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## Calcium signaling: a therapeutic target in cancer chemoresistance

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### Abstract

Innate and acquired resistances to therapeutic agents are responsible for the failure of cancer treatments. Due to the multifactorial nature of resistance, the identification of new therapeutic targets is required to improve cancer treatment.

Calcium is a universal second messenger that regulates many cellular functions such as proliferation, migration, and survival. Calcium channels, pumps and exchangers tightly regulate the duration, location and magnitude of calcium signals. Many studies have implicated dysregulation of calcium signaling in several pathologies, including cancer. Abnormal calcium fluxes due to altered channel expression or activation contribute to carcinogenesis and promote tumor development. However, there is limited information on the role of calcium signaling in cancer resistance to therapeutic drugs. This review discusses the role of calcium signaling as a mediator of cancer resistance, and assesses the potential value of combining anticancer therapy with calcium signaling modulators to improve the effectiveness of current treatments.

## Introduction

Standard chemotherapy is a class of cytotoxic drugs formulated to fight against the proliferation, invasion and metastasis of cancer cells. The interaction of chemotherapeutic drugs with either DNA or proteins alters or halts cellular functions and induces cell death, mainly by apoptosis <sup>[1]</sup>. Cytotoxic agents, like alkylating agents (nitrogen mustards, ethylenamine and methylenamine derivatives, alkyl sulfonates, nitrosoureas, triazines or platinum-containing antineoplastic agents), stabilizers of DNA cuts (topoisomerase inhibitors, including anthracycline) or antimetabolites (5-fluorouracil) interfere with DNA or its synthesis to prevent proliferation. Mitotic spindle poisons (vinca alkaloids or taxane) act on the cytoskeleton, particularly tubulin. Hormonal therapy, signal transduction inhibitors, proteasome inhibitors (bortezomib, carfilzomib) or differentiation agents act on cell proliferation, cell survival or cell differentiation. Antibodies used in immunotherapy, like rituximab (anti-CD20), target specific proteins of cancer cells to inhibit their signaling pathways. Combining chemotherapeutic agents increases treatment response efficacy, but a vast majority of cancer cells develop chemoresistance <sup>[2]</sup>. Decreased treatment effectiveness or resistance to treatment is the consequence of two distinct mechanisms: the intrinsic resistance of cells to therapeutic agents, which precedes exposure to the drugs, and drug resistance acquisition, which requires prior exposure to drugs. Several studies have documented the role of mutations in tumor suppressor genes or proto-oncogenes as drivers of chemoresistance. In addition, DNA damage repair and alteration of mitochondrially controlled survival or cell death are critical for chemoresistance <sup>[2]</sup>.

Calcium ( $\text{Ca}^{2+}$ ) is a ubiquitous intracellular second messenger that controls a variety of cellular functions such as cell differentiation, migration, proliferation, exocytosis, contraction, metabolism and gene expression <sup>[3-6]</sup>. At the plasma membrane,  $\text{Ca}^{2+}$  signals are modulated by voltage-gated  $\text{Ca}^{2+}$  channels (VGCC),  $\text{Ca}^{2+}$  release-activated calcium channels (CRAC), transient receptor potential channels (TRP) and  $\text{Ca}^{2+}$  pumps and exchangers. VGCC are mostly found in excitable cells (neurons and muscle cells) and are responsible for  $\text{Ca}^{2+}$  entry activated by plasma membrane depolarization. In non-excitabile cells,  $\text{Ca}^{2+}$  entry is typically triggered by activation of G protein coupled receptors (GPCR) or receptor tyrosine kinases (RTKs). Stimulation of these receptors, which couple to isoforms of phospholipase C (PLC), results in the production of 1,4,5-trisphosphate ( $\text{IP}_3$ ) and diacylglycerol (DAG).  $\text{IP}_3$  triggers  $\text{Ca}^{2+}$  release from the endoplasmic reticulum (ER) through  $\text{IP}_3$  receptors ( $\text{IP}_3\text{R}$ ) and consequently depletes ER  $\text{Ca}^{2+}$  stores. This store depletion activates store-operated  $\text{Ca}^{2+}$  entry (SOCE) mediated by CRAC channels. In some instances, DAG activates store-independent  $\text{Ca}^{2+}$  entry channels (SICE) encoded by canonical TRP (TRPC) channels. DAG can also be enzymatically converted into arachidonic acid, which activates the store-independent arachidonate-regulated  $\text{Ca}^{2+}$  (ARC) channels.

The plasma membrane  $\text{Ca}^{2+}$  ATPase (PMCA) and the sodium-calcium exchanger (NCX) are responsible for discontinuation of  $\text{Ca}^{2+}$  signals by extruding  $\text{Ca}^{2+}$  from the cytosol to the external space [7–10].

Intracellular organelles, including the ER and mitochondria, are major intracellular reservoirs of  $\text{Ca}^{2+}$ . In addition to IPR, ryanodine receptors (RyR) are involved in  $\text{Ca}^{2+}$  release from ER, while ER  $\text{Ca}^{2+}$  uptake is mediated by the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) [11]. The voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane and the mitochondrial calcium uniporter (MCU) on the inner mitochondrial membrane are responsible for  $\text{Ca}^{2+}$  uptake into the mitochondria, while the mitochondrial  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCLX) and the mitochondrial  $\text{H}^+/\text{Ca}^{2+}$  antiporter (LETM1) mediate mitochondrial  $\text{Ca}^{2+}$  extrusion [11,12]. Over the last decade, it has become evident that  $\text{Ca}^{2+}$  channels and transporters act as novel regulators of specific steps in tumor progression.

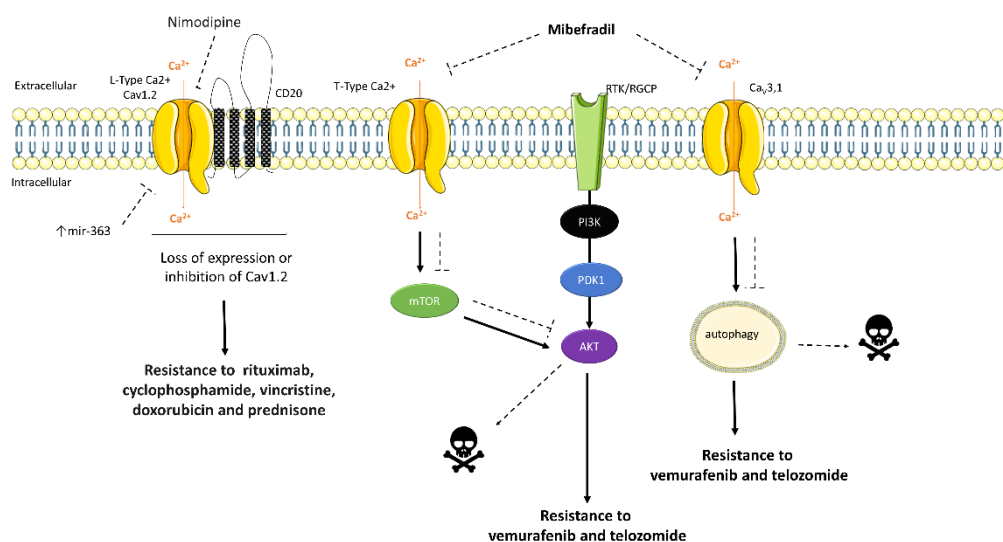
$\text{Ca}^{2+}$  signaling is a critical regulator of many cancer hallmarks, such as angiogenesis, invasiveness and migration [13]. Several studies have documented the role of VGCC-dependent entry, SOCE, SICE and  $\text{Ca}^{2+}$  exchangers in cancer cell proliferation, migration and invasion [14–25].  $\text{Ca}^{2+}$  transfer between the ER and mitochondria is also involved in cancer aggressiveness [26]. In the ER,  $\text{IP}_3\text{R}$ , RyR and SERCA expression are altered in cancer cells [27–34]. MCU complex and its regulators, the mitochondrial  $\text{Ca}^{2+}$  uptake 1 and 2 (MICU1 and MICU2) and EMRE, a metazoan specific subunit, are dysregulated in hepatocellular carcinoma, breast, pancreatic and colorectal cancers [35–39]. NCLX, the major extrusion mediator of mitochondrial matrix  $\text{Ca}^{2+}$ , has recently been shown to be involved in colorectal cancer [40]. While evidence indicates that  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$  signalling in general play a vital role in cancer [41], their role in chemoresistance is less understood. In this review, we aim to provide an overview of the literature on the involvement of  $\text{Ca}^{2+}$  channels in cancer chemoresistance.

