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ORIGINAL ARTICLE

TARGETING TRPC3: ADVANCES IN DRUG DISCOVERY AND THE PATH TO CLINICAL APPLICATIONS

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ABSTRACT : The transient receptor potential canonical 3 (TRPC3) channel represents a critical molecular target with significant therapeutic potential across multiple disease domains. Recent advances in pharmacological research have unveiled sophisticated strategies for selectively modulating this ion channel, promising transformative interventions in neurological, cardiovascular, and oncological conditions. Pioneering research has demonstrated remarkable progress in developing highly selective TRPC3 inhibitors. The breakthrough pyrazole derivative Pyr3 marked a significant milestone, providing the first selective inhibition mechanism with minimal off-target effects. Subsequent developments, such as the novel compound 60a, have further refined targeting strategies, exhibiting enhanced potency and unprecedented selectivity for TRPC3 channels. TRPC3 channels play pivotal roles in diverse pathological processes, including neurodegeneration, cardiac remodeling and cancer progression. Emerging pharmacological interventions focus on precise channel modulation, with promising applications in Alzheimer's disease management, cardiac dysfunction treatment and potential anti-cancer strategies. The channel's unique molecular architecture enables complex interactions with cellular signaling pathways, suggesting multifaceted therapeutic approaches. Contemporary research explores advanced approaches like photopharmacology to achieve spatiotemporally precise channel interventions. The development of compounds with improved metabolic stability and selective binding characteristics represents a critical advancement in translational medicine. Computational modeling and structural biology techniques have provided unprecedented insights into the channel's molecular configuration, enabling more targeted drug design strategies. Despite significant progress, substantial research gaps remain in fully understanding TRPC3's complex molecular mechanisms. Future investigations must focus on developing more sophisticated pharmacological agents with enhanced specificity and minimal systemic side effects. The intricate nature of TRPC3's activation and inactivation processes requires comprehensive interdisciplinary research approaches. The ongoing exploration of TRPC3 as a therapeutic target demonstrates immense potential for developing innovative molecular interventions across multiple medical domains. By continuing to unravel the channel's complex functional characteristics, researchers can potentially revolutionize treatment strategies for challenging medical conditions, offering hope for more precise and personalized therapeutic approaches.

Key words : TRPC3, ion channel modulation, pharmacological targeting, neurological disorders, molecular therapeutics.

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INTRODUCTION

TRPC3 emerges as a critical molecular target with profound implications for understanding complex cellular processes and disease mechanisms (Onohara *et al,* 2006). As a non-selective cation channel, TRPC3 represents a sophisticated molecular gateway that plays a pivotal role in cellular communication and signal transduction across multiple physiological systems. The molecular architecture of TRPC3 is characterized by

