Regulation of calcium signaling in lung cancer

Haihong Yang, Qi Zhang, Jianxing He, Wenju Lu

State Key Laboratory of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical College, Guangzhou 510120, PR China

ABSTRACT Lung cancer is the most common malignant tumor in the world. Calcium is a ubiquitous cellular signal, which is crucial in cancer. This review presents regulation of calcium signaling in lung cancer. Altered expression of specific Ca^{2+} channels and Ca^{2+}-binding proteins are characterizing features of lung cancer, which regulate cell signaling pathway leading to cell proliferation or apoptosis. Chemoresistance is frequent in lung cancer. Altered endoplasmic reticulum Ca^{2+} homeostasis of lung cancer cell is correlated with drug resistance. Hypoxia has a vital role in tumor angiogenesis, metastasis, apoptosis. And Ca^{2+} channels are open induced by hypoxia with the increase of Ca^{2+} influx causing tumor growth.

KeyWords: calcium; lung cancer; endoplasmic reticulum; calcium channels; calcium-binding protein

J Thorac Dis 2010; 2: 52–56.

Calcium, as the second messenger, is essential signal transduction element involved in cell growth including cell cycle, differenation, proliferation and apoptosis. Calcium signaling is activated in the cell with pathological condition, which leading to intracellular environment changing and cell abnormal reaction. In general, prolonged increases in Ca^{2+} or long-lasting Ca^{2+} -oscillations (hours) are believed to trigger proliferation, while short lasting, high amplitude elevations of Ca^{2+} can increase mitochondrial Ca^{2+} level and promote cell death (1-3). Therefore, careful control of calcium signaling is required for cell survival. The intracellular calcium concentration plays an important role in cell activities, regulated by release from endoplasmic reticulum stores or influx through a variety of Ca^{2+} ion channels (4). Voltage-gated (VGCC), receptor-gated (ROCC) and store-operated (SOCC) channels in the membrane, along with ryanodine receptors (RynR) and inositol triphosphate receptors (IP3R) at the ER store, provides fluxes of Ca^{2+} to the cytoplasm. Furthermore calcium pumps and ion exchangers are involved in the Ca^{2+} releasing too (5,6). ATPases pumps transport Ca^{2+} against a concentration gradient, including the plasmalemmal Ca^{2+}-ATPase (PMCA) in the plasma membrane which is responsible for the efflux to Ca^{2+} out of cells, and the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) which pump Ca^{2+} from cytoplasm into ER. Ca^{2+} exchangers such as Na+/Ca^{2+} exchanger are crucial in the transport of Ca^{2+} in neurons and cardiac cells (7,8).

ER Ca^{2+}-homeostasis is one of the most important apoptosis pathways. And Ca^{2+} is the crucial effector, so careful control of calcium in ER is important for the cell apoptosis. Figure 1 shows the releasing of Ca^{2+} from ER. Signaling pathway involved in the Ca^{2+} release from the ER are the PLC-IP3 and MAPK, activated by calcium-sensing G-protein-coupled receptor (GPCR). The key receptors regulating Ca^{2+} release from the ER are IP3R and RyR, and SERCA force calcium against the concentration gradient from the cytoplasm into ER. Furthermore Ca^{2+} modulation is performed by calreticulin in the ER (9,10). Reducing of the Ca^{2+} in ER can result from Ca^{2+}-influx from the extracellular space. SOCC in the membrane is activated by the emptying of the intracellular Ca^{2+}-stores causing Ca^{2+} influx. This process is name by store-operated calcium entry (SOCE). SOCE plays a vital role in the cell function including emiocytosis, enzyme activity, cell cycle and apoptosis (11). The most popular channel in SOCE is calcium-release activated calcium (CRAC) channel. Stim1 as the ER Ca^{2+} sensor, the highly Ca^{2+}-selective CRAC channel Orai1 and transient receptor potential (TRPC) as the effector of membrane, expressed in cells (12,13). Moreover Stim1-Orai1 and Stim1-TRPC are important protein complexes in CRAC, and there maybe functional interactions among Orai1, TRPCs, and Stim1 in regualting cell proliferation and apoptosis (14-16).