## Plasma membrane $\text{Ca}^{2+}$ fluxes

### a) Voltage-gated $\text{Ca}^{2+}$ channels (VGCC)

VGCC, also known as  $\text{Ca}_v$ , are implicated in  $\text{Ca}^{2+}$  influx controlled by plasma membrane depolarization. The diverse  $\text{Ca}_v1$ ,  $\text{Ca}_v2$  and  $\text{Ca}_v3$  subunits are related to six  $\text{Ca}^{2+}$  current signatures (L-, N-, P-, Q-, R- and T-type  $\text{Ca}^{2+}$  channels) and are largely active in excitable cells [7]. Nevertheless, VGCC have also been detected in normal and malignant non-excitable cells [42]. In 2015, a meta-analysis described VGCC channel for mRNA in different types of cancer. The results indicated that VGCC mRNA are up-regulated in cancer samples compared to normal tissues [43]. In addition, it would appear that the  $\alpha 2\delta 1$  subunit of VGCC is a marker of cancer stem cells, and likely contributes to chemoresistance [44].

The T-type ( $Ca_v3$ ) and L-type  $Ca^{2+}$  ( $Ca_v2$ ) channels are the two main kinds of VGCC aberrantly expressed in different cancers and involved in chemoresistance process [43]. A significant inverse correlation was observed between L-type  $Ca_v1.2$  expression and multidrug resistance in two independent diffuse large B-cell lymphoma (DLBCL) cohorts. In DLBCL rituximab-resistant patients, a decrease of mRNA and protein expression of  $Ca_v1.2$  is associated with a lower CD20 stability compared with rituximab-sensitive patients [45]. Zhang et al. demonstrated that  $Ca_v1.2$  expression is directly regulated by miR-363, whose high expression is associated with worse prognosis in DLBCL. VGCC agonists and antagonists support the participation of these channels in cancer cell lines viability [46–48]. The combined use of rituximab and an agonist of the L-type calcium channel, Bay K8644, significantly increases apoptosis processes in DLBCL cell lines and markedly reduces tumor volume *in vivo* [45]. Administration of mibefradil or silencing of T-type calcium channels reduces glioblastoma cell growth (U251, U87 and T98G), and increases apoptosis by decreasing surviving expression and AKT phosphorylation [49].  $Ca_v3.1$  is associated with increasing autophagy and viability in vemurafenib-resistant melanoma cells with a BRAF V600E mutation. The T-type calcium channel blocker mibefradil reduces autophagy as well as cell viability, migration and invasion [50]. Interestingly, this information confirms results from Mickisch et al. (1990), which demonstrated that the treatment of multidrug-resistant nephrotic patients' tumors with chemotherapy and calcium channel blockers (verapamil, diltiazem, flunarizine, nifedipine, and its derivatives nimodipine and nitrendipine) reduced tumor viability compared to samples that had been exposed to chemotherapy alone [51] (Fig.1). We will discuss further the therapeutic potential of VGCC inhibitors in the fight against cancer cell chemoresistance.



**Fig.1: Voltage-Gated- $Ca^{2+}$  channels are associated to survival of chemoresistant cells  $Ca_v1.2$  downregulation by miR-363 contributes to drug resistance in diffuse large B-cell lymphoma. In**

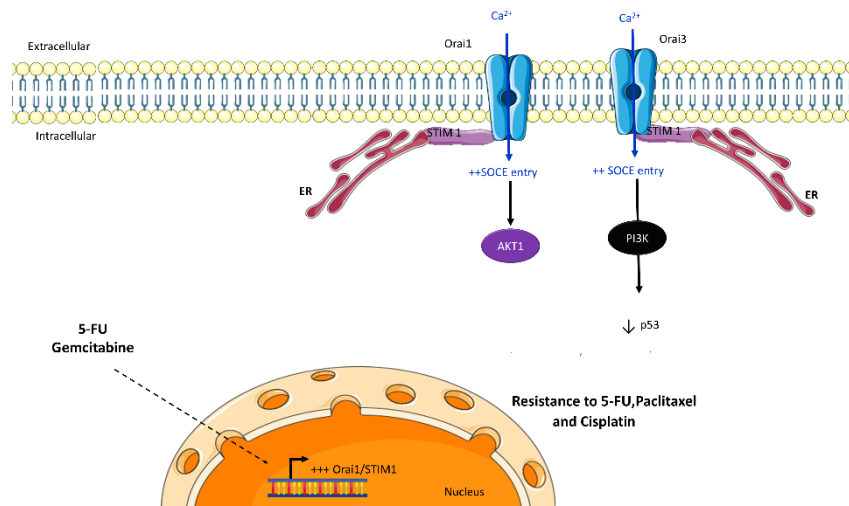
glioblastoma cells, mibefradil inhibits T-Type  $\text{Ca}^{2+}$  channels and induces cell death in an AKT/mTOR-dependent pathway. In vemurafenib-resistant melanoma cells with a BRAF mutation, T-Type calcium channel blocker mibefradil reduces autophagy as well as cell viability in a  $\text{Ca}_v3.1$ -dependent pathway.

b)  $\text{Ca}^{2+}$  release activated channels (CRAC)

In non-excitable cells, encompassing most cancer cells, store-operated  $\text{Ca}^{2+}$  entry (SOCE) is the major and most studied  $\text{Ca}^{2+}$  entry pathway. It is initiated by the activation of GPCR,  $\text{IP}_3$  production and  $\text{IP}_3\text{R}$  opening, which leads to  $\text{Ca}^{2+}$  release from ER. ER  $\text{Ca}^{2+}$  store depletion triggers the activation of the ER luminal  $\text{Ca}^{2+}$  sensors, stromal interaction molecules 1 and 2 (STIM1 and STIM2), which gain an extended conformation, translocate to highly specialized ER-plasma membrane junctions near to active CRAC channels encoded by three Orai proteins (Orai1-3).

