Transcript receptor potential channel C5 in cancer chemoresistance

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The transient receptor potential (TRP) superfamily contains at least 28 homologs in mammalian. These proteins form TRP channels are permeable to monovalent and divalent cations and participate in a variety of physiological functions. Dysregulation of TRP channels is responsible for numerous diseases. This review provides a brief short overview of mammalian TRP channels with a focus on TRPC5 and its role in cancers. Dysregulation of TRPC5 interrupts Ca2+ homeostasis in cancer cells, which activates signaling pathways that are highly associated with cancer progression, especially cancer chemoresistance. Based on the important role of TRPC5, we also discuss the potential of TRPC5 as a target for therapeutic intervention. Either direct targeting of TRPC5 or indirect interruption of TRPC5-related signaling pathways may effectively overcome cancer chemoresistance.

Keywords: transient receptor potential channel C5; cancer chemoresistance; drug target

Overview of TRP channels

The 28 transient receptor potential (TRP) family members constitute 6 sub-groups in mammals: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin). Generally, TRP proteins reside in the plasma membrane as six transmembrane-domain polypeptide subunits, which usually require four subunits to assemble homo- or hetero-oligomeric pores into functional channels. TRP channels are permeable to both monovalent and divalent ions, except for TRPV5 and TRPV6, which are specific for Ca2+ ions, and TRPM4 and TRPM5, which are highly selective for monovalent cations.

TRP channels exist in almost every tissue and cell type. They provide a molecular framework for understanding important physiological functions, such as sensory transduction, neuronal growth-cone guidance, and vascular function. For example, their participation in the response to thermal and chemical nociceptive stimuli is one of the most widely-studied roles in sensory transduction. These stimuli activate TRPV1, TRPM8, and TRPA1 channels in afferent sensory neurons to induce pain[3]. In addition, TRP channels (especially TRPM5) are critical in taste receptors for sensing sweet, bitter, and umami modalities[3]. Furthermore, TRPC channels participate in mediating attractive and repulsive growth-cone turning during axonal pathfinding[3]. TRP channels, such as those in the TRPC, TRPV, and TRPM subgroups, are also essential mediators of vascular functions such as arterial tone, angiogenesis, and permeability[4].

Given the important physiological roles of TRP channels, TRP channelopathies are associated with a range of diseases[5]. For example, mutation of TRPP2 leads to autosomal dominant polycystic kidney disease[6], and mutations in TRPV4 have been associated with skeletal dysplasias such as autosomal dominant skeletal dysplasia and Charcot-Marie-Tooth disease[7,8].

As one of the most widespread and life-threatening diseases, the relationship between cancer and TRP channels has also been studied. The main role of TRP channels in cancer is mediating a dysregulated Ca2+ homeostasis either by triggering Ca2+ entry pathways or changing membrane polarization. TRP channels interfere with critical cancer signaling pathways via dysfunction in Ca2+ signaling, causing perturbations in proliferation, apoptosis, gene transcription, and angiogenesis. For example, dysfunctional TRPM8[9], TRPV1[10], TRPC6, TRPC1, and TRPC4[11] promote malignancy, and TRPC6 contributes to the angiogenesis process in cancers[12,13]. Recently, we identified an essential role for TRPC5 in the occurrence and progression of chemoresistance in different cancers studied in
**Introduction to TRPC5**

TRPC5 is a homolog of the TRPC subgroup. The TRPC subgroup includes seven members (TRPC1-TRPC7). TRPC3, 6, and 7 are highly similar in structure and function, and TRPC4 and TRPC5 share structural and functional similarities. The TRPC proteins are ubiquitously expressed in mammalian cells, except for TRPC2, which is absent in humans, world monkeys, and apes."hibited by TRPC5 overexpression due to the non-selective extrusion of amphipathic drugs by p-gp. These drugs include Adriamycin, paclitaxel, and 5-fluorouracil, and each has a different mode of action.

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**Ca**^{2+} influx is sufficiently versatile to transmit various cancer signals. Cancer cells appear to employ TRPC5-related Ca**^{2+} signals in addition to those producing p-gp to acquire chemoresistance (Figure 1A). The Wnt/β-catenin pathway is activated when Ca**^{2+} is manipulated via TRPC5 channels. Subsequently, Wnt/β-catenin mediates the epithelial-mesenchymal transition of cancer cells, which is an important step in malignancy and chemoresistance development because of the high self-renewal, anti-apoptotic, and migratory features of mesenchymal cells. Additionally, TRPC5/Ca**^{2+} dysregulation has been demonstrated to promote tumor angiogenesis mediated by hypoxia-inducible factor 1 (HIF-1). The dense vasculature in the tumor not only enables cancer cells to escape from sites exposed to high doses of anti-cancer drugs, but it also garners additional nutrition to aid tumor survival, which in turn results in a poor chemotherapeutic outcome.

