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CALCIUM CHANNELS, BIOMARKERS OF CANCER

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ABSTRACT

Ion channels behave differently based on cellular location. Well established research characterizes the regulation of intracellular Ca^{2+} concentration by calcium channels, which is integral to Ca^{2+} dependent signaling cascades. Ca^{2+} dependent signaling cascades initiate cellular differentiation and apoptosis. Previous research suggests if calcium channel expression changes due to genetic mutation, the change in function may promote tumorigenesis and neoplastic cell proliferation. Altered calcium channels expression may also avert apoptosis, further contributing to cell proliferation and increased chemoresistance. Since calcium channels behave differently in neoplastic cells, scientists may develop calcium channel biomarker assays for diagnosis and prognosis. In this review, the expression changes per cancer cell type, utilizing calcium channels as biomarkers, and the main concerns are discussed.

Keywords: Biomarkers, plasma membrane channels, calcium pumps, tumorigenesis, cancer treatment and diagnosis.

I. INTRODUCTION

The U.S. National Cancer Institute reports cancer as the second most common cause of death [64]. Until cancer is eradicated, efforts to improve early detection methods, treatment interventions, and survivorship remain paramount. A new interest in oncology research concerns the difference in ion channel concentrations between non-neoplastic and neoplastic cells. [9, 65]. In non-neoplastic cells, calcium channels and pumps maintain intracellular Ca^{2+} concentration. Fluctuations in intracellular Ca^{2+} concentrations spark signal cascades ultimately responsible for the cell cycle progression, autophagy, cell death, and gene expression [1, 2, 3, 4, 5]. Intracellular and intercellular calcium channels are found throughout several cellular structures described below:

1. Transient receptor potential (TRP) channels, voltage-gated calcium channels (VGCC), ligand-gated ionotropic P2X receptors, mechano-sensitive Piezo channels, and store-operated Ca^{+2} entry pathway facilitated stromal communication molecule 1 (STIM1) and ORAI1 channels [4,6,7].
2. Ca^{+2}-ATPase (PMCA), Sarcoplasmic/endoplasmic reticulum Ca^{+2} - ATPase (SERCA), and Golgi network secretory pathway Ca^{+2} /Mn2+-ATPase (SPCA).[6,8]
3. Inositol 1,4,5-trisphosphate (IP3) receptor (IP3R).[13]
4. Two-pore channels (TPC), and mitochondrial calcium uniporter (MCU)complex, and mitochondrial Na+/Ca^{+2} exchanger (NCLX)[20]
5. Lysosomal ion channels(uniporter) or called TPC .

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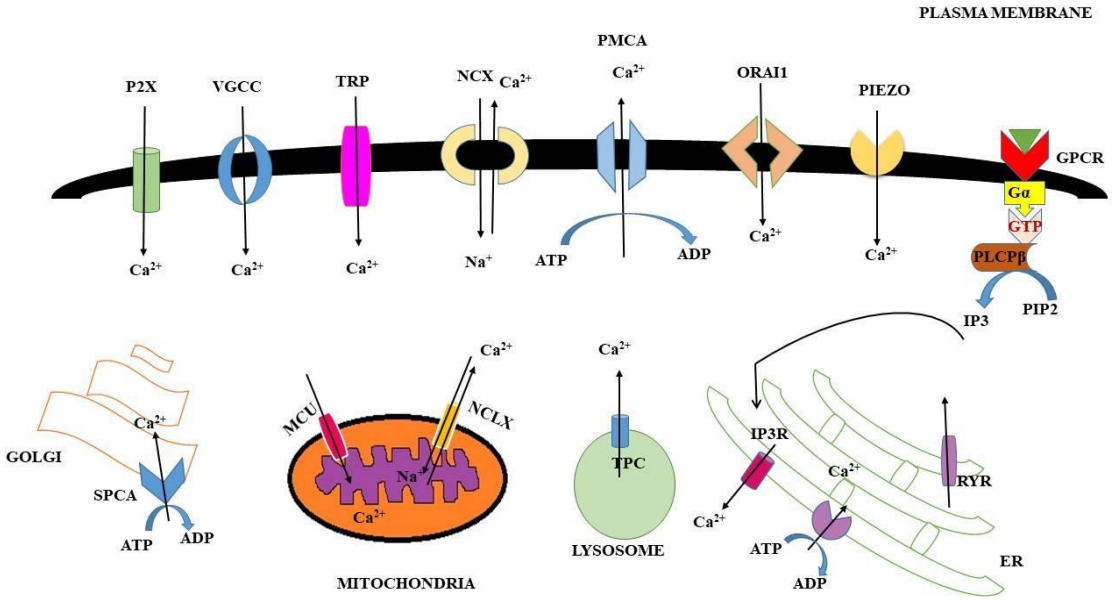

Figure 1: Schematic view of major calcium channels present in a mammalian cell. (Transient receptor potential (TRP) channels, voltage-gated calcium channels (VGCC), ligand-gated ionotropic P2X receptors, mechano-sensitive Piezo channels, and store-operated Ca+2 entry pathway facilitated stromal communication molecule 1 (STIM1) and ORAI1 channels,Ca+2-ATPase (PMCA), Sarcoplasmic/endoplasmic reticulum Ca+2 - ATPase (SERCA), and Golgi network secretory pathway Ca+2 /Mn2+-ATPase (SPCA), Inositol 1,4,5-trisphosphate (IP3) receptor (IP3R), 1. Two-pore channels (TPC), and mitochondrial calcium uniporter (MCU)complex, and mitochondrial Na+/Ca+2 exchanger (NCLX) & Lysosomal ion channels(uniporter) or called TPC)

A change in ion channel function may result in tumorigenesis, specifically in calcium channels [6, 10, 58]. Additional research suggests expression changes are directly linked to genes that is code for the ion channels [65]. Mutated calcium channels and pumps may also encourage tumor cell proliferation, catalyze chemoresistance, and delay apoptosis [6, 8, 63, 65]. In this review, the possible role and function of calcium channels in tumorigenesis and tumor cell proliferation is discussed. If the role(s) and function(s) prove significant, calcium channels may serve as a novel biomarker for early detection methods, concomitant treatments, and evaluation of disease progression.