SOCE is associated with the pro-migration and pro-invasion activity of cancer cells. High expression of SOCE proteins is correlated with poor survival prognosis in different tumor types [52]. Some evidence suggests that increased SOCE has a role in chemoresistance (Fig.2). Orai1 and STIM1 overexpression are associated with SOCE increase in cisplatin-resistant A2780cis ovarian cancer cells. It seems that AKT-dependent pathway activation is responsible for SOCE increase. 2-Aminoethoxydiphenylborane (2-APB), a non-selective SOCE blocker, and SH6, an AKT selective inhibitor, increase A2780cis sensitivity to cisplatin, and SH6 normalizes SOCE magnitude to the level of sensitive cells [53]. In addition, ovarian cancer IGROV1 resistant cell lines, cisplatin-resistant (IGROV1-CP) and *Solanum incanum* extract SR-T100-resistant (IGROV1-SRT) show increased SOCE compared to the parental cell lines. STIM1, STIM2 and Orai3 protein expression decrease in drug resistant cell lines while TRPC1, Orai1 and Orai2 increase in those models. Inhibition of SOCE by pharmacological tools such as SKF-96365, YM-58483 or 2-APB sensitizes chemoresistant IGROV1 cells to chemotherapeutic agents. However, the signaling pathways involved in this sensitization are not clear [54]. Orai3 overexpression in breast cancer correlates to chemoresistance in patients and cell lines. Orai3 acts through a PI3K/SgK1 pathway and inhibits paclitaxel, cisplatin and 5-FU induced apoptosis. These studies did not characterize the exact  $\text{Ca}^{2+}$  flux pathway to which Orai3 contributes [55]. Sun and collaborators have observed a SOCE increase in human osteosarcoma MG63 cisplatin-resistant cells compared to sensitive cells due to STIM1 protein overexpression. A 24-hour cisplatin treatment decreases STIM protein expression and SOCE in sensitive cells, but not in drug-resistant cells. The survival of resistant cells seems to be linked to the cisplatin-induced ER stress inhibition by STIM1. In fact, STIM1 inhibition sensitizes cells to cisplatin, while its overexpression promotes cell survival [56]. A common overexpression of STIM1 and the Ribonucleoside diphosphate reductase 1 (RRM1) has been observed in gemcitabine-resistant pancreatic cancer cells. The high expression of STIM1 is associated with increased SOCE and impaired

ER stress, leading to increased nuclear factor of activated T-cells (NFAT) activity and epigenetic reprogramming. However, RRM1 (but not STIM1) is required to induce chemoresistance [57]. Orai1/STIM1-mediated SOCE is involved in 5-FU or gemcitabine resistance in hepatocellular carcinoma cells and pancreatic adenocarcinoma [58,59]. These findings suggest that Orai1 expression is a predictor of 5-FU sensitivity for hepatocarcinoma and pancreatic adenocarcinoma treatment.



**Fig.2: Store Operated Ca<sup>2+</sup> Channel (SOCE) involvement in chemoresistance.** Increased SOCE is associated with cisplatin, 5-FU, paclitaxel or gemcitabine-resistance in several cancer models. Active AKT signaling or exposition to 5-FU or gemcitabine increases Orai1 and/or STIM1 expression. The use of SOCE inhibitor such as 2-APB attenuates chemoresistance to cisplatin, 5-FU and gemcitabine.

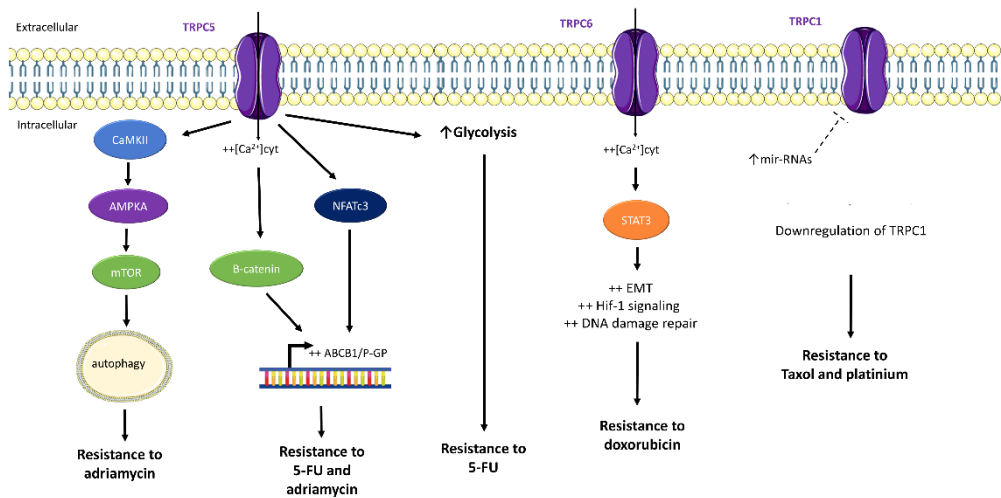
c) Transient receptor potential channels (TRP)

TRP channels are non-selective cation Ca<sup>2+</sup> permeable channels. They are grouped in seven families: canonical TRP (TRPC), vanilloid TRP (TRPV), melastatin TRP (TRPM), ankyrin TRP (TRPA), mucolipin TRP (TRPML), polycystin TRP (TRPP) and no mechanoreceptor potential C TRP (TRPN). TRP channels are activated downstream receptor tyrosine kinase receptors and G protein-coupled receptor by diverse mechanisms.

Several studies suggest that TRP channel expression is altered in cancers [17,60–62] but there is little information available about the role of TRP channels in chemoresistance. Though there are 28 members of the TRP channel family, few channels have been described to be involved in cancer chemoresistance and these are: TRPC5, TRPC6, TRPC1 TRPM2, TRPM8 and TRPA1 (Fig.3 and 4).

In a study on multi-drug resistant hepatocellular carcinoma, Wen and colleagues demonstrated the pivotal role of  $\text{Ca}^{2+}$  entry through TRPC6 channels, which were overexpressed in these cells and identified STAT3 activation as a downstream signaling pathway in MDR. *In vitro*, blocking TRPC6 by either siRNA or SKF-96365 attenuated multi-drug resistance in hepatocellular carcinoma cell lines, while targeting TRPC6 *in vivo* showed a synergistic antitumor effect when combined with doxorubicin [63]. The role of TRPC5 in chemoresistance has been described in several models. In adriamycin-resistant breast cancer cells MCF-7/ADM, adriamycin treatment increases TRPC5 expression. Knockdown of TRPC5 by siRNA reduces autophagy and chemoresistance by downregulating of a  $\text{CaMKII}\beta/\text{AMPK}\alpha/\text{mTOR}$  pathway (Zhang et al., 2017). Silencing of TRPC5 by siRNA or with a blocking antibody reduces P-glycoprotein expression in adriamycin-resistant MCF-7 cells, which leads to nuclear drug localization and cell death [65]. TRPC5 and transcription factor NFATC3 overexpression in adriamycin, paclitaxel and 5-FU resistant cells are associated to a decrease of mir-320a expression due to DNA methylation alteration in MCF-7 and HCT-8 cell lines, as well as in breast- and colorectal-cancer-resistant cells [66]. In 5-FU-resistant HCT-8 and LoVo colon cancer cell lines, common TRPC5 and GLUT1 over-expression has been identified compared to 5-FU-sensitive cells. The TRPC5-dependent activity increases cytosolic  $\text{Ca}^{2+}$  concentration, and is associated with high glycolytic activity, promoting survival of resistant cells. Inhibition of glycolysis leads to decreased ATP production and induces mitochondrial  $\text{Ca}^{2+}$  overload, which in turn triggers the sensitization of resistant cells [67]. A common increase in TRPC5 and ABCB1 mRNA, a well-known pump required for drug efflux, has been identified in colorectal cancer cell lines. Activation of TRPC5-dependent  $\text{Ca}^{2+}$  signaling ensures nuclear translocation of  $\beta$ -catenin, leading to the expression of ABCB1. It also mediates resistance to 5-FU [68]. On the contrary, in ovarian cancer, downregulation of TRPC1 contributes to drug resistance. TRPC1 expression is significantly decreased in cisplatin-resistant (A2780 and SKOV3) and carboplatin-resistant (A2780) ovarian cancer cell lines. Further, a study has shown that 8 microRNAs that target TRPC1 are associated with drug resistance in cancer [61].