Lung cancer is the most common malignant tumor in the world. Non-small cell lung cancer (NSCLC) is the majority of lung cancer, approximately 80% of total malignancies, with a 5-year survival of only 15%. The other 20% of total lung cancer is small cell lung cancer (SCLC). Here we focus on how Ca^{2+} might contribute to tumorigenesis and tumor growth in lung cancer.

Calcium channels in cancer

No potential conflict of interest.

Corresponding author: Wenju Lu and Jianxing He, State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou 510120, PR China. Tel: +86-20-83337792, Fax: +86-20-83350363. E-mail: Dr. Wenju Lu: wlu92@yahoo.com; Dr. Jianxing He: jianxing@gird.cn.

Submitted Feb 6, 2010. Accepted for publication Feb 15, 2010.
Available at www.jthoracdis.com

ISSN: 2072-1439

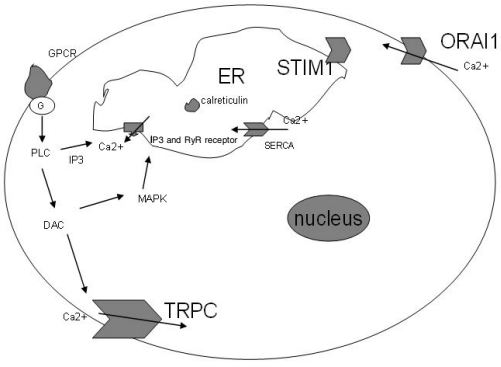

Fig.1 Calcium releasing from ER or influx from the extra cell

Previous data suggest that carcinogenic stimuli cause local increase in the Ca^{2+} concentration leading to activation of proto-oncogenes and to inactivation of tumor-suppressor genes, which lead to the manifestation of a malignant phenotype. Tumor cell proliferation maybe stimulated by persistant increase of Ca^{2+}, in contrary the transitory fulminic increase of Ca^{2+} induce the activation of mitochondrial apoptotic pathway (17). As described above, local increases in Ca^{2+} concentration can be caused by efflux from the ER or influx from the extra cell through Ca^{2+} channels. Most reports show the Ca^{2+} channels increase in the malignant tumors, and the correlations between these channels (VGCC, ROCC and SOCC) and tumor have been addressed widely. Moreover, SOCE induced by SOCC is mostly investigated in the malignant tumor now. T-type Ca^{2+} channels play an important role in controlling cell growth. Similarly the mRNA and protein expression of TRPC famliy are found increasing in the cell lines of breast, prostate and liver cancer, therein TRPC1 and TRPC6 are most popular (18-21). Furthermore, tumor cells growth could be inhibited by silencing these Ca^{2+} channels genes expression. Signal pathway activation, i.e., GPCR-PLC-IP3 or GPCR-PLC-DAG, are improtant for SOCE induced by TRPC, which lead to the increase of calcium concetration activating calcium binding proteins and nuclear transcription factors, causing tumor cell proliferation (22).

Stim1 and Orai1 are essential for tumor cell migration and proliferation in vitro and vivo. In breast cancer, reduction of Orai1 or Stim1 by RNA interference in highly metastatic human breast cancer cells or treatment with a pharmacological inhitor of SOCC decreased tumor metastasis in animal models (23). In liver cancer, it's reported that TRPC6, Stim1 and Orai1 regulate tumor migration and proliferation together (24). SOCE amplitude could be reduced by Stim1 and Orai1 knockdowns, suggesting possible cooperation between these proteins and TRPC6 in controlling tumor proliferation and apoptosis. However the mechanism is still unknown.

L-type calcium channel (LTCC) is widely studied in VGCC. It was shown that colon cancer cells expressed LTCCmRNA, comprising an alph-1D and a beta-3 subunit. The selective calcium channel agonist could dose-dependently increase intracellular Ca^{2+} levels and the level of apoptosis in colon cancer cells. On the contrary, the inhibitor of calcium channels could abolish completely the above results (25). However Berchtold had the contrary report in B-lymphoma and breast cancer cells (26). The inhibitor of LTCC reduced the level of calcium-dependent NF-κ B in tumor cells which expressing LTCC subunit Cav1.3 gene, causing the decrease of calcium influx and the increase of apoptosis in tumor cells. The difference of the above results may be due to the different subunits of LTCC expressed by tumor cells, determining Ca^{2+} to participate in proliferation or apoptosis in tumor cells.

