



Subcellular localization of TRPM2 determines the fate of cancer cells, apoptosis or survival

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Zhao *et al.* have recently shown TRPM2 channel as a potential therapeutic target to control oral squamous cell carcinoma (1).

TRPM2 channel is a member of transient receptor potential (TRP) superfamily and Ca⁺-permeable non-selective cation channel broadly expressed in brain, spleen, liver, pancreatic β -cell and immunocytes (2). TRPM2 is well known to be activated by oxidative stress and an endogenous agonist adenosine diphosphoribose (ADPR), and has sensitivity to temperature (3). Ca⁺-influx through its activation leads cell death upon oxidative stress (4). Most recently, functional expression of TRPM2 has been shown in warm-sensitive neurons in hypothalamus preoptic area and sensory/autonomic neurons, suggesting its roles in the regulation of body temperature (5,6). TRPM2 was reported to function in plasma membrane to cause intracellular Ca⁺-elevation and membrane depolarization (2). On the other hand, the function as a Ca⁺ release channel was also reported in lysosomal membrane of dendritic cell and INS-1 β -cell (7,8).

Head and neck squamous cell carcinoma (HNSCC) is a malignant cancer with high mortality and poor prognosis with an annual incidence of around 600,000 worldwide (9). Although several therapeutic approaches to control HNSCC has been challenged, the efficiency is still limited (10). Zhao *et al.* compared the TRPM2 expression between SCC

and normal tissues, and evaluated the function of TRPM2 in cancer survival. TRPM2 expression was shown to be significantly higher in carcinoma compared with papilloma and control human tongue tissues. Correspondingly, TRPM2 expression was significantly higher in carcinoma cell lines (SCC9 and SCC25) than in control epithelial cells (HIOEC). Although the functional expression of TRPM2 in plasma membrane was confirmed by whole-cell patch-clamp recordings in carcinoma SCC9 cells, most of immunoreactive signals were located in nucleus. These results are consistent with the previous reports from two independent groups. Zeng *et al.* showed that TRPM2 expression was increased in prostate cancer tissues of human patients and subcellular localization of TRPM2 was different between non-cancerous and cancerous prostate epithelium cells (11). TRPM2 was highly localized in nucleus of cancer cells (PC-3 and DU-145) in contrast to its localization in plasma membrane in normal (RWPE-1) and benign cells (BPH-1). The same report showed that down-regulation of TRPM2 by siRNA attenuated the cell proliferation in prostate cancer cells but not in normal and benign cells, suggesting that nuclear TRPM2 in cancer cells promotes proliferation. Hopkins *et al.* also showed increased nuclear localization of TRPM2 in breast adenocarcinoma cells (MCF7 and MDA-MB-231) compared with

non-cancerous cells (MCF10A and HMEC), and pharmacological inhibition of TRPM2 and gene silencing of TRPM2 induced lagging of cancerous cell proliferation without affecting in non-cancerous cells (12). These data suggest that altered subcellular localization of TRPM2 to nucleus provides the function to enhance proliferation of cancerous cells, which seems to be different from TRPM2 function in plasma membrane.

Zhao *et al.* have also shown that TRPM2 could be involved in migratory activity and cell survival of cancer cells. Down-regulation of TRPM2 by shRNA lowered migratory activity of SSC9 carcinoma cells. In addition, surprisingly, down-regulation of TRPM2 also increased the number of apoptotic cells double-labeled with propidium iodide and annexin V with increased p21 and decreased p53 expression, suggesting the apoptosis independent of the p53-p21 pathway. These data suggest that a basal activity or function of TRPM2 facilitates cancer survival.

TRPM2 is a Ca⁺-permeable non-selective cation channel. Given functional expression of TRPM2 in nucleus, its activation might cause change in nuclear Ca⁺ concentrations [Ca⁺]_n, even though there still remain unsolved questions if TRPM2 could function as ion channel in nucleus and which outer or inner membrane of double-membrane nuclear envelope TRPM2 is arranged in. [Ca⁺]_n is elevated by the propagation of cytosolic Ca⁺-increase, however, Ca⁺-mobilizing machineries such as IP₃ receptor are localized in nuclear envelope, suggesting that [Ca⁺]_n is also increased by Ca⁺-release from nuclear cistern or continuing ER with outer membrane of nuclear envelope (13). Such regulated [Ca⁺]_n signal is considered to modulate gene expression. Regulation of gene expression has been reported for L-type voltage-dependent Ca⁺ channel (LVCC) which is not directly mediated by Ca⁺-elevation through activated channels. Cleaved C-terminal fragment of LVCC (calcium channel activated transcriptional regulator, CCAT) translocates to nucleus and regulates transcription (14). The novel discovery by Zhao *et al.* provided the possibility of TRPM2 channel as a therapeutic target to control oral squamous cell carcinoma. Clinical effectiveness without side effects could be provided by inhibition of TRPM2 in nucleus without affecting its function in plasma membrane or by inhibiting nuclear translocation of TRPM2 in cancer cells. To realize the goal, further analyses are needed to explore the detailed TRPM2 function in nucleus and molecular mechanism that changes subcellular localization of TRPM2 in cancer cells.

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