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Journal of Cellular Signaling Commentary

Emerging Role of TRPML1 Mucolipin Endolysosomal Channel in Cancer

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Abstract

The transient receptor potential mucolipin 1 (TRPML1) is an endolysosomal channel belonging to the TRP family. Clinically, mutations of TRPML1 have been responsible for a severe lysosomal storage disorder called mucolipidosis type IV.

The TRPML1 channels localize mainly in the endosome/lysosome compartments, where they control the endocytosis, exocytosis and autophagy processes.

TRPML1 is a reactive oxygen species sensor that orchestrates an autophagy-dependent program, to mitigate oxidative stress. In homeostatic condition TRPML1 controls cell viability; mild stress stimulates macroautophagy or chaperone-mediated autophagy and cell survival, whereas in severe cellular stress conditions it triggers autophagic cell death or apoptosis.

Changes in TRP channels expression are associated with cancer transformation. In the same view, both up and down-regulation of TRPML1 mRNA and protein expression is associated with different cancer types. HRAS-mutated head and neck and bladder urothelial cancers, non-small-cell lung carcinoma, melanomas, triple-negative breast cancers and pancreatic cancer, all show TRPML1 up-regulation. At the other hand, TRPML1 is down-regulated in glioblastoma and reduction/loss of TRPML1 represents a negative prognostic factor.

An increased level of complexity of the TRPML1 channel is represented by its capability to form homo- and heterodimers with other members of TRPML or two-pore channels forming new functional channels. Finally, the TFEB transcriptional factor, targeting the TRPML1 promoter is altered in pancreatic cancer and is associated with poor prognosis of non-small-cell lung carcinoma patients.

Overall, we present interesting and recent data strongly suggesting for an important role played by TRPML1 in cancer. Further researches are needed to understand in depth contribution of this channel in the neoplastic transformation and progression of cancer.

Keywords: TRP; TRPML1; Ion channel; Lysosome; Autophagy; Cell death; Cancer

Commentary

The transient receptor potential mucolipin 1 (TRPML1) channel is a proton-impermeable, cation-selective channel codified by the *MCOLN1* gene located on human chromosome 19 (19p13.2-13.3). It belongs to the TRP family and TRPML subfamily of endosome/lysosome Ca^{2+} channels, also consisting of TRPML2 and TRPML3 channels [1].

The TRPML1 has been identified as a genetic determinant of mucolipidosis type IV (MLIV), a severe lysosomal storage disorder (LSD) that displays cognitive, linguistic, visual and motor deficits [1,2]. Loss of TRPML1 promotes reactive oxygen species (ROS) production, and oxidative damage represents an important pathogenic factor in

MLIV pathogenesis [3].

Basically, TRPML1 plays a role in the homeostatic control of steady state of cells by regulating cell viability. In normal cells, growth factor or glucose deprivation, starvation as well as mild oxidative stress trigger the macroautophagy or the chaperone-mediated autophagy, that rescues the stress-exposed cells to death, whereas severe cellular or oxidative stress stimulate cell death through autophagy cell death or apoptosis [4].

Up- or down-regulation of baseline TRPML1 protein expression is associated with the acquisition of a tumor phenotype, strongly suggesting that changes in their expression likely represent an early event in tumorigenesis of glioblastoma (GBM). In this regard, glioma stem/progenitor-like cells, the source origin of GBM express the TRPML1 channels (Unpublished data). Moreover, activation of TRPML1 by specific agonist induces cytotoxic effects, whereas pharmacological or genetic inhibition of TRPML1 expression induces defective autophagy [3].

In this regard, HRAS-mutated head and neck and bladder urothelial cancers [5,6], non-small-cell lung carcinoma (NSCLC) [7], melanomas [5,8], triple-negative breast cancers [9] and pancreatic cancers patients [10] showed TRPML1 up-regulation. On the contrary, we evidenced for the first time, that TRPML1 is expressed although at lower levels in GBM tissues and cell lines as compared to normal human astrocytes, both at mRNA and protein levels [11]. The mechanisms that accompany changes in TRPML1 expression during cancer development and progression are still not understood. Gain or loss of functions, epigenetic alteration in the methylation state might be suggested to be involved.