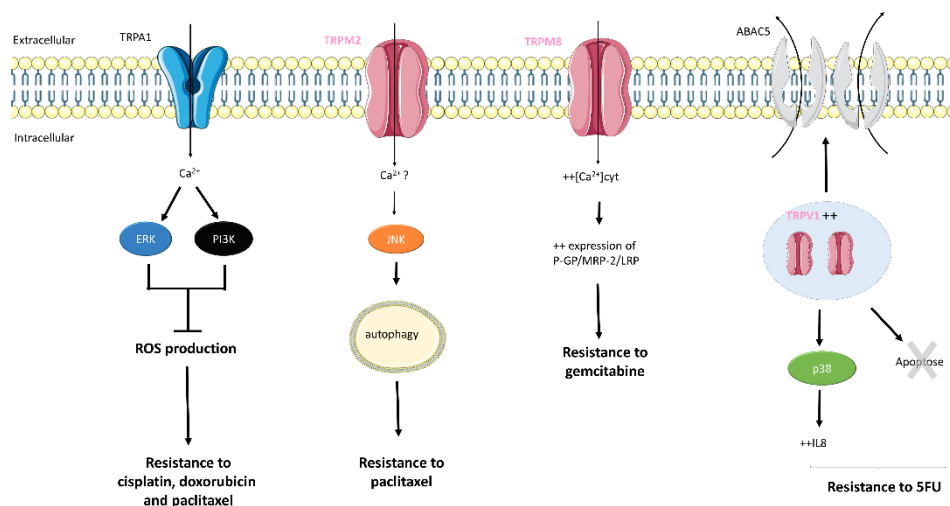


**Fig.3: Transient Receptor Protein Canonical channel (TRPC) involvement in chemoresistance**  
 Adriamycin treatment increases TRPC5 expression, leading to an activation of a calmodulin-dependent signaling pathway (CaMKII/AMPKA/mTOR), autophagy and chemoresistance. TRPC5 overexpression increases intracellular  $\text{Ca}^{2+}$ ,  $\beta$ -catenin nuclear translocation and ABCB1 expression, and leads to chemoresistance to 5-FU. TRPC5 overexpression increases P-GP expression in a NFATc3-dependent pathway, leading to alteration of adriamycin localization and chemoresistance. In 5-FU resistant cells, TRPC5 and GLUT1 are overexpressed. TRPC5 activity increases glycolysis and chemoresistance to 5-FU. TRPC6 mediates STAT3 activation and increases EMT, HIF-1 signaling and DNA damage repair, leading to chemoresistance to doxorubicin. The downregulation of TRPC1 expression by mir-RNAs contributes to resistance to platinum and Taxol®.

In 2018, Takahashi and colleagues showed that TRPA1 promotes resistance to ROS-producing chemotherapies. Notably, TRPA1 inhibition decreased live cell number and increased cell death in response to carboplatin, doxorubicin and paclitaxel. In an HCC1569 xenograft model, TRPA1 knockdown suppressed tumor growth and sensitized tumors to carboplatin treatment, which was associated with increased apoptosis [69].

The second member of the melastatin subfamily, TRPM2, is now considered a potential therapeutic target in several types of cancer [70]. In gastric cancer cell lines, TRPM2 regulates autophagy in a JNK-dependent pathway. It also plays a role in the maintenance of mitochondrial function and controls bioenergy production, promoting resistance to paclitaxel and/or doxorubicin treatment [71]. In 2018, Liu and collaborators showed that the expression and activity of multidrug resistance-associated proteins, P-GP, MRP-2 and LRP correlated with TRPM8 expression in gemcitabine-resistant pancreatic cancer cell lines [72].

Patients with glioblastoma multiforme (GBM) have a high resistance to temozolomide, carmustine and doxorubicin. Cannabidiol (CBD) enhances TRPV2 expression and activation. This leads to increased chemosensitivity of human GBM cells to the cytotoxic effects of the chemotherapeutic agents. It appears that TRPV2 activation by CBD increases doxorubicin uptake into glioma cells [73]. In the same vein, it has been shown that the activation of TRPV1 in MCF-7 breast cancer cells increases apoptosis and oxidant effects of cisplatin [74–76]. Nevertheless, the involvement of TRPV1 in chemotherapy is controversial with some studies suggesting that while TRPV1 expression is upregulated in 5-FU-resistant non-small-cell lung cancer, the chemoresistance of these cells is independent of TRPV1 channel function. Others suggested that bTRPV1 overexpression induces 5-FU resistance by upregulation of the drug transporter ABCA5, enhancing DNA repair efficiency and leading to inhibition of apoptosis. In this case, TRPV1 overexpression seems to activate the p38 MAPK signaling pathway and increase IL-8 secretion to promote cell survival [77].



**Fig.4: Involvement of other Transient Receptor Protein (TRP) families in chemoresistance** TRPA1 inhibits cisplatin, doxorubicin or paclitaxel-induced ROS production and cell death by activating PI3K and ERK-dependent pathways. TRPM2 controls autophagy in a JNK-dependent pathway, leading to resistance to paclitaxel and/or doxorubicin. In gemcitabine resistant pancreatic cells, TRPM8 expression and activity regulates multidrug-resistant associated proteins (P-GP, MRP-2, LRP). TRPV1 involvement in chemotherapy is unclear. Activation of TRPV1 in breast cancer leads to apoptosis, but its activity and expression participate in 5-FU resistance in resistant non-small-cell lung cancer cells. TRPV1 overexpression increases drug transporter ABCA5 expression, leading to apoptosis inhibition and activation of the p38 MAPK pathway. It also increases IL-8 secretion to promote resistance to 5-FU.

d) Transporters and exchangers

The plasma membrane  $\text{Ca}^{2+}$  pumps and exchangers are ion transporters that enable  $\text{Ca}^{2+}$  transport out of the cell to maintain  $\text{Ca}^{2+}$  concentrations in the cytosol. Chronic elevation of  $\text{Ca}^{2+}$  concentration leads to mitochondrial  $\text{Ca}^{2+}$  overload and cell death. In this regard, the inhibition of plasma membrane  $\text{Ca}^{2+}$  pumps and exchangers seems to be relevant in treatments that sensitize cancer cells to apoptosis.

Two groups have described a link between  $\text{Ca}^{2+}$  pumps and exchangers and resistance to cisplatin in ovarian cancer. PMCA2/3/4 pumps are downregulated in ovarian cancer cisplatin-resistant cells MDAH/DDP compared to MDAH-sensitive cells, while PMCA1 and NCX3 are increased in platinum-resistant lineage [20]. NCX3 NCKX4, NCKX5 and NCKX6 exchangers are overexpressed in A2780 cisplatin-resistant cells, while NCX1 and NCX2 are downregulated. Administration of a  $\text{Na}^+/\text{Ca}^{2+}$  exchanger inhibitor, KB-R7943, reduces NCX/NCKX activity and sensitizes resistant cells to cisplatin [23].