Calcium channels and lung cancer

Lambert Eaton myasthenic syndrome (LEMS) is usually associated with SCLC. VGCC (P/Q subtype) antibodies are often found in these patients, which play a pathogenic role in LEMS. Monstad et al showed that VGCC antibodies were seen in a proportion of SCLC patients, thus similar immunoreaction maybe exist in SCLC. But the VGCC antibodies do not correlate with the prognosis of the SCLC (27). There are a few researches about calcium channels in NSCLC. Report by Carlisle, et al. showed that nicotine could activate LTCC inducing the increase of Ca^{2+} influx in 273T NSCLC cell line, which inhibited by the inhibitor of nicotinic acetylcholine receptor or PI3K (28). A study performed in NSCLC cell lines found that overexpression of CACNA2D2 gene (a subunit of the Ca^{2+}-channel complex) induced apoptosis in H1299, H358, H460 and A549 cell lines through elevating intracellular free Ca^{2+} level (29).

Calcium–binding proteins and lung cancer

Ca^{2+} appears to exert mitosis or apoptosis of cells as a secondary messenger or signal transducer determined by its location, intracellular concentration and so on. Ca^{2+} store, releasing and uptake in all cells except muscle cell are regulated by ER. After IP3 binding with IP3 receptor of ER, Ca^{2+} channels are open associated with the increase of intracellular Ca^{2+} concentration. Then Ca^{2+}-dependent proteins or Ca^{2+}-binding proteins are stimulated exerting cell biological effects. A number of Ca^{2+}-binding proteins have been characterized as having properties, to play a role as putative intracellular Ca^{2+} receptors.

The reaction to Ca^{2+} in cells lies on Ca^{2+}-binding proteins and Ca^{2+}/CaM -dependent kinase. CaM has a vital role in transferring signal out of cells into intracellular biological effects as the predominant receptor of Ca^{2+}. CaM is a small, heat and acid-stable protein which exists as a monomer and presents four similar but distinguishable Ca^{2+}-binding domains allowing interacting with different poteins (30). It was found that the CaM level of lung cancers was significantly higher than that of host lungs, benign lung diseases and normal lungs and significantly correlated with the histopathological grading and TNM staging of lung cancers. Moreover, there was a significant positive correlation between the cellular DNA content and tissue CaM level in lung cancers. So it's be-

lieved that CaM plays an important role in the proliferation of lung cancer cells (31). CaMⅡ phosphorylation could activate all kinds of kinases or transcription factors regulating tumor proliferation and apoptosis. Death - associated protein kinase (DAPK) is one of these kinases, which involved in DNA damage-induced apoptosis and showed low level in the early stage of NSCLC. Thus DAPK is crucial in the progression of NSCLC (32). Camp-regulatory element-binding protein (CREB) is a key transcription factor in NSCLC, which can be activated through phosphorylation by a number of kinases including Ca^{2+}/CaM-dependent kinases. CREB is overexpressed and constitutively phosphorylated in NSCLC, and appears to play a direct role indisease pathogenesis and prognosis (33).

Calcineurin (CaN) is serine/threonine protein kinase regulated by Ca^{2+}/CaM, which exert biological effects through dephosphorylation. Maxeine, et al demonstrated that nuclear factor of activated T cells c2 (NFATc2) mediated by CaN expressed low level of mRNA in NSCLC, furthermore more and large tumors were developed and T cell immunity decreased in NFATc2 (-/-) mice (34). Mitochondrial stress can cause resistance to apoptosis in cancer. Both insulin and insulin-like growth factor-1 receptor (IGF1R) are increased in response to mitochondrial stress. CaN is activated as part of this stress signaling. In A549 lung cancer cell line, inhibiting CaN expression using inhibitor or small interference RNA could inhibit significantly the IGF1R pathway which is important in tumor cell proliferation and reduced apoptosis (35).