How TRPC5 becomes enriched is still a mystery, although epigenetic regulation may play a role. MicroRNA-320a (miR-320a), which may be a tumor suppressor, has been demonstrated to target and degrade the mRNA of both TRPC5 and NFATC3. However, the promoter in the gene encoding miR-320a is hypermethylated in chemoresistant cancer cells, which silences the miRNA and activates the TRPC5-NFATC3-p-gp pathway. Because epigenetic responses are sensitive to environmental stresses, as they can rapidly respond to certain circumstances (such as challenges from chemotherapeutic agents) to regulate various critical genes/networks, epigenetic regulation on TRPC5 and NFATC3 may suggest that this network is important and effective for developing chemoresistance.

Any tumor mass is heterogeneous, and some cancer cells may develop TRPC5-related chemoresistance when surviving chemotherapy while others may not directly confront the cytotoxicity of a drug and remain sensitive, which would not favor cancer progression. However, chemoresistant cancer cells usually adopt ways towards survival not only by inheriting genomic or epigenetic changes via replication but also by directly transmitting TRPC5 signals to their ‘weaker’ neighbors. To achieve transmission, the chemoresistant cancer cells pack the overexpressed TRPC5 proteins into mobile sub-
cellular structures known as extracellular vesicles (EVs) and transfer TRPC5 to sensitive cancer cells\(^{[18]}\) (Figure 1B). Because part of the phospholipid bilayer membrane of an EV contains the plasma membrane of the donor cells\(^{[53]}\), TRPC5 channels are already present on the EV membrane. When the EV finally merges with a recipient cell, TRPC5 is immediately activated on the plasma membrane that promotes the development of TRPC5-NFATC3-p-gp-mediated chemoresistance. Therefore, TRPC5’s packaging into the limited EV volume serves a vital role in chemoresistant signaling in cancer cells. In addition, in the field of EV biology, the cumulative evidence suggests that ion channels, including TRPC5 and other different TRP channels, are preferentially built into EVs because they are easily transferred and can quickly activate a variety of signaling pathways in recipient cells. Therefore, it is valuable to explore the type and mechanism of TRP channels that are packaged and transferred by EV during certain physiological or pathological conditions.

To date, most chemoresistance is observed during the later period of treatment, where patients are suffering from toxic-
ity in the presence of futile chemotherapy. However, TRPC5 is a good candidate for diagnosing chemoresistance and may help avoid exposing cancer patients to unnecessary chemotherapy. Based on our previous studies on cancer EVs, which are densely localized to the circulatory system and precisely reflect the pathological features of the donor cells \cite{34-36}, we demonstrated that the quantity of TRPC5 mRNA in circulating EVs correlates with the clinical response to chemotherapy \cite{18} (Figure 1B). Therefore, if validated in a larger population, it may not only be possible to predict chemoresistance by analyzing TRPC5 levels in peripheral blood before initiating chemotherapy but also allow us to monitor the development of chemoresistance during or after chemotherapy.

**TRPC5 channel as a potential drug target**

To date, compared with other features of cancer progression, such as anti-apoptosis and angiogenesis, an effective means of inhibiting or reversing chemoresistance in the clinical setting remains elusive. However, TRPC5-based studies may provide insight into the development of anti-chemoresistance drugs. Inhibition of TRPC5 with siRNAs, the TRPC5-specific blocking antibody T5E3, and the pharmacological TRPC5 antagonist aminoethoxydiphenyl borate have been demonstrated to reduce chemoresistance to different chemotherapeutic agents in breast and colorectal cancers in vitro and in vivo. These observations suggest that therapeutic intervention targeting TRPC5 can effectively diminish chemoresistance. Additionally, combining TRPC5 modulators with chemotherapeutic agents may enhance routine chemotherapeutic regimes, as has been demonstrated in animal models \cite{177}.

Because TRP channels, including TRPC5, occur in all cell types and modulate numerous cellular functions, side effects may present a major hurdle in TRP-based therapy. Therefore, TRP treatment accompanied by suitable drug delivery technology represents a reasonable strategy. In recent years, advances have been made in organ-specific drug delivery in the anti-tumor field, and nanocarriers with homing peptides could provide a basis for TRP-based treatment \cite{177}. Furthermore, EVs have garnered excitement in the drug delivery field because they are naturally occurring stable vehicles that transport functional proteins, lipids, mRNAs, and miRNAs. Therefore, as TRP channels may vitally participate in the activity of EVs, and EVs naturally target specific recipient cells, engineered EVs may be quite effective for delivering agents in TRP-mediated therapies.

**Conclusion**

TRPC5 channel research has unveiled a pathogenic role for TRPC5 and highlights its potential for aiding the development of successful cancer therapies and diagnostic tools. Furthermore, translational research needs to be combined with clinical, pharmaceutical, and other fields of research to maximize the success of developing clinically useful TRPC5 drugs.

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