II. DISCUSSION

The different expressions of specific Ca^{2+} channels may be linked to the hallmarks of cancer[65]. If so, researchers can redirect efforts towards those channels. The following discussion reviews the classes of calcium channels suspected to play a role in cancer development.

2.1: Transformed calcium channels:

Normally in a cell function its own cell cycle , apoptosis, autophagy and cell division by the calcium ion regulation that is performed in a normal way[1,2,4]. But in case of cancer the calcium ion channels do not function as a normal way[6,8] . It is found that , most of the cancer types show abnormal expressions of calcium channels that promote tumors[10,58]Here we have gathered the information about these types of calcium channels below that show abnormal functions or transformed activity.

Inositol 1,4,5-trisphosphate (IP_3) receptor:

The endoplasmic reticulum (ER) stores the most calcium ions. In the ER, the major calcium channel, IP_3, regulates intracellular Ca^{2+} concentration [13]. Previous research characterized three isoforms of IP_3 and their altered expression patterns in different cancer types [16]. The isoforms are IP3R1, IP3R2 and IP3R3 [14, 16].

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IP3R1in Glioblastoma Decreased ,IP3R2 in lung cancer Increased & IP3R3 Glioblastoma Increased overall[6,11,14,15] .Their expression patterns and downstream effects are described in Table 1.

		Changes due to cancer		
Channels	**Cancer type**	**mRNA**	**protein**	**activity**
IP3R1	Glioblastoma	Decreased	Not done	Decreased
IP3R2	lung cancer	Increased	Not done	Increased
IP3R3	Glioblastoma	Increased	Increased	Increased

Table 1: Different activity of IP3R channels during cancer.[6, 11, 13, 14, 15, 16].Here it is shown that how all IP3R channels are over expressed or down expressed in different types of cancer with mRNA ,proteins ,expressions.

1. Ca^{+2} –ATPase:

Ca^{2+}-ATPases also actively regulate calcium concentration. Further divisions of Ca^{2+}-ATPases is location dependent, such as the plasma membrane Ca^{+2} -ATPases (PMCA), ER/SR Ca^{+2} -ATPases (SERCA), and golgi-derived vesicle secretory pathway Ca^{+2} -ATPases (SPCA) [16, 19]. Previous colorectal research associated SERCA2 and SERCA3 to cancer cell migration and tumorigenesis [16, 17]. Arbabian *et al* identified SERCA3 proteins responsible for increased cell differentiation in lung adenocarcinoma cell lines [18]. SERCA2 in Oral cancer, Colon and lung cancer found Decreased, SERCA3in Colon cancer Not found any records,SPCA1in Breast cancer found Increased,SPCA2 in Breast cancer Increased for PMCA2 in Breast cancer Increased & PMCA4in Colon cancer Decreased.[6,15,16,17,18].Differences in expression between cancer types is described in Table 2.

		Changes due to cancer		
Ca^{+2} ATPase	**Cancer types**	**mRNA**	**Protein**	**Activity**
SERCA2	Oral cancer, Colon and lung cancer	Decreased	Decreased	Increased
SERCA3	Colon cancer	Not done	Decreased	Decreased
SPCA1	Breast cancer	Increased	Not done	Increased
SPCA2	Breast cancer	Increased	Increased	Increased
PMCA2	Breast cancer	Increased	Increased	Increased
PMCA4	Colon cancer	Decreased	Not done	Decreased

Table 2: Difference expressions of calcium ATPase channels due to cancer [6, 15, 16, 17, 18]. Here it is shown that how all ATPase channels are over expressed or down expressed in different types of cancer with mRNA ,proteins ,expressions.

2. Mitochondrial Ca^{+2} uni-porter (MCU) channels and Plasma membrane Ca^{+2} channels:

MCU channels in the mitochondria behave differently depending on the cancer type. In breast cancer for example, MCUs are overexpressed. Previous research described downregulation of MCUs and the staving off apoptosis as a result [16,20]. The same effects are seen in their plasma membrane cousins, such as voltage-gated Ca^{+2} channels (VGCC), TRP channels, purinergic receptors, ORAI and STIM [16]. Each of these plasma membrane Ca^{+2} channels demonstrate altered expression patterns in different cancer cell lines [16]. Previous research described changes in L-type and T-type calcium channels in cancer cells [21]. Among all members of TRP subfamilies, TRPC, TRPM, and TRPV are strongly related to cancer invasion and disease progression [22]. TRPC6 found highly expressed in esophageal carcinoma [23], its mRNA ,proteins concentration are found very high in that type of cancer,and as a result its activity also increased[6,12,23].The TRPM7 is related to cancer cell proliferation [24]. It also shows high activity in Pancreatic cancer[16,23] The extensive characterization of purinergic receptors linked with cancer survival, migration and invasion [25]. These ion channels mainly P2X are highly expressed in cancer[25,66]. The different expressions of MCU and plasma membrane Ca^{2+} channels in cancer types are described in Table 3.