unique sensory features, most notably its direct recognition and activation by diacylglycerols (DAG) (Numaga-Tomita *et al*, 2016). Abundantly expressed in the cerebellum, cerebrum, and smooth muscles, this channel is essential for regulating neurogenesis and calcium signaling. Its distinctive structural elements include an unusually long S3 helix and a remarkable ability to sense external stimuli through a cavity-like feature located above the lipid bilayer (Gupta *et al*, 2024). Disease pathogenesis linked to TRPC3 spans a broad spectrum of medical conditions. Dysfunction of this channel has been critically associated with neurodegenerative diseases, cardiac hypertrophy, and ovarian adenocarcinoma (Harada *et al,* 2012). In the cardiovascular system, TRPC3 plays a significant role in cardiac remodeling, particularly through its involvement in the angiotensin II and noradrenaline-induced nuclear factor of activated T cells (NFAT) activation pathway. This mechanism contributes to maladaptive cardiac processes, including arrhythmias and heart failure. The channel's significance extends to neurological and immunological domains(Bhatt *et al,* 2024). TRPC3 demonstrates a remarkable capacity to regulate calcium entry through multiple mechanisms, including intricate interactions with the sodium-calcium exchanger NCX1. Its expression varies across different tissue types and developmental states, suggesting a nuanced role in cellular function and differentiation (Ghai *et al*, 2022). Therapeutic potential for TRPC3 is particularly promising, with researchers exploring multiple intervention strategies. Innovative approaches include photopharmacology and optochemical genetics, which offer unprecedented precision in targeting this molecular mechanism (Abhishek *et al,* 2024). The development of specific inhibitors like Pyrazole 3 (Pyr3) represents a significant breakthrough, demonstrating the potential for highly selective channel modulation (Oda *et al,* 2017). The channel's molecular complexity presents both challenges and opportunities for drug discovery. Its unique structural features, including a highly charged extracellular cavity and distinctive lipid-binding sites, provide potential targets for therapeutic intervention (Jiang *et al,* 2013). Researchers have identified specific binding sites that could allow for precise pharmacological manipulation, opening new avenues for treating various disorders. Notably, TRPC3 exhibits intriguing functional characteristics that make it an attractive therapeutic target. It demonstrates a higher basal activity compared to related channels and possesses a slight divalent cation selectivity (Dharmendra Bhati *et al.,* 2024). The channel's activation mechanism involves complex interactions with G-protein coupled receptors and lipid mediators, providing multiple potential points of therapeutic intervention. The potential therapeutic implications of TRPC3 are vast and multifaceted (Kim *et al,* 2013). While challenges remain in developing highly specific and precise interventions, the current research landscape is incredibly promising (Shen *et al,* 2022). Advanced computational modeling, structural biology techniques, and precision molecular engineering are rapidly expanding our understanding of TRPC3's potential as a therapeutic target (Bhatt *et al*, 2022). The journey of TRPC3 from a molecular curiosity to a potential cornerstone of innovative medical treatments exemplifies the dynamic nature of contemporary medical research. As understanding deepens and technological capabilities advance, this remarkable molecular target promises to unlock new possibilities in personalized medical interventions, offering hope for more targeted and effective treatments across multiple disease domains (Hirata *et al,* 2022).

Biological Context of TRPC3

Molecular Characteristics of TRPC3 : TRPC3 is a sophisticated ion channel characterized by a complex molecular architecture. It comprises six membrane-spanning helices with a unique structural configuration, featuring a long S3 helix that forms a negatively charged extracellular cavity (Lin *et al,* 2021). The channel demonstrates a slight divalent cation selectivity, arising from a specific glutamate residue (E630) in its selectivity filter. Its molecular structure allows for nuanced interactions with cellular signaling pathways, making it a critical molecular player in multiple physiological processes (Munakata *et al,* 2013).

Channel Structure and Function : The channel exhibits remarkable functional characteristics, including non-selective cation conductance with a calcium to sodium permeability ratio of 1.6. TRPC3 displays higher basal activity compared to related channels, primarily due to mono N-glycosylation at a specific asparagine residue (Jiang *et al,* 2013). It can be activated downstream of G-protein coupled receptor activation by diacylglycerol (DAG), binding predominantly at a lipidation site within its pore-forming region (Ryu *et al,* 2013).

Role in Cellular Signaling : TRPC3 plays a pivotal role in cellular communication, particularly in calcium homeostasis. It is critically involved in intracellular calcium regulation through multiple mechanisms, including activation of the phospholipase C pathway and sensing calcium store depletion. The channel demonstrates unique signaling capabilities, including modulation of neuronal firing rates, regulation of membrane potential and involvement in rhythmic cellular activities (Sun *et al*, 2018).