### **Intracellular calcium fluxes**

#### a) Endoplasmic Reticulum

The endoplasmic reticulum is the main source of intracellular calcium and seems to be a critical anticancer drug target because sustained massive ER  $\text{Ca}^{2+}$  release is often associated with mitochondrial-dependent cell death [81]. Interestingly, several studies have demonstrated that cisplatin-induced- $\text{Ca}^{2+}$  release from ER is altered in chemoresistant cells (Fig.5). The cytosolic  $\text{Ca}^{2+}$  increase observed after cisplatin treatment is reduced in cisplatin-resistant MFC-7 compared to drug-sensitive cells [82]. This work is supported by other studies in which cisplatin treatment induces ER stress in SKOV3, but not in cisplatin-resistant SKOV3/DDP. This leads to cytosolic  $\text{Ca}^{2+}$  increase, mitochondrial  $\text{Ca}^{2+}$  overload and apoptosis of cisplatin-sensitive cells, but not in resistant cells [83]. Cisplatin-induced apoptosis in sensitive and resistant ovarian cancer cells (A2780s/A2780cp and OV2008/C13\*) is regulated by P73 and the expression level of calpain, a calcium-dependent protease. Cisplatin treatment increases cytosolic  $\text{Ca}^{2+}$  concentration in sensitive cells but it does not affect the cytosolic  $\text{Ca}^{2+}$  concentration of resistant cells. The cytosolic  $\text{Ca}^{2+}$  concentration increase in sensitive cells is possibly due to the mobilization of intracellular  $\text{Ca}^{2+}$  stores, because it is not affected by extracellular  $\text{Ca}^{2+}$  removal [84].

Pharmacological inhibition of BCL-2/BCL-XL (ABT737) or their silencing by siRNA sensitizes cisplatin resistant SKOV3/DDP, COC1/DDP and A2780/DDP cell lines to cisplatin through ER  $\text{Ca}^{2+}$  release, cytosolic  $\text{Ca}^{2+}$  increase and a mitochondrial  $\text{Ca}^{2+}$  increase. This phenomenon is reduced in the presence of a non specific inhibitor, 2-ABP and these data were interpreted to mean that ER  $\text{Ca}^{2+}$  release through  $\text{IP}_3\text{R}$  mediates cisplatin sensitivity [85]. However, the extracellular  $\text{Ca}^{2+}$  concentration used during

experiments is not indicated in this article and 2-APB is known as a TRP and Orai channels inhibitor. While the role of IP<sub>3</sub>R in cisplatin sensitivity is uncertain, a significant decrease in IP<sub>3</sub>R mRNA was observed in MDAH/DDP ovarian cancer cells compared to cisplatin-sensitive cells, supporting the idea of defective Ca<sup>2+</sup> release in resistant cells. Similarly, a very strong decrease in RYR2 expression is measured in these cells, while the expression of RYR1 is increased. The expression of SERCA1/2/3 pumps is also reduced in cisplatin-resistant cells <sup>[20]</sup>. In multidrug-resistant acute myeloid leukemia, SERCA inhibitor CXL017 demonstrates selective toxicity to its HL60/MX2-resistant counterpart without effect on HL60 cells, suggesting SERCA activity has a role in chemoresistant cell survival <sup>[86]</sup>.

All the previous studies were performed on cisplatin-resistant cells, but it seems that the mechanism is conserved in Taxol<sup>®</sup>-resistant cells. In the A549 lung cancer cell line and its Taxol<sup>®</sup>-resistant counterpart, ER Ca<sup>2+</sup> release is decreased in resistant cells. It reflects a lower ER Ca<sup>2+</sup> load, which correlates to Bcl-2 overexpression in resistant cells. In addition, IP<sub>3</sub>R and RYR responses are lower in Taxol<sup>®</sup>-resistant cells during stimulation by CMC (4-chloro-m-cresol) or ATP <sup>[87]</sup>. Taken together, these data suggest that chemoresistance manifests as a result of alterations in ER Ca<sup>2+</sup> release driven by dysregulation of ER Ca<sup>2+</sup> release channels and resistance to ER stress.

#### b) Mitochondria

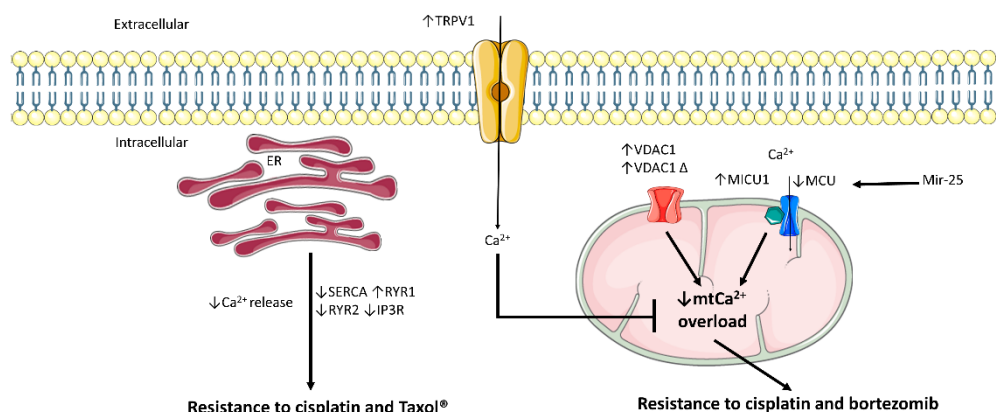
Mitochondria do not only function to produce ATP but are *bon fide* signaling organelles that are also critical for cellular Ca<sup>2+</sup> homeostasis. Mitochondrial Ca<sup>2+</sup> plays an important role in the control of cell death <sup>[88]</sup>. Several studies have described the role of mitochondrial Ca<sup>2+</sup> channels in the regulation of cancer cell survival and chemosensitivity <sup>[36,40,89,90]</sup>, but there are no available data on the role of those channels in chemoresistance cells.

The Ca<sup>2+</sup> derived from the extracellular medium or released by the intracellular stores passes across the outer mitochondrial membrane (OMM) through the voltage-dependent anion channel (VDAC) and reaches the internal matrix *via* the MCU complex, located at the inner mitochondrial membrane (IMM). VDAC1 is overexpressed in various cancer cell types <sup>[91]</sup>. VDAC1 silencing by siRNA has been shown to prevent cisplatin-induced apoptosis and Bax activation in non-small-cell lung cancer cells <sup>[92]</sup>. VDAC1 has also been described as an anchor protein for the anti-apoptotic proteins BCL-2 and BCL-XL. Fixation of BCL-2 on VDAC1 is able to decrease the conductance of the VDAC1 channel and protect against apoptosis <sup>[93]</sup>. The key role of VDAC1 in apoptosis versus survival is demonstrated by findings that VDAC1 expression is linked to chemoresistance in patients. In fact, a truncated channel-forming active VDAC1-ΔC was detected in tumor tissues of patients with advanced chemotherapy-resistant lung adenocarcinoma <sup>[94–96]</sup>. Under hypoxic conditions, activation of hypoxia-inducible factor 1 (HIF-1)

induces expression of VDAC1- $\Delta$ C, which confers selective protection against apoptosis and allows maintenance of ATP production and cell survival. In another study, transcript analysis of dexamethasone-resistant acute lymphoblastic leukemia patients showed significantly lower expression of VDAC1 compared to control samples<sup>[97]</sup>. All these studies demonstrate an important role of VDAC1 and VDAC1- $\Delta$ C in cancer pathophysiology and treatment resistance (Fig.5).