		Changes due to cancer		
Channels	**Cancer type**	**mRNA**	**Protein**	**Activity**
CaV1.2 (L-type α1C)	Colon cancer	Increased	Not done	Increased
CaV3.1(T-type α1G)	Glioma	Increased	Not done	Increased
Cav3.2	Prostate cancer	No significant difference	Increased	Increased
TRPC1	Breast cancer	Increased	Increased	Increased
TRPC3	Ovarian cancer	Increased	Increased	Increased
TRPC6	Glioma and esophageal cancer	Increased	Increased	Increased
TRPM7	Pancreatic cancer	Increased	Increased	Increased
TRPM8	Pancreatic cancer	Increased	Increased	Increased
TRPV1	Bladder cancer	Decreased	Decreased	Decreased
TRPV6	Breast cancer	Increased	Increased	Increased
ORAI1	Breast cancer, glioma, melanoma	Increased	Nothing different	Increased
ORAI3	Breast cancer, lung cancer	Increased	Increased	Increased

TABLE 3: Different activity of plasma membrane calcium channels in cancer [6, 12, 16, 20, 25, 26, 27, 28, 29, 30]. Here it is shown that how all plasma membranes channels are over expressed or down expressed in different types of cancer with mRNA ,proteins ,expressions.

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2.2: Calcium channels as biomarkers

Since calcium channels behave differently in neoplastic cells, especially per cancer type, this information may lead to novel biomarkers for cancer. The following discusses the current research and possible uses for calcium channels in oncology diagnosis and treatment.

1. Chemoresistance and uncontrolled cell division:

Previous research suggests increased in Ca^{2+} dependent signaling causes downstream changes in telomerase activity [31]. Eventually, this causes uncontrolled cell proliferation normally prevented in non-neoplastic cells [31]. Inhibition of Ca^{2+} channel expression also regulates the cell division [32, 33]. ORAI1/STIM1 and TRP channels may also participate but differently. Previous research described changes in channel behavior leads to chemoresistance increase by the AKT pathway, autophagy, and transcription factor's like NF-κB,c-myc and p53 to eventually promote tumorigenesis. [36, 37, 38, 55].

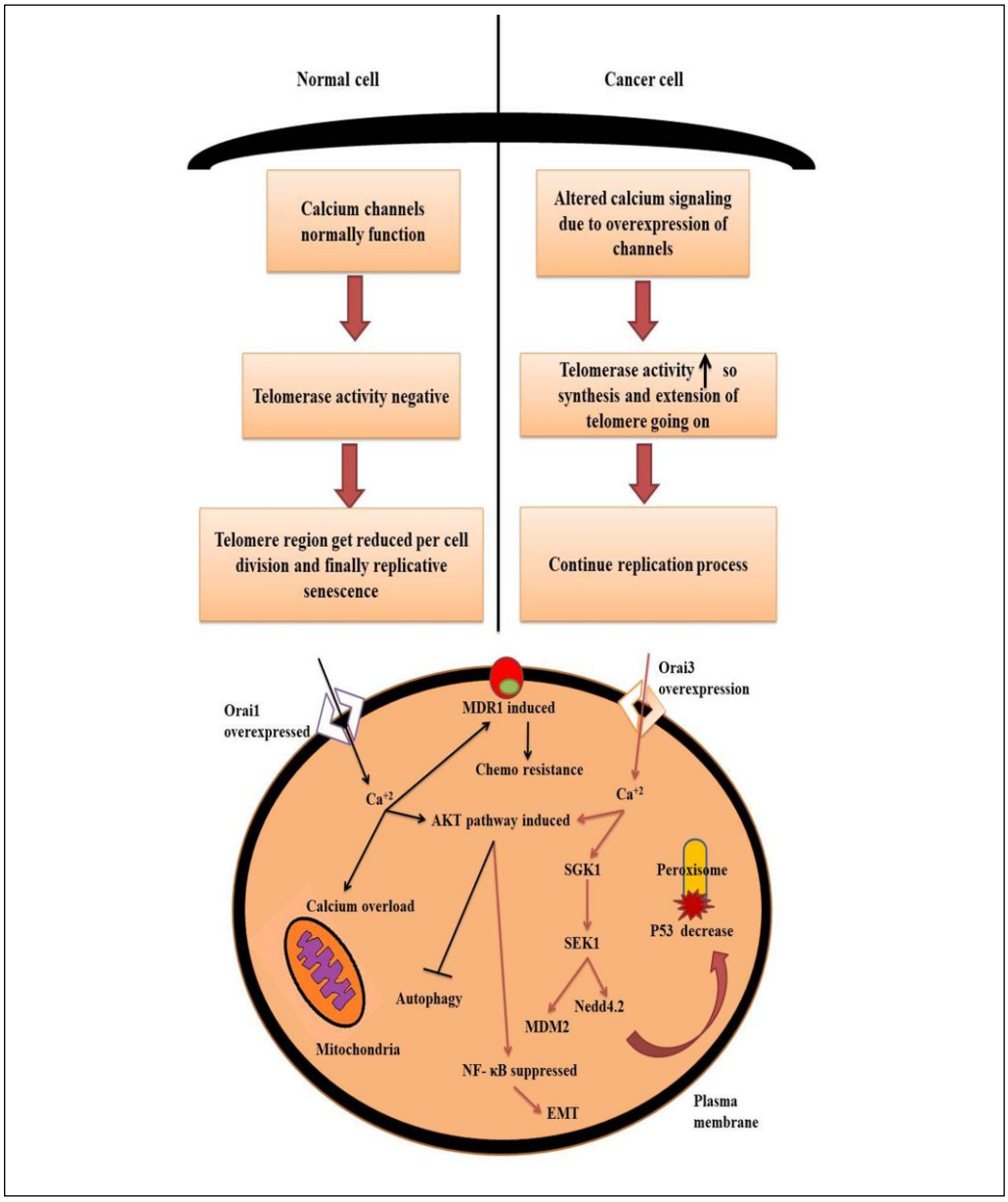

Fig. 2. Description of calcium signal cascade changes in non-neoplastic and neoplastic cells.[66,65].Here in the first picture you can see how in case of cancer due to over expression of calcium its promote cancer compare to normal cells. On the other picture it is described that how cancer cell get chemoresistency.