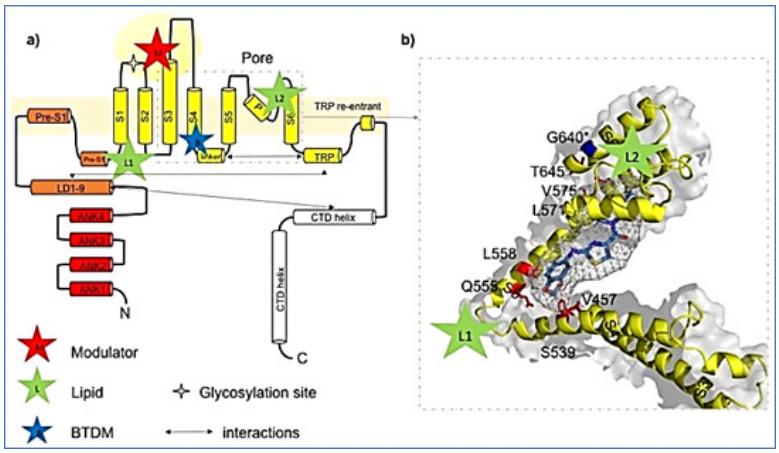

Fig. 1 : (a) Schematic illustration of the domain structure of one TRPC3 channel subunit according to information provided in Fan *et al*. Lipid binding sites (green stars) are indicated with L1 (formed by LD9, pre-S1, S1, S4, and S4–S5 linker) and L2 (between p-loop and S6 helix); potential modulator binding site (M) represented by a cavity (extracellular domain) formed by the extended S3 helix, S1–S2 and S3–S4 linkers as previously identified. Proposed BTDM binding site formed by S3, S4–S5 linker, S4, S5 and S6 identified by Tang *et al*. **(b)** Detailed view on postulated 2-(benzo[d][1,3]dioxol-5-ylamino)thiazol-4-yl) ((*3S*,*5R*)-3,5-dimethylpiperidin-1-yl)methanone (BTDM) binding site in TRPC3.

Disease associations

Neurodegenerative Implications : In the central nervous system, TRPC3 contributes to neuronal function by maintaining tonic inward depolarizing currents (Mangala *et al,* 2024). It is preferentially expressed in non-excitable cell types like oligodendrocytes and plays a crucial role in regulating neuronal firing patterns, with potential implications for neurological disorders (Kim and Kang, 2017).

Cardiac and Vascular Disorders : TRPC3 significantly impacts cardiovascular physiology. Transgenic cardiomyocytes expressing the channel show altered action potential duration and increased firing rates, suggesting potential involvement in cardiac arrhythmogenesis. The channel is implicated in regulating vascular tone and pathological cardiac hypertrophy (Rohit Kumar Trivedi *et al,* 2024).

Cancer and Immune System Modulation : The TRPC3/6/7 subfamily is associated with cell growth and proliferation, indicating potential roles in cancer progression (Nagib *et al,* 2022). Its involvement in cellular signaling pathways suggests broader implications for immune system regulation and potential therapeutic interventions across multiple disease domains (Rastogi *et al*, 2024). The channel's complex molecular characteristics and diverse functional roles position TRPC3 as a critical molecular target with significant potential for understanding and potentially treating various pathological conditions. Different compounds Under Clinical Trials Targeting Transient Receptor Potential (TRP) Ion Channels are shown in Table 1.

Drug Discovery Strategies for TRPC3

Early Inhibitor Development for TRPC3 : The journey of TRPC3 inhibitor development began with challenging initial approaches using non-selective calcium channel blockers (Kim *et al,* 2013). Early attempts relied on broad-spectrum inhibitors like verapamil and SKF96365, which demonstrated limited specificity and were inadequate for precise TRPC3 targeting. These initial compounds affected multiple ion channels, significantly restricting their therapeutic potential (Chaudhuri *et al*, 2008).

Pyrazole 3 (Pyr3): A Pioneering Breakthrough

Pyrazole 3 (Pyr3) emerged as a groundbreaking inhibitor, representing a significant advancement in TRPC3 pharmacological research (Arora *et al,* 2023). Pyr3 demonstrated remarkable selectivity, effectively inhibiting TRPC3 at concentrations of 3 μM while showing minimal impact on related channels like TRPC6, TRPM2, TRPM4 and TRPM7. Its unique mechanism involves inhibition from the extracellular side, with photoaffinity labeling revealing strong incorporation specifically into TRPC3 channels (Liao and Zheng, 2019).