The MCU channel complex is composed of pore-forming proteins (MCU, MCUb) and regulatory components (EMRE, MICU1/2/3). Mitochondrial Ca<sup>2+</sup> overload due to MCU permeability causes mPTP opening and the release of cytochrome C and factors that initiate apoptosis. Regarding the involvement of MCU in chemoresistance, there is evidence that in human colon cancer, microRNA-25 decreases mitochondrial Ca<sup>2+</sup> uptake by MCU downregulation, causing resistance to apoptosis and promoting cancer cell proliferation and resistance to proapoptotic stimuli, as re-expression of MCU channel sensitizes cancer cells to treatment<sup>[36,98]</sup>. In breast cancer, overexpression of MCU and the decrease of MICU1 expression are correlated with poor patients survival<sup>[99]</sup>. MCU expression is correlated with breast tumor size, lymph node infiltration, metastasis and invasiveness potential<sup>[35]</sup>. In an MDA-MB-231 xenograft model, MCU knockout induces a reduction in tumor size and metastasis<sup>[37]</sup>. In ovarian cancer, high levels of MICU1 contribute to chemoresistance by inhibiting the mitochondrial Ca<sup>2+</sup> response to cisplatin. Inhibition of MICU1 reduces tumor growth by reinstatement of chemosensitivity and apoptosis induction<sup>[89]</sup>. NCLX is the major extrusion mediator of mitochondrial matrix Ca<sup>2+</sup>, and is essential for Ca<sup>2+</sup> homeostasis and viability<sup>[100]</sup>. Recently, Pathak et al. (2020) showed that the loss of NCLX in colorectal cancer cells inhibits mitochondrial Ca<sup>2+</sup> extrusion, enhances caspase 3 activation and increases the chemoresistance to 5FU<sup>[40]</sup>.

One study showed that TRPV1 blockade by AMG9810, in combination with bortezomib (an anti-cancer drug inhibiting the proteasome), sensitizes bortezomib-resistant-cells by increasing ROS production, ER stress and mitochondrial Ca<sup>2+</sup> overload. However, the description of the localization of TRPV1 in the study of Beider et al. is unclear. Mitochondrial Ca<sup>2+</sup> measurements were performed, but there is no data available regarding in consequences of AMG9810 on cytosolic Ca<sup>2+</sup><sup>[101]</sup> (Fig.5).



**Fig.5: Endoplasmic reticulum and mitochondria control cell death and chemoresistance** In resistant cells,  $\text{Ca}^{2+}$  release from ER decreases and correlates to alteration of RYR,  $\text{IP}_3\text{R}$ , SERCA protein expression. TRPV1 overexpression promotes chemoresistance to bortezomib and carfilzomib, reducing mitochondrial  $\text{Ca}^{2+}$  uptake. Overexpression of MICU1, VDAC1 and VDAC1  $\Delta$  correlates with chemoresistance. Mir-25 downregulates MCU expression and inhibits mitochondrial  $\text{Ca}^{2+}$  overload.

### Calcium signaling as a therapeutic target

Overall, since available data implicates  $\text{Ca}^{2+}$  signaling in chemoresistance (Table 1), it could be worthwhile to test pharmacological tools targeting  $\text{Ca}^{2+}$  signaling mediators as chemotherapeutic agents.

As VGCC participate in chemoresistance, their blockers could be relevant as new anticancer drugs. Mibefradil, a T- and L-type  $\text{Ca}^{2+}$  channel blocker, was approved as an antihypertensive drug by the US Food and Drug Administration (FDA) in 1997. However, it inhibited cytochromes P450, CYP3A4 and 2D6 leading to an increase of drug concentration in the liver and in blood associated to toxicities for patients. Therefore, Mibefradil was withdrawn<sup>[102]</sup>. The second example of VGCC blocker is Nifedipine, which has been used in the clinic for a long time to treat hypertension and angina. Despite the potential role of VGCC in cancer, long-term treatment with Nifedipine does not seem to alter the risk of developing breast cancer<sup>[103]</sup>. Verapamil, another L-type  $\text{Ca}^{2+}$  channel blocker, has shown interesting results as an anticancer drug. It increases patient survival in anthracycline-resistant metastatic breast carcinoma and in advanced non-small lung cancer when co-administrated with vindesine and ifosfamide<sup>[104,105]</sup>. However, a phase III clinical trial showed that Verapamil combined with standard chemotherapy (vincristine, doxorubicin and dexamethasone) did not improve survival in multiple myeloma<sup>[106]</sup>.

In the last two decades, SOCE has emerged as a clinically relevant and highly reproducible biomarker of cancer prognosis and response to treatment. Unfortunately, all currently available inhibitors directed against SOCE lack selectivity. In 2018, only four SOCE inhibitors had been tested in phase I of clinical trials (CM2489 for psoriasis, CM4620 for pancreatitis, RP3128 for asthma, and RP4010 for non-Hodgkin lymphomas). Of those four drugs, only CM4620 is currently in phase II. Carboxyamidotriazole (CAI), a synthetic indirect inhibitor of SOCE, has undergone clinical validation for use in association with chemotherapy/radiotherapy in a number of different cancers (clinical trial numbers: NCT00006486, NCT00005045, NCT00003869, NCT00019461, NCT00019019, NCT00004146, NCT03401190, NCT02958982, NCT03119467) <sup>[107,108]</sup>.

As it has been described previously, TRPC5 seems to be involved in chemoresistant cancer. Interestingly, GFB-887, a TRPC5 inhibitor, has been tested recently in clinical trials on healthy patients or on patients with fibromyalgia syndrome (Clinical trials numbers : NCT03970122, NCT03015662). Two new trials are currently in recruitment, and are focused on the role of GFB-887 in glomerular diseases, but not on cancer (clinical trial numbers: NCT04387448, NCT04950114). It could be interesting to test GFB-887 in combination with standard chemotherapy on resistant-cancer cells expressing TRPC5 (see the transient receptor potential channels section) to study its efficacy as an anticancer drug.

Although the therapeutic potential of Ca<sup>2+</sup> channels in the fight against cancer should be pursued, it should be noted that these channels are expressed in many tissues, and that non-specific effects are a common point described in all the studies quoted previously. In fact, the toxicity of Ca<sup>2+</sup> channels blockers on normal cells shall be considered. Further work is clearly needed to improve the selectivity of these inhibitors. Developing inhibitors that exclusively target tumor cells could radically change the thinking about pharmacological cancer treatment. While Ca<sup>2+</sup> channel inhibitors are unlikely to be used as first-line chemotherapy, combining conventional chemotherapy with Ca<sup>2+</sup> channel blockers could sensitize resistant cancer cells to the chemotherapeutic drug. In this context, it would be necessary to determine whether complete block of Ca<sup>2+</sup> flux is required, or whether a partial inhibition is sufficient to achieve anticancer effects.