Our findings demonstrated that activation of GBM cell lines with MK6-83 specific for the TRPML1 and TRPML3 channels, in T98 and U251 cells lacking of the TRPML3 mRNA expression, induces $[Ca^{2+}]_i$ rise and caspase-3-dependent apoptosis. Neither calcium release, nor caspase activation nor apoptosis are evidenced in TRPML1-silenced GBM cells treated with MK6-83 [11].

The TRPML1 protein, as the other members of TRPML subfamily, is localized at subcellular levels in the endosome/lysosome compartments where it controls the vesicular trafficking, the fission/fusion events, the endocytosis/exocytosis and the biogenesis and the maintenance of the integrity of lysosomes [12]. Interestingly, in GBM cells, we confirmed its subcellular localization in lamp-1 positive structure, but we also demonstrated the expression of TRPML1 in the perinuclear and nuclear region of GBM cells. This result is not a really surprise, because other TRP channels (e.g., TRPM2) are expressed in the nucleus of tumor cells, but not normal cells [13]. In this regard, we are conducting studies to understand the mechanism involved in the nuclear translocation, the contribution of the transcription factor EB (TFEB), and whether the TRPML1 protein directly affects the transcription of genes involved in neoplastic transformation or progression.

TRPML1 is considered a ROS sensor that orchestrates an autophagy-dependent program, to mitigate oxidative stress whether it is possible, or activating cell death mechanism in cells undergone severe DNA damage [4]. In this regard, we found that exposure of GBM cells to the mitochondrial respiration inhibitor, carbonyl cyanide m-chlorophenylhydrazone, commonly used to induce ROS generation, reduces the mitochondrial transmembrane potential and induces autophagic cell death, with both Ca^{2+} release and ROS generation [11]. Overall, the severe alteration of mitochondria and the subsequent cell death strongly suggest for a ROS-mediated mitophagy process.

Which are the molecular mechanisms and signaling pathways acting both up- and down-stream the TRPML1 receptors? TRPML1 is activated by phosphatidylinositol-3,5-biposhate and inhibited by phosphatidylinositol-4,5-biphoshate, suggesting that the phosphoinositide (PI) pathway may be important in TRPML1-mediated signaling [14]. Thus, a role for Protein kinase B (AKT)/extracellular signal-regulated kinase (ERK) as well as mammalian target of rapamycin complex 1 (mTORC1) and RAS-ERK in TRPML1-expressing cancer cells has been provided [5,15].

In regard to the clinical relevance of the modification of the TRPML1 levels in cancer, high levels of TRPML1 expression has been found associated with poor clinical characteristics of pancreatic cancers patients [10], and on the contrary, mostly important for clinical significance, TRPML1 is down-regulated or lose in GBM cells. In this regard, our data strongly demonstrated that reduction or complete abrogation of TRPML1 expression represents a negative prognostic factor in GMB patients [11]. In addition, on the basis of the residual TRPML1 expression might be possible to stratify different risks of mortality in GBM patients.

Moreover, TRPML1 heteromerizes with the two-pore channels (e.g., TPC1 and TPC2) or TRPML3 to form new functional channels. In this regard, a role of TPCs in cancer cell migration and tumor dissemination has been provided by Nguyen [16]; silencing of TPCs reduces the integrin β1-mediated adhesion, migration of invasive tumor cells and the formation of lung metastasis in an *in vivo* mouse model. In addition, a role for TPC2 in tumorigenesis of melanoma cells has been recently reported [17].

Finally, TFEB dislocates in the nucleus, where it activates a lot of genes, including TRPML1. Altered TFEB expression and activity has been associated with pancreatic cancer proliferation [18] and NSCLC autophagy, motility and poor prognosis [19]. Finally, kidney specific TFEB overexpression in transgenic mice resulted in renal clear cells and papillary carcinoma with hepatic metastasis [20].

Taken together, these finding strongly suggest for a role of TRPML1 as a target of different cancer cells and potentially suggest a novel therapeutic approach.

Conflicts of Interest

Authors declare no conflict of interest.

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