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2. Evasion of apoptosis and autonomous cell growth:

Calcium dependent signaling triggers apoptosis [39, 40]. TRPV6, TRPM2, and P2X channels inhibit apoptosis [41, 42, 43, 54]. The BCl-2 genes, IP3R ER channel and low intracellular Ca^{2+} concentration inhibit apoptosis. To maintain cell proliferation , neoplastic cells must exhibit a variety of expressions. The VGCC and TRP channels perform a key role in this matter. [45, 46, 47, 48, 49, 50, 53]. Overall calcium channels create high sensitivity to mitogen and growth factor secretion [51, 52, 56, 57].

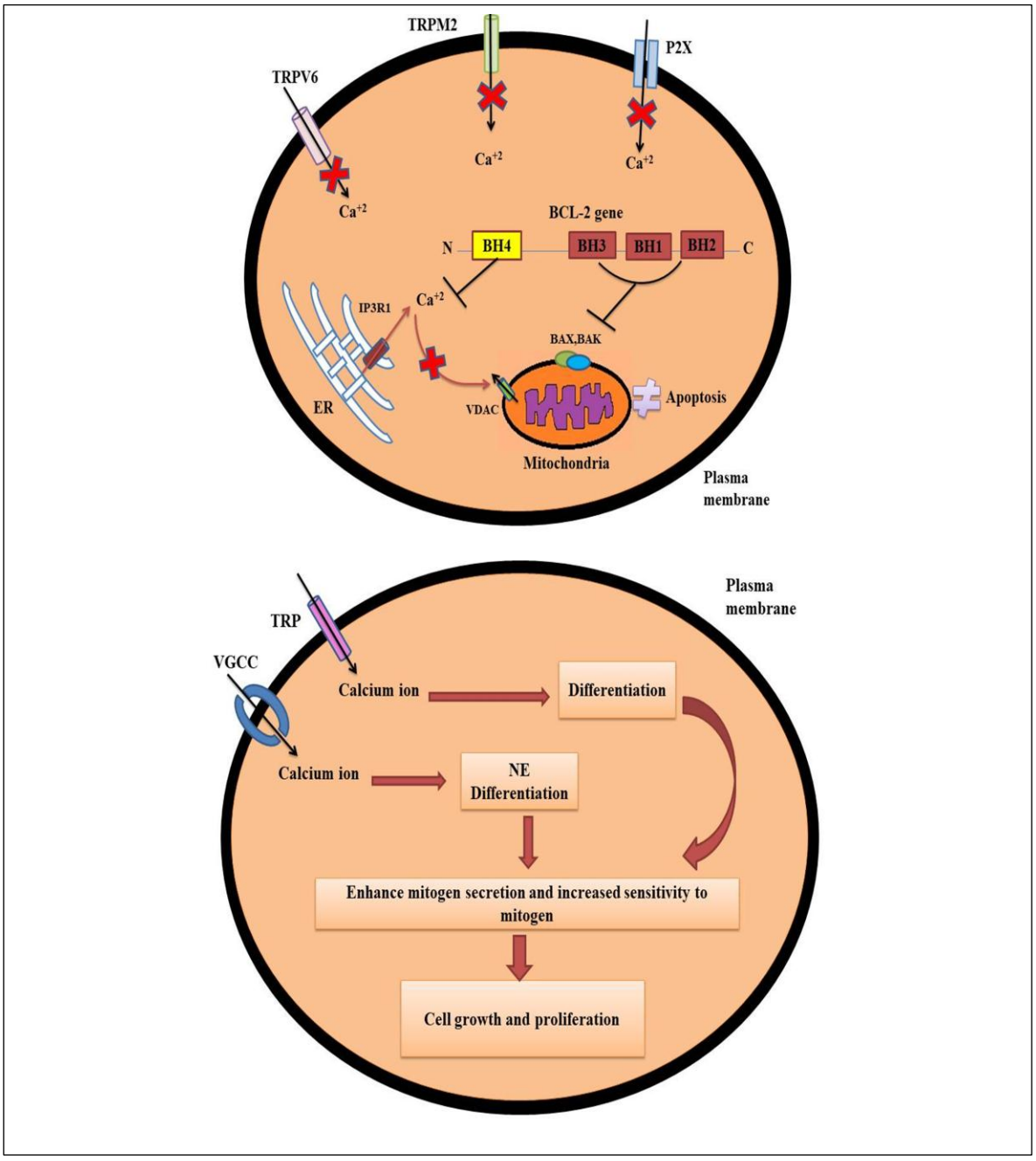

Fig.3 Calcium channel and cell death evasion and autonomous cell growth.[65,66].here it is shown by signaling pathways how due to calcium disruption a cancer cell can evade cell death and promote cell growth.