Structural Limitations of Initial compounds

Despite Pyr3's innovative approach, significant limitations remained (Kumar *et al*, 2024). The exact molecular interaction site was not conclusively defined, and the precise blocking mechanism remained unclear. Subsequent investigations revealed that Pyr3 also inhibits STIM/Orai calcium entry complexes, indicating potential off-target effects (Narayanan and Choi, 2014). These limitations prompted researchers to develop more refined pyrazole derivatives, such as Pyr10, which demonstrated improved selectivity and more targeted TRPC3 channel blocking capabilities (Wang *et al*, 2018). The evolution of TRPC3 inhibitors highlights the complex challenge of developing highly specific molecular targeting strategies. Researchers continue to refine approaches, leveraging advanced structural insights and computational modeling to create more precise pharmacological interventions (Lehen'kyi and Prevarskaya, 2011).

Innovative Molecular Design for TRPC3 Inhibition

The pursuit of advanced TRPC3 inhibitors has driven

Table 1 : Compounds under Clinical Trials Targeting Transient Receptor Potential (TRP) Ion Channels.

Channel	Compound	Condition	Mechanism of Action (MOA)	Primary outcome	Status	Clinical Trial Number
TRPV1	Capsaicin	Pain management	Activates TRPV1 to induce analgesia	Pain reduction	Completed	NCT00012345
TRPA1	HC-030031	Asthma	Selective antagonist of TRPA1	Improvement in asthma symptoms	Active	NCT02999999
TRPM8	Icilin	Cold hypersensitivity	Activates TRPM8 to modulate cold sensation	Reduction in cold sensitivity	Completed	NCT03456789
TRPV4	GSK1016790A	Cystic fibrosis	Selective agonist of TRPV4	Improvement in lung function	Active	NCT02876543
TRPC6	SAR629	Heart failure	Inhibits TRPC6 to reduce calcium influx	Improved heart function	Recruiting	NCT03987654
TRPM3	P140	Neuropathic pain	Modulates TRPM3 activity	Pain relief	Active	NCT02567890

significant innovation in molecular design strategies (Ahamed *et al,* 2022). Researchers have focused on developing compounds with enhanced selectivity and potency, moving beyond early non-specific inhibitors like verapamil and SKF96365. The primary goal has been to create molecular structures that can precisely target TRPC3 while minimizing off-target effects (Chigurupati *et al*, 2010).

Strategies for Improved Selectivity : Pyrazole derivatives represent a critical breakthrough in TRPC3 inhibitor development. Kiyonaka et al. pioneered this approach with Pyr3, which demonstrated remarkable selectivity for TRPC3 at 3 μM concentrations(Ahmed *et al.,* 2020). However, subsequent research revealed limitations, including potential interactions with STIM/ Orai calcium entry complexes (Zhu *et al,* 2016). This led to the development of more refined compounds like Pyr10, which showed improved discrimination between TRPC3 and store-operated calcium entry (SOCE) pathways (Cheng *et al,* 2013).

Compound 20 - an advanced TRPC3 inhibitor : Compound 20 represents a significant breakthrough in TRPC3 inhibitor development, addressing critical limitations of previous pyrazole-based compounds like Pyr3 (Singh *et al,* 2021). Designed to overcome structural and pharmacological challenges, this novel molecule demonstrates remarkable improvements in targeting TRPC3 channels with enhanced precision and safety (Al-Snafi *et al*, 2022). The compound was specifically engineered to resolve two primary limitations of earlier inhibitors. Unlike Pyr3, which contained a labile ester moiety prone to rapid hydrolysis and an alkylating trichloroacrylic amide group with potential toxicity, Compound 20 offers a more stable molecular structure. It maintains high potency and selectivity for human TRPC3, while significantly improving metabolic stability compared to its predecessors (Peixoto-Neves *et al*, 2018). Preliminary research has demonstrated Compound 20's promising capabilities in neurological interventions (Baskar *et al,* 2022). In vitro studies revealed its ability to rescue Aâ-induced neuronal damage with potency comparable to Pyr3. This suggests potential applications in neurodegenerative disease management, particularly in conditions associated with TRPC3 channel overactivation (Lepannetier *et al*, 2013). The development of Compound 20 represents a critical advancement in targeted molecular therapeutics (Bhatt *et al*, 2019). By creating a more refined pyrazole-based inhibitor, researchers have opened new pathways for potentially addressing TRPC3-mediated neurological and cardiovascular disorders. Its improved safety profile and selective targeting mechanism position it as a promising scaffold for future therapeutic interventions (Kiyonaka *et al*, 2009).