ER stress can induce cell apoptosis, which is one of the most important pathways of apoptosis in vivo. The imbalance of the ER Ca^{2+} homeostasis results in ER stress and cell apoptosis. Calreticulin is important Ca^{2+}-binding protein in ER. The cell is more sensitive to apoptosis while the protein is overexpressed. Recent investigation suggests that in the SCLC (H1339) and NSCLC (HCC) cell lines the ER Ca^{2+}-content was reduced and correlated with a decreased level of calreticulin compared to NHBE cell line, which could lead to reduced apoptosis in cells (36).

Calcium and chemoresistance

Chemotherapy often leads to encouraging reponses in lung cancer. But, in the course of the treatment, resistance to chemotherapy ultimately limits the life expectancy of the patient. Intracellular calcium concentration may play a role in the development of chemoresistance. Altered Ca^{2+} homeostasis of cell is correlated with cisplatin or Taxol resistance in NSCLC cell lines (A549 and EPLC) or SCLC cell line (H1339). The Ca^{2+} content of the ER is decreased with the low level of SERCA expression in chemoresistant lung cancer cell lines. Thus a reduced Ca^{2+} content of the ER maybe induce chemoresistance in lung cancer (37,38).

Multi drug resistance (MDR) is a process where malignant cells become resistant to structurally diverse chemotherapeutic agents exposure to a single type of cytotoxic drug. Certain cell lines have been associated with a decrease of drug accumulation due to enhanced efflux of drugs, which is attributed to the overexpression of the P-gp (39). Calcium channel and calmodulin antagonist could reverse the drug resistance due to MDR. It has been suggested that the antagonist may have pharmacological effects like calmodulin or protein kinase C inhibition causing P-gp primary structure or post translational modification and changing of functional state of P-gp (30).

Calcium, hypoxia and lung cancer

Calcium channels are open induced by hypoxia with the increase of Ca^{2+} influx. During the progression of malignant tumor, with the tumor size increasing hypoxia can occur in the local region. Thus hypoxia has a vital role in tumor angiogenesis, metastasis, apoptosis and chemoresistance. Hypoxia inducible factor 1 (HIF-1) is important protein involved in regulation of the transcriptional of a variety of genes related to oxygen homeostasis and hypoxia, which is crucial in the occurrence and development of NSCLC (40,41). The mutation of PI3K or PTEN is one of the most important mechanisms related to HIF-1α activation under normoxic condition. However, HIF-1 proteins could be stimulated through MAPK pathway no matter hypoxia or not, and increasing of Ca^{2+} influx and calmodulin would act upstream of ERK in the hypoxia signal transduction pathway leading to enchanced HIF-1 transcriptional activity (42,43). In NSCLC, induced by hypoxia, Zhang et al. reported that nicotine increased HIF-1α and VEGF expression in A549 cell line, which could be inhibited after blocked by Ca^{2+}/calmodulin inhibitor (44).

No matter whether hypoxia or normoxia exists, NF-κB is the vital transcriptional factor in the progress of tumor development. Under normoxic condition, the expression of LTCC subunit Cav1.3 mRNA is increased in B-cell lymphoma and breast cancer cell lines. Moreover CaM-dependent NF-κB is activated with the increasing of Ca^{2+} influx (26).ER stress or overload (accumulation of proteins in the ER membrane) can lead to efflux of Ca^{2+} from ER through IP3R or RyR activating NF-κB pathway (45). However now there is no similar research under hypoxic condition. In liver and brain cells, NF-κB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1α in vivo and vitro (46). But the above result is still unidentified in lung tissues, so we believe it is possible that CaM-dependent NF-κB is activated to hypoxic condition by the increase channels of Ca^{2+} and play a vital role in regulating HIF-1α or other downstream genes which may be enhanced by nicotine.

Conclusion

Ca^{2+} regulates various cellular processes by activating or inhibiting cellular signaling pathways and Ca^{2+}-regulated proteins, and it deserves to do further researches in lung cancer. Since tumorigenesis and tumor growth in lung cancer are complicated and multiple factor resulted, the role of Ca^{2+} in lung cancer cells is complicated

too, which is determined by its location and combined proteins, moreover different subtypes of Ca^{2+} channel may play a various role in it.

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