### **Ca<sup>2+</sup> activated K<sup>+</sup> channels in chemoresistance**

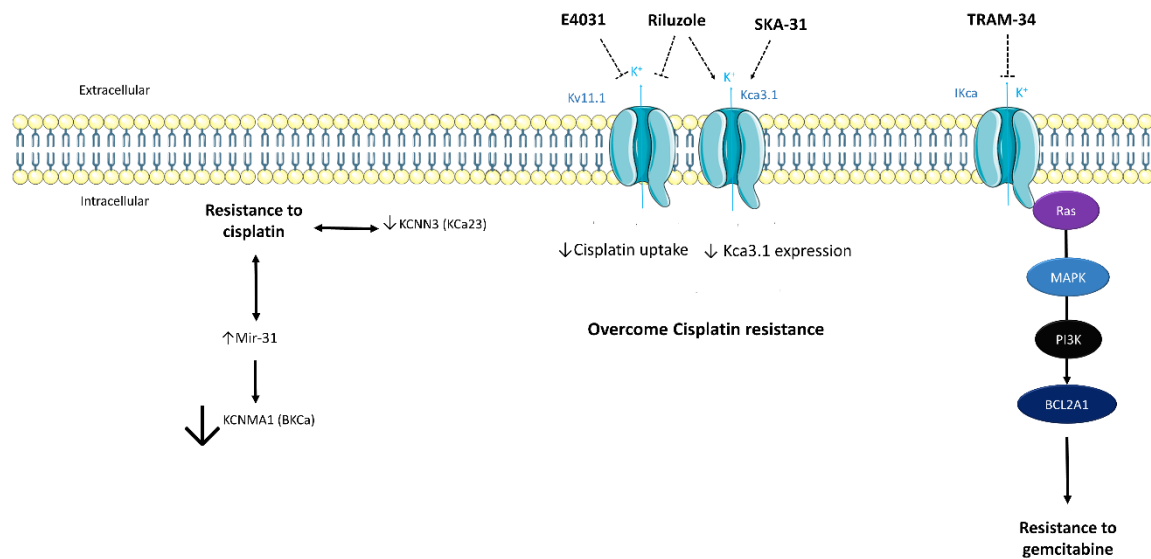
Ca<sup>2+</sup> fluxes across the plasma membrane are modulated by the membrane potential. Ca<sup>2+</sup> activated potassium channels (KCa) can potentiate Ca<sup>2+</sup> fluxes by promoting plasma membrane hyperpolarization. KCa are grouped in three sub-families—small conductance (SK), intermediate

conductance (IK) and big conductance (BK) <sup>[109]</sup>. Several studies have described a role of KCa in the regulation of Ca<sup>2+</sup> fluxes and their contribution to cancer cell aggressiveness <sup>[15,19,110,111]</sup>.

In chemoresistant sublines, there is little information on the role of those channels in drug resistance (Fig.6). The majority of available data seem to indicate that KCa inhibition or downregulation participates in chemoresistance. In ovarian cancer patients' tissues, the decrease of KCNN3 (KCA2.3-3) mRNA and protein expression correlates with lower patient survival and increases drug resistance <sup>[112]</sup>. Mir-31 increased-expression correlates to KCNMA1 (Ca<sup>2+</sup> activated K<sup>+</sup> channel large conductance subfamily M alpha, member 1) downregulation. In MCP1 and CP70 ovarian cancer cisplatin resistant sublines, Mir-31 is overexpressed and KCNMA1 is downregulated. Inhibition of BK channels or KCNMA1 knockdown in cisplatin-sensitive A2780 cells induces chemoresistance <sup>[113]</sup>. Regulation of KCa expression may facilitate absorption of cisplatin into colon cancer HCT-116 and HCT-8 cells. Cisplatin-resistant colon cancer cells overexpress KCa3.1 and K<sub>v</sub>11.1. Activation of KCa3.1 by SKA-31 and inhibition of K<sub>v</sub>11.1 by E4031 synergistically provides cisplatin induced-apoptosis and inhibition of cell proliferation. Blocking K<sub>v</sub>11.1 activity decreases KCa3.2 expression, leading to cisplatin-dependent cell death. This suggest that K<sub>v</sub>11.1 induces chemoresistance while KCa3.1 activity promotes cell death. Similar results have been obtained with riluzole treatment, known to be a KCa3.1 activator and a K<sub>v</sub>11.1 inhibitor <sup>[114]</sup>.

To our knowledge, only one paper identified KCa activity as an activator of chemoresistance. In gemcitabine-resistant breast cancer cells, IKCa is responsible for BCL-2-linked-protein (BCL2A1) overexpression, which suppresses apoptosis in Ras-MAPK- and PI3K/AKT-dependent pathways. Inhibiting IKCa by TRAM-34 reduces chemoresistance and tumor size, as well as MAPK and PI3K pathway activity <sup>[115]</sup>.





**Fig.6: Ca<sup>2+</sup> Activated K<sup>+</sup> channels participate in both chemoresistance and cell death** KCa inhibition or downregulation leads to chemoresistance. Those mechanisms act in a transcriptional manner. First, Mir-31 overexpression is responsible for KCNMA1 downregulation in chemoresistant cells. Inhibition of BK channels or KCNMA1 knockdown induces resistance to cisplatin-sensitive cells. Second, KCa3.1 participates in cisplatin uptake and cell death. In chemoresistant cells, K<sub>v</sub>11.1 regulates KCa3.1 expression. K<sub>v</sub>11.1 inhibition by E4031 increases KCa3.2 expression and leads to cisplatin uptake and cell death. In this regard, activation of KCa by riluzole or SKA-31 sensitizes cells to cisplatin. One study however has described KCa as an activator of chemoresistance. IKCa proteins mediate a Ras/MAPK/PI3K/Bcl-2 pathway that promotes chemoresistance to gemcitabine. Inhibition of IKCa by TRAM-34 induces cell death.

### Ca<sup>2+</sup> activated K<sup>+</sup> channel activators and inhibitors

Due to the relationship between Ca<sup>2+</sup> channels and KCa in cancer cells, developing new inhibitors of KCa could be an effective way to trigger cancer cell death. Our laboratory has described the role of the SK3-Orai1 complex in cancer cell migration [15,19] and we have shown that alteration of that complex reduces metastasis in mice. To our knowledge, this interaction has never been studied in chemoresistant models. Several KCa activators are available on the market. However, none are used as cancer treatments. The first KCa channel activator approved by the FDA is chlorzoxazone. SKCa channel activator chlorzoxazone is used for episodic ataxia and spasticity [116,117]. Riluzole, another SKCa activator, reduces arthritic pain, improves ataxia symptoms and is approved as a treatment for amyotrophic lateral sclerosis [118–120]. Interestingly, Blyufer and collaborators have reviewed its role as an anticancer drug. Several studies have shown the synergistic effect of riluzole with other drugs (paclitaxel, cisplatin, sorafenib) in cancer cell lines that decrease cell proliferation and viability [121]. BMS204352, also known as maxipost, is a BK and K<sub>v</sub>7 activator tested in phase III of a clinical trial for

acute ischemic stroke (NCT03887325). However, it has never been tested in cancer studies. Only one KCa inhibitor has been tested in clinical trials. Senicapoc is an IK inhibitor that has been tested for Alzheimer’s disease (NCT04804241) and dehydrated stomatocytosis (NCT04372498). While it was tested in phase I and II clinical trials (NCT00861211 ; NCT00861185) for the treatment of asthma, there is no information available on its potential anticancer properties.

Targeting KCa as an anticancer drug could be relevant because of the participation of KCa in membrane Ca<sup>2+</sup> flux regulation. Pharmacological tools targeting KCa could prevent side effects usually observed with Ca<sup>2+</sup> channel blockers. Moreover, the drugs studied in clinical trials appear to be well tolerated by patients. However, there is insufficient data on when KCa inhibitors or activators could be used, because the mechanisms surrounding these channels in chemoresistance are not well understood.