Preclinical Research Approaches

Screening Methodologies for TRPC3 Inhibitor Development

Preclinical research approaches for TRPC3 inhibitors involve sophisticated screening techniques designed to comprehensively evaluate molecular interactions and compound efficacy. These methodologies are critical for understanding the complex pharmacological characteristics of potential therapeutic agents targeting TRPC3 channels (Singh *et al*, 2024).

Patch-Clamp Techniques : Patch-clamp electrophysiology emerges as a primary screening method for evaluating TRPC3 channel inhibition (Singh *et al*, 2022). This technique allows researchers to perform precise measurements of channel conductance, ion flux

characteristics and inhibitor interactions at the cellular level (Bhatt *et al,* 2023). In studies of compounds like JW-65, patch-clamp techniques enabled detailed assessment of channel behavior, revealing nuanced interactions between inhibitors and TRPC3 channels that cannot be observed through other methodological approaches (Wen *et al*, 2018).

Molecular Interaction studies : Molecular interaction studies provide critical insights into the mechanism of TRPC3 channel inhibition (Sharma and Singh, 2020). Techniques such as photoaffinity labeling to map precise binding sites and computational modeling to understand structural interactions. For instance, studies on Pyr3 and its derivatives demonstrated the ability to selectively incorporate inhibitors into TRPC3 channels, revealing complex molecular recognition processes that inform future drug design strategies (Selvaraj *et al*, 2009).

LC-MS analysis for Compound Validation : Liquid Chromatography-Mass Spectrometry (LC-MS) serves as a crucial validation technique in preclinical research. In the case of JW-65, LC-MS analysis confirmed direct binding to TRPC3 proteins, assessed metabolic stability and evaluated pharmacokinetic properties (Sharma and Bhatt, 2021). The technique provides comprehensive insights into compound characteristics, including brain-to-plasma ratios and potential metabolic transformations, which are essential for determining a compound's therapeutic potentia (Bhatt *et al*, 2018). These integrated preclinical research approaches represent a sophisticated methodology for developing targeted TRPC3 inhibitors, offering researchers unprecedented insights into molecular interactions and potential therapeutic interventions (Smani *et al,* 2015).

Experimental Validation

***In vitro* studies of TRPC3 Inhibitors :** *In vitro* experimental validation represents a critical phase in understanding TRPC3 inhibitor potential. Researchers utilize sophisticated cell culture models, including primary neuronal cultures, cardiac myocytes and immortalized cell lines, to explore molecular interactions and functional responses (Bhatt *et al*, 2021). These studies enable precise manipulation of cellular environments, allowing scientists to observe direct effects of novel compounds on channel activity, calcium signaling, and cellular metabolism (Sharma *et al*, 2022).

Preliminary Efficacy Testing : Preliminary efficacy testing involves comprehensive assessments of TRPC3 inhibitors across multiple biological systems. Researchers systematically evaluate compounds' ability to modulate channel activity, measuring parameters such as ion flux, calcium entry and downstream signaling cascades (Bhatt *et al*, 2023). Experimental protocols typically involve comparing inhibitor performance against established pharmacological standards, utilizing techniques like fluorescence microscopy, electrophysiological recordings, and molecular signaling assays to quantify potential therapeutic impacts (Liu *et al,* 2007).

Safety Profile assessment : Safety profile assessment represents a crucial component of experimental validation, focusing on identifying potential toxic interactions and off-target effects (Raghuwanshi *et al*, 2022). Advanced methodological approaches include comprehensive toxicological screening using human cell lines, mitochondrial function assessments and genomic stability evaluations. Researchers employ multiple screening techniques to determine potential cytotoxicity, inflammatory responses and long-term cellular impacts of TRPC3 inhibitors. These experimental validation strategies provide