3. Angiogenesis and metastasis:

TRPC1,TRPC4, and TRPM sub types of calcium channels play a crucial role in angiogenesis and metastasis [44,59,60]. The calcium dependent signaling influences the [increased] secretion of antigenic factors, which may result to induced autocrine or potentially paracrine signaling. This ultimately causes angiogenesis downstream [61,35]. Previous research also suggests STIM1 and ORAI1 may influence cell migration [62].

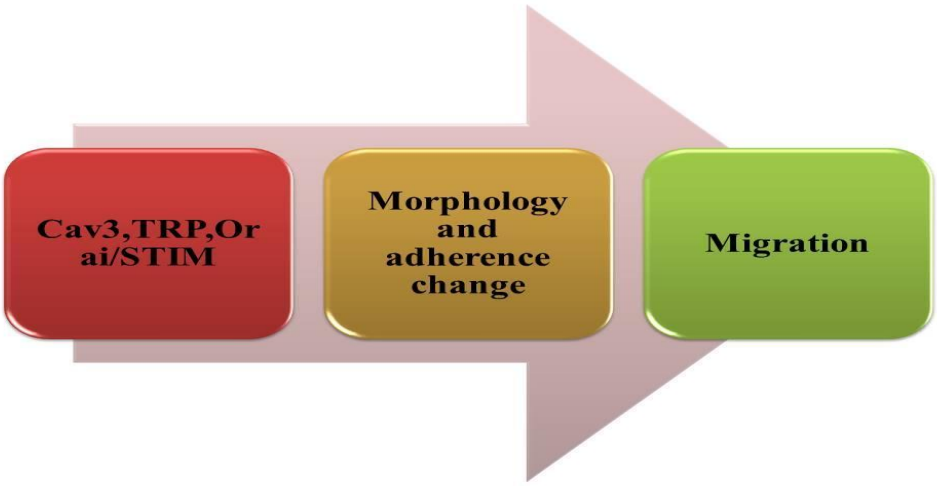

Fig. 4 Calcium and migration .Here it is shown that how, due to plasma membrane calcium channels activity promote cancer metastasis.

Drugs targeted to calcium channels-

1. Ca+2 -ATPase inhibitors – A PMCA selective inhibitor [Pt (O, O0-acac) (γ-acac) (DMS)] is used and for SERCA pump, thapsigargin(TG), is used .

2. Voltage-gated Ca+2 channel inhibitors- The dihydropyridine Ca+2 channel blocker, amlodipine, A mibefradil derived novel compound, NNC-55-0396, was developed to selectively target Ca+2 channel .

3. TRP channel regulators- The imidazole compound SKF-96365 for TRP channels(Bruce JIE, Elliott AC2000). TH-1177 was developed as a TRPV channel blocker, GSK1016790A is a selective to TRPV4.

4. Orai inhibitors – The first Orai1 inhibitor used in cancer study is SKF-96365. Yang *etal.* Another commonly used SOCE inhibitor is 2-APB. ML-9 .RO2959 is a novel, potent and selective SOCE inhibitor.

3: Calcium and cancer – problems and future direction

As discussed above, expression changes in calcium channels may promote tumorigenesis and cancer cell proliferation. Current calcium channel blockers may be used as concomitant medications with chemotherapy and radiotherapy to improve prognosis [34].

1. The main concern is possible adverse reactions in non-neoplastic tissues. Normal cells also contain calcium channels vital to normal physiological processes. Regulating or blocking calcium channels indiscriminately may cause cascading physiological imbalances throughout all non-neoplastic tissues. Therefore, any blocker or regulator must be cancer target specific.
2. Additional research is needed to characterize structural changes in cancer cell membrane proteins to better target calcium channel blockers.
3. Further research is also needed to characterize possible cellular proteins present that may influence the gene expression of calcium channels.

4. Lots of research is going on in this field but a more deep understanding and experiment is needed to understand the total signaling pathway of calcium channels ,how the genes that code for the channels proteins are differentially expressed in cancer .

The sincere hope understands the role and function of calcium channels in cancer cells will lead to biomarker assays for diagnosis and prognosis.

III. CONCLUSION

So, after discussing all the factors, now it is becoming obvious that Ca+2 channels/transporters/pumps are involved in a varied range of cancers. Abundant studies have now proven that some cancers are connected with major variations in the expression of specific Ca+2channels and pumps and that inhibition of some of these proteins prevents the proliferation and/or metastasis of cancer cells. With this review we also understood how calcium promotes the main cancer hallmarks and what major channels that is major targets. There are lots of problems stated above if that are solved then it can helpful for treatment. At this point it is now expected that a more detailed understanding of the roles of calcium channels in the key processes involved in cancer that will facilitate the development of improved molecular-targeted tools for diagnosis and treatment in future.

