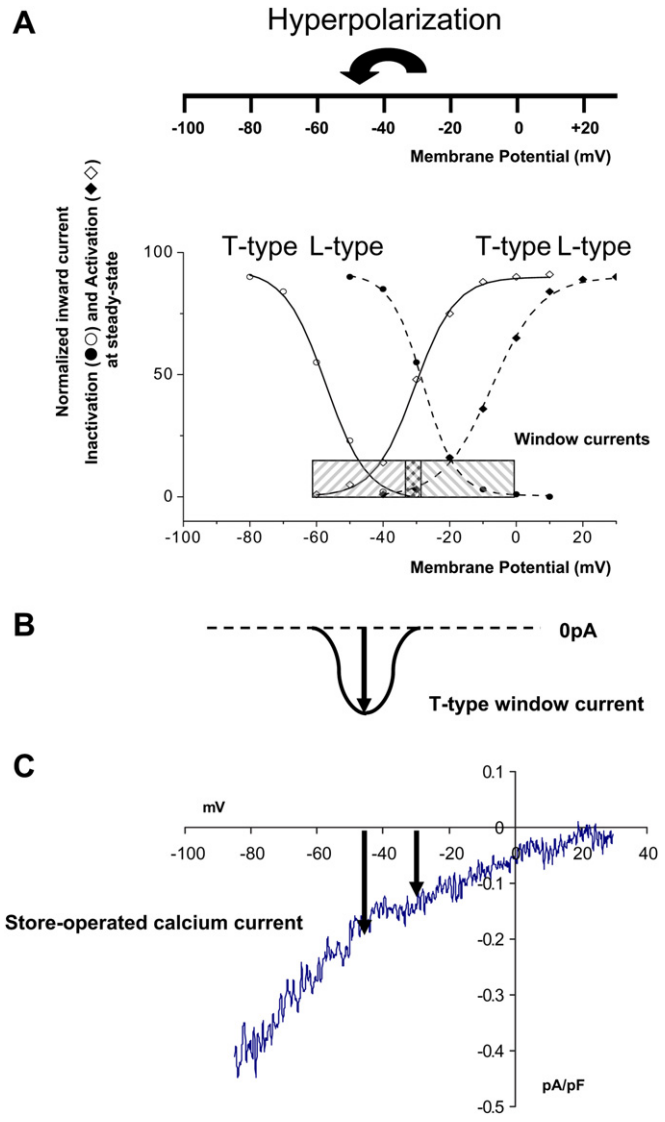

Fig. 1. Effects of a hyperpolarizing potential jump from −30 to −45 mV. A) T-type (right hatched) an L-type (left hatched) window currents at steady-state. Window currents range of potential approximately between −60 and −30 mV and between −35 and −5 mV for T-type (solid line) and for L-type (dash line) channels respectively. B) Window inward calcium current for T-type calcium channels evoked by the jump in membrane potential. C) Typical store-operated calcium currents with arrows indicating the increase in inward current induced by the potential jump.

from opening and/or increased expression of K^+ channels. This could lead to an increase in cytosolic free calcium concentration resulting from an increase in the window calcium current in a similar manner as myoblasts differentiation [41]. This indeed could be associated to a change in T-type channels expression in transformed cells [36].

This pattern also works for SOCE and NCCE channels (Fig. 1B). They both are activated at all potential and show strong inward rectification [42,43]. A constitutive calcium entry should therefore very sensitive to changes in membrane potential to more negative values (Fig. 1B). The changes in membrane potential measured during cell cycle should increase calcium influx in G1-S phases and reduce it in G2/M.

Constitutive Ca^{2+} entry also can activate Ca^{2+}-dependent K^+ channels [44] which will further hyperpolarize membrane potential with different outcomes, an increase in influx for SOCE and NCCE channels and a possible exit from the window for voltage-dependent calcium channels. The presence of both L-type and

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