**Table 1: Main evidences of calcium fluxes involvement in chemoresistance**

Drug resistance family	Channel involved	Cancer type	Patient samples, animals and cell lines	Description	Reference
signal transduction inhibitors (verumafenib, bortezomib)	Ca <sub>v</sub> 3.2	Melanoma	BRAF <sup>V600E</sup> mutant Vemurafenib-S and Vemurafenib-R human melanoma	Inhibition of VGCC = apoptosis induction, impairs migration and invasion	[50]
	TRPV1	Myeloma	Patient samples RPMI8226, U266, NCI-H929, OPM-1 and OPM-2	TRPV1 inhibition increases mitochondrial calcium levels, mitochondrial membrane depolarization and ROS accumulation	[101]
alkylating agents (cisplatin)	T-Type Ca <sup>2+</sup> channels	Glioblastoma cells	U251, U87 and T98G	T-Type Ca <sup>2+</sup> channels confers viability and resistance to chemotherapy	[49]
	Orai1	Ovarian cancer	A2780 and A2780cis	+++ SOCE mediating chemoresistance to cisplatin	[53]
	Orai1 TRPC1	Ovarian cancer	IGROV1, IGROV1CP and IGROV1SRT	+++ SOCE = +++ cell migration and chemoresistance to cisplatin	[54]

	STIM1	Osteosarcoma	MG63 and patient samples	inhibits ER stress induced by cisplatin and leads to chemoresistance	[56]
	NCX3, NCKX4, NCKX5, and NCKX6	Ovarian cancer	A2780	overexpression and activity increase cisplatin-induced cell death resistance	[23]
	TRPA1	Breast and lung cancer	H1792, H647, A549, H23, H358, and sNF96.2, MCF-10A, HCC1569, HCC38, HCC202, HCC70, HCC1500, MDAMB-175, T47D, and BT-549	Overexpression inhibits chemotherapy-induced ROS production and cell death	[69]
	KCa3.2	Colorectal cancer	HCT-116, HCT-29, HCT-8 and H630	Cisplatin uptake into resistant cells depends on KCa3.2 channel activity	[114]
	BKca or KCa1.1	Ovarian cancer	A2780, MCP1, CP70, OVCAR5	miR-31 represses BKca or KCa1.1 expression, which lead to chemoresistance	[113]
	STIM1	Pancreatic ductal adenocarcinoma	CFPAC-1, L3.6pl, Panc1, BxPC-3, HCT116, DLD-1, SJSA, MG63, HEK293T	overexpression is responsible for ER stress tolerance, activation of NFAT and epigenetic alteration, but is not responsible for 5-FU chemoresistance	[59]
	Orai1 STIM1	Pancreatic adenocarcinoma	Panc1, ASPC1, BxPC3, MiaPaca2, Capan1, H6C7	Chemotherapy increases Orai1/STIM1 expression, which controls anti-apoptotic pathways	[58]
	Orai1 STIM1	Hepatocellular carcinoma	HepG2	Overexpression inhibits 5-FU	[59]

				induced autophagy and cell death	
Antimetabolites (5-FU, Gemcitabine)	TRPC5	Colorectal cancer	HCT-8, LoVo	Promotes nuclear $\beta$ -catenin accumulation and ABCB1 expression in resistance to 5-FU	[68]
	TRPC5	Colorectal cancer	HCT-8, LoVo, patient samples	Regulates glycolysis and chemoresistance to 5-FU	[67]
	TRPC5	Breast and colorectal cancer	MCF-7, HCT-8	Mir-320a is downregulated in resistant cells, and is responsible for TRPC5 and NFATc3 overexpression, which promotes chemoresistance	[66]
	TRPC5	Breast cancer	Patient samples, mice, MCF-7, T47D and MDA-MB 231	Induces autophagy in a CaMKK $\beta$ /AMPK $\alpha$ /mTOR pathway, leading to chemoresistance	[64]
	TRPC5	Breast cancer	MCF-7	Overexpression upregulates P-GP expression and resistance to adriamycin	[65]
	TRPM8	Pancreatic cancer	Primary tissues, PDE, SW1990, PANC-1, CAPAN-1 and BXPC3	TRPM8 activity controls multidrug resistance-associated protein expression	[72]
	TRPV1	Non-small-cell lung cancer	HEK293T and A549	TRPV1 activity increases ABCA5 drug transporters and contributes to resistance to 5-FU.	[77]
	Anthracyclines (adriamycin, doxorubicin)	TRPM2	Gastric cancer cells	AGS and MKN45	TRPM2 regulates autophagy in a JNK-dependent pathway and leads to

				paclitaxel/doxorubicin resistance.	
	TRPC6	Hepatocellular carcinoma	Huh7 and HepG2, nude mice	TRPC6 activates a STAT3 pathway to confer resistance to doxorubicin	[63]
immunotherapy	Ca <sub>v</sub> 1.2	Diffuse large B-cell lymphoma	Patients and OCI-ly7, OCI-ly8, and OCI-ly3 DLBCL cell lines	Mir-363 decreases Ca <sub>v</sub> 1.2 expression and confers resistance to rituximab	[45]

## Conclusion

During last decade, several studies have indicated that many Ca<sup>2+</sup> channels are highly expressed in human cancer cells and tissues, where they regulate a number of cellular processes, including proliferation, migration, invasion and apoptosis resistance. A correlation between the expression levels of these channels and resistance to cytotoxic drugs has also been reported in some cases, supporting their putative role as predictive markers for chemotherapy treatment. Here, we summarized the instances where dysregulation of Ca<sup>2+</sup> signaling contributes to chemoresistance in cancers. It should be noted that every cancer type or model of cancer cell resistance develops its own Ca<sup>2+</sup> signaling signature. It is likely that in each case the resistance profile of a specific cancer type is dependent on the type of drug used and its mechanism of action, as well as to the different types of tumor cells. Most studies have reported the involvement of one Ca<sup>2+</sup> channel or another in chemoresistance, but there is now evidence that several Ca<sup>2+</sup> channels may work in combination with other channels to promote malignant behaviors<sup>[109]</sup>. For instance, simultaneous activation of KCa3.1 and inhibition of K<sub>v</sub>11.1 with riluzole has been shown to synergistically increase apoptosis and overcome cisplatin resistance<sup>[114]</sup>. Thus, the identification of new onco-complexes of channels involved in chemoresistance might allow for the establishment of new, promising therapeutic approaches mixing pharmacological modulators of calcium channels with established chemotherapies. Clearly, additional studies are necessary to thoroughly characterize the molecular network of Ca<sup>2+</sup> channels in resistance to drug treatment in different cancers. Among drugs capable of interacting with Ca<sup>2+</sup> channels, few molecules display real specificity while for most drugs toxicity profiles of these drugs are not yet available, except for molecules used in cardiovascular medicine. As we gain further knowledge of the various Ca<sup>2+</sup> signaling networks involved in chemoresistance and progression of different types of cancers, combination therapies utilizing Ca<sup>2+</sup> channels and transporters as targets might prove impactful in combating chemoresistance to established cancer therapies.

## Authors contributions

M. Potier-Cartereau conceived the idea for this review article, O Romito performed the literature search, data analysis, and drafted the review. O Champion, W. Raoul, M. Gueguinou, A. Robert, M Trebak, C Goupille and M Potier-Cartereau critically revised the manuscript.

## Authors' notes

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## Conflict of interest

Mohamed Trebak is a paid consultant of Seeker Biologics Inc. The other authors declare that they have no conflict of interest.

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