IV. REFERENCES

1. Carafoli, E. The calcium-signalling saga: tap water and protein crystals. Nat Rev Mol Cell Biol **4,** 326–332 (2003) doi:10.1038/nrm1073
2. Hofer, A., Brown, E. Extracellular calcium sensing and signalling. Nat Rev Mol Cell Biol **4,** 530–538 (2003) doi:10.1038/nrm1154
3. Christina R. Kahl, Anthony R. Means, Regulation of Cell Cycle Progression by Calcium/Calmodulin-Dependent Pathways, Endocrine Reviews, Volume 24, Issue 6, 1 December 2003, Pages 719–736, https://doi.org/10.1210/er.2003-0008
4. Anne-Sophie Borowiec, Gabriel Bidaux, Natascha Pigat, Vincent Goffin, Sophie Bernichtein, Thierry Capiod, Calcium channels, external calcium concentration and cell proliferation, European Journal of Pharmacology,Volume 739,2014,Pages 19-25,ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2013.10.072.
5. Noriko Takuwa, Wei Zhou, Yoh Takuwa,Calcium, calmodulin and cell cycle progression, Cellular Signalling,Volume 7, Issue 2,1995, Pages 93-104, ISSN 0898-6568, https://doi.org/10.1016/0898-6568(94)00074-L.
6. Monteith, G.R., Davis, F.M. and Roberts-Thomson, S.J., 2012. Calcium channels and pumps in cancer: changes and consequences. Journal of Biological Chemistry, 287(38), pp.31666-31673.
7. Duncan, L.M., Deeds, J., Hunter, J., Shao, J., Holmgren, L.M., Woolf, E.A., Tepper, R.I. and Shyjan, A.W., 1998. Down-regulation of the novel gene melastatin correlates with potential for melanoma metastasis. Cancer research, 58(7), pp.1515-1520.
8. Prevarskaya, N., Skryma, R. and Shuba, Y., 2018. Ion channels in cancer: are cancer hallmarks oncochannelopathies?. Physiological reviews, 98(2), pp.559-621.
9. Zhang, Y., Zhang, J., Jiang, D., Zhang, D., Qian, Z., Liu, C. and Tao, J., 2012. Inhibition of T-type Ca2+ channels by endostatin attenuates human glioblastoma cell proliferation and migration. British journal of pharmacology, 166(4), pp.1247-1260.
10. Patton, A.M., Kassis, J., Doong, H. and Kohn, E.C., 2003. Calcium as a molecular target in angiogenesis. Current pharmaceutical design, 9(7), pp.543-551.
11. Minaguchi, T., Waite, K.A. and Eng, C., 2006. Nuclear localization of PTEN is regulated by Ca2+ through a Tyrosil phosphorylation–independent conformational modification in major vault protein. Cancer research, 66(24), pp.11677-11682.

12. Cook, S.J. and Lockyer, P.J., 2006. Recent advances in Ca2+-dependent Ras regulation and cell proliferation. Cell calcium, 39(2), pp.101-112.

13. Akl, H., La Rovere, R.M., Janssens, A., Vandenberghe, P., Parys, J.B. and Bultynck, G., 2015. HA14-1 potentiates apoptosis in B-cell cancer cells sensitive to a peptide disrupting IP3 receptor/Bcl-2 complexes. International Journal of Developmental Biology, 59(7-8-9), pp.391-398.

14. Kang, S.S., Han, K.S., Ku, B.M., Lee, Y.K., Hong, J., Shin, H.Y., Almonte, A.G., Woo, D.H., Brat, D.J., Hwang, E.M. and Yoo, S.H., 2010. Caffeine-mediated inhibition of calcium release channel inositol 1, 4, 5-trisphosphate receptor subtype 3 blocks glioblastoma invasion and extends survival. Cancer research, 70(3), pp.1173-1183.

15. Monteith, G.R., McAndrew, D., Faddy, H.M. and Roberts-Thomson, S.J., 2007. Calcium and cancer: targeting Ca 2+ transport. Nature Reviews Cancer, 7(7), pp.519-530.

16. Cui, C., Merritt, R., Fu, L. and Pan, Z., 2017. Targeting calcium signaling in cancer therapy. Acta pharmaceutica sinica B, 7(1), pp.3-17.

17. Brouland, J.P., Gélébart, P., Kovacs, T., Enouf, J., Grossmann, J. and Papp, B., 2005. The loss of sarco/endoplasmic reticulum calcium transport ATPase 3 expression is an early event during the multistep process of colon carcinogenesis. The American journal of pathology, 167(1), pp.233-242.

18. Arbabian, A., Brouland, J.P., Apáti, Á., Pászty, K., Hegedűs, L., Enyedi, Á., Chomienne, C. and Papp, B., 2013. Modulation of endoplasmic reticulum calcium pump expression during lung cancer cell differentiation. The FEBS journal, 280(21), pp.5408-5418.

19. Aung, C.S., Ye, W., Plowman, G., Peters, A.A., Monteith, G.R. and Roberts-Thomson, S.J., 2009. Plasma membrane calcium ATPase 4 and the remodeling of calcium homeostasis in human colon cancer cells. Carcinogenesis, 30(11), pp.1962-1969.

20. Mallilankaraman, K., Doonan, P., Cárdenas, C., Chandramoorthy, H.C., Müller, M., Miller, R., Hoffman, N.E., Gandhirajan, R.K., Molgó, J., Birnbaum, M.J. and Rothberg, B.S., 2012. MICU1 is an essential gatekeeper for MCU-mediated mitochondrial Ca2+ uptake that regulates cell survival. Cell, 151(3), pp.630-644.

21. Kale, V.P., Amin, S.G. and Pandey, M.K., 2015. Targeting ion channels for cancer therapy by repurposing the approved drugs. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1848(10), pp.2747-2755.

22. El Hiani, Y., Ahidouch, A., Lehen'kyi, V.Y., Hague, F., Gouilleux, F., Mentaverri, R., Kamel, S., Lassoued, K., Brûlé, G. and Ouadid-Ahidouch, H., 2009. Extracellular signal-regulated kinases 1 and 2 and TRPC1 channels are required for calcium-sensing receptor-stimulated MCF-7 breast cancer cell proliferation. Cellular Physiology and Biochemistry, 23(4-6), pp.335-346.

23. Gkika, D. and Prevarskaya, N., 2011. TRP channels in prostate cancer: the good, the bad and the ugly?. Asian journal of andrology, 13(5), p.673.

24. Guilbert, A., Gautier, M., Dhennin-Duthille, I., Haren, N., Sevestre, H. and Ouadid-Ahidouch, H., 2009. Evidence that TRPM7 is required for breast cancer cell proliferation. American Journal of Physiology-Cell Physiology, 297(3), pp.C493-C502.

25. Giannuzzo, A., Pedersen, S.F. and Novak, I., 2015. The P2X7 receptor regulates cell survival, migration and invasion of pancreatic ductal adenocarcinoma cells. Molecular cancer, 14(1), p.203.

26. Yang, L., Yang, L., Tian, W., Li, J., Liu, J., Zhu, M., Zhang, Y., Yang, Y., Liu, F., Zhang, Q. and Liu, Q., 2014. Resveratrol plays dual roles in pancreatic cancer cells. Journal of cancer research and clinical oncology, 140(5), pp.749-755.

27. Motiani, R.K., Hyzinski-García, M.C., Zhang, X., Henkel, M.M., Abdullaev, I.F., Kuo, Y.H., Matrougui, K., Mongin, A.A. and Trebak, M., 2013. STIM1 and Orai1 mediate CRAC channel activity and are

essential for human glioblastoma invasion. Pflügers Archiv-European Journal of Physiology, 465(9), pp.1249-1260.

28. Kondratska, K., Kondratskyi, A., Yassine, M., Lemonnier, L., Lepage, G., Morabito, A., Skryma, R. and Prevarskaya, N., 2014. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1843(10), pp.2263-2269.
29. Flourakis, M., Lehen'kyi, V., Beck, B., Raphael, M., Vandenberghe, M., Abeele, F.V., Roudbaraki, M., Lepage, G., Mauroy, B., Romanin, C. and Shuba, Y., 2010. Orai1 contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells. Cell death and disease, 1(9), pp.e75-e75.
30. Yang, N., Tang, Y., Wang, F., Zhang, H., Xu, D., Shen, Y., Sun, S. and Yang, G., 2013. Blockade of store-operated Ca2+ entry inhibits hepatocarcinoma cell migration and invasion by regulating focal adhesion turnover. Cancer letters, 330(2), pp.163-169.
31. Aung, H.H., Wang, C.Z., Ni, M., Fishbein, A., Mehendale, S.R., Xie, J.T., Shoyama, A.Y. and Yuan, C.S., 2007. Crocin from Crocus sativus possesses significant anti-proliferation effects on human colorectal cancer cells. Experimental oncology, 29(3), p.175.
32. Rosenberger, S., Thorey, I.S., Werner, S. and Boukamp, P., 2007. A novel regulator of telomerase S100A8 mediates differentiation-dependent and calcium-induced inhibition of telomerase activity in the human epidermal keratinocyte line HaCaT. Journal of Biological Chemistry, 282(9), pp.6126-6135.
33. Alfonso-De Matte, M.Y., Yang, H., Evans, M.S., Cheng, J.Q. and Kruk, P.A., 2002. Telomerase is regulated by c-Jun NH2-terminal kinase in ovarian surface epithelial cells. Cancer research, 62(16), pp.4575-4578.
34. HELSON, L., 1984. Calcium channel blocker enhancement of anticancer drug cytotoxicity—a review. Cancer drug delivery, 1(4), pp.353-361.
35. Kiwit, J.C.W., Hertel, A. and Matuschek, A.E., 1994. Reversal of chemoresistance in malignant gliomas by calcium antagonists: correlation with the expression of multidrug-resistant p-glycoprotein. Journal of neurosurgery, 81(4), pp.587-594.
36. Kondratska, K., Kondratskyi, A., Yassine, M., Lemonnier, L., Lepage, G., Morabito, A., Skryma, R. and Prevarskaya, N., 2014. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1843(10), pp.2263-2269.
37. Kay Klapproth, Sandrine Sander,et al, The IKK2/NF-_B pathway suppresses MYC-induced lymphomagenesis, 2009; DOI 10.1182/blood-2008-09-181008
38. Nabissi, M., Morelli, M.B., Santoni, M. and Santoni, G., 2013. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. Carcinogenesis, 34(1), pp.48-57.
39. Hengartner, M.O., 2000. The biochemistry of apoptosis. Nature, 407(6805), pp.770-776.
40. Orrenius, S., Zhivotovsky, B. and Nicotera, P., 2003. Regulation of cell death: the calcium–apoptosis link. Nature reviews Molecular cell biology, 4(7), pp.552-565.
41. Hara, Y., Wakamori, M., Ishii, M., Maeno, E., Nishida, M., Yoshida, T., Yamada, H., Shimizu, S., Mori, E., Kudoh, J. and Shimizu, N., 2002. LTRPC2 Ca2+-permeable channel activated by changes in redox status confers susceptibility to cell death. Molecular cell, 9(1), pp.163-173.
42. Chow, J., Norng, M., Zhang, J. and Chai, J., 2007. TRPV6 mediates capsaicin-induced apoptosis in gastric cancer cells—Mechanisms behind a possible new “hot” cancer treatment. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1773(4), pp.565-576.

43. Feng, Y.H., Li, X., Wang, L., Zhou, L. and Gorodeski, G.I., 2006. A truncated P2X7 receptor variant (P2X7-j) endogenously expressed in cervical cancer cells antagonizes the full-length P2X7 receptor through hetero-oligomerization. Journal of Biological Chemistry, 281(25), pp.17228-17237.

44. Wissenbach, U., Niemeyer, B.A., Fixemer, T., Schneidewind, A., Trost, C., Cavalié, A., Reus, K., Meese, E., Bonkhoff, H. and Flockerzi, V., 2001. Expression of CaT-like, a novel calcium-selective channel, correlates with the malignancy of prostate cancer. Journal of Biological Chemistry, 276(22), pp.19461-19468.

45. Howe, M.C., Chapman, A., Kerr, K., Dougal, M., Anderson, H. and Hasleton, P.S., 2005. Neuroendocrine differentiation in non-small cell lung cancer and its relation to prognosis and therapy. Histopathology, 46(2), pp.195-201.

46. Makretsov, N., Gilks, C.B., Coldman, A.J., Hayes, M. and Huntsman, D., 2003. Tissue microarray analysis of neuroendocrine differentiation and its prognostic significance in breast cancer. Human pathology, 34(10), pp.1001-1008.

47. Grabowski, P., Schindler, I., Anagnostopoulos, I., Foss, H.D., Riecken, E.O., Mansmann, U., Stein, H., Berger, G., Buhr, H.J. and Scherübl, H., 2001. Neuroendocrine differentiation is a relevant prognostic factor in stage III–IV colorectal cancer. European journal of gastroenterology and hepatology, 13(4), pp.405-411.

48. Moody, T.W., Chan, D., Fahrenkrug, J. and Jensen, R.T., 2003. Neuropeptides as autocrine growth factors in cancer cells. Current pharmaceutical design, 9(6), pp.495-509.

49. Mariot, P., Vanoverberghe, K., Lalevée, N., Rossier, M.F. and Prevarskaya, N., 2002. Overexpression of an α1H (CaV3. 2) T-type calcium channel during neuroendocrine differentiation of human prostate cancer cells. Journal of Biological Chemistry, 277(13), pp.10824-10833.

50. Tsavaler, L., Shapero, M.H., Morkowski, S. and Laus, R., 2001. Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins. Cancer research, 61(9), pp.3760-3769.

51. Bidaux, G., Roudbaraki, M., Merle, C., Crépin, A., Delcourt, P., Slomianny, C., Thébault, S., Bonnal, J.L., Benahmed, M., Cabon, F. and Mauroy, B., 2005. Evidence for specific TRPM8 expression in human prostate secretory epithelial cells: functional androgen receptor requirement. Endocrine-related cancer, 12(2), pp.367-382.

52. Andersson, D.A., Nash, M. and Bevan, S., 2007. Modulation of the cold-activated channel TRPM8 by lysophospholipids and polyunsaturated fatty acids. Journal of Neuroscience, 27(12), pp.3347-3355.

53. Tsavaler, L., Shapero, M.H., Morkowski, S. and Laus, R., 2001. Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins. Cancer research, 61(9), pp.3760-3769.

54. Guilbert, A., Dhennin-Duthille, I., Hiani, Y.E., Haren, N., Khorsi, H., Sevestre, H., Ahidouch, A. and Ouadid-Ahidouch, H., 2008. Expression of TRPC6 channels in human epithelial breast cancer cells. BMC cancer, 8(1), p.125.

55. Cai, X. and Liu, X., 2008. Inhibition of Thr-55 phosphorylation restores p53 nuclear localization and sensitizes cancer cells to DNA damage. Proceedings of the National Academy of Sciences, 105(44), pp.16958-16963.

56. Prevarskaya, N., Zhang, L. and Barritt, G., 2007. TRP channels in cancer. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1772(8), pp.937-946.

57. Bolanz, K.A., Hediger, M.A. and Landowski, C.P., 2008. The role of TRPV6 in breast carcinogenesis. Molecular cancer therapeutics, 7(2), pp.271-279.

58. Folkman, J., 2002, December. Role of angiogenesis in tumor growth and metastasis. In Seminars in oncology (Vol. 29, No. 6, pp. 15-18). WB Saunders.

59. Munaron, L., 2006. Intracellular calcium, endothelial cells and angiogenesis. Recent patents on anti-cancer drug discovery, 1(1), pp.105-119.

60. Kwan, H.Y., Huang, Y. and Yao, X., 2007. TRP channels in endothelial function and dysfunction. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1772(8), pp.907-914.

61. Wei, C., Wang, X., Chen, M., Ouyang, K., Song, L.S. and Cheng, H., 2009. Calcium flickers steer cell migration. Nature, 457(7231), pp.901-905.

62. Potier, M., Gonzalez, J.C., Motiani, R.K., Abdullaev, I.F., Bisaillon, J.M., Singer, H.A. and Trebak, M., 2009. Evidence for STIM1-and Orai1-dependent store-operated calcium influx through I CRAC in vascular smooth muscle cells: role in proliferation and migration. The FASEB Journal, 23(8), pp.2425-2437.

63. Yoshida, J., Ishibashi, T. and Nishio, M., 2007. G1 cell cycle arrest by amlodipine, a dihydropyridine Ca2+ channel blocker, in human epidermoid carcinoma A431 cells. Biochemical pharmacology, 73(7), pp.943-953.

64. Cuddapah VA, Sontheimer H. Ion channels and transporters [corrected] in cancer. 2. Ion channels and the control of cancer cell migration. American Journal of physiology. Cell Physiology. 2011 Sep;301(3):C541-9. DOI: 10.1152/ajpcell.00102.2011.

65. Prevarskaya, N., Skryma, R. and Shuba, Y., 2010. Ion channels and the hallmarks of cancer. Trends in molecular medicine, 16(3), pp.107-121.

66. Maklad, A., Sharma, A. and Azimi, I., 2019. Calcium signaling in brain cancers: roles and therapeutic targeting. Cancers, 11(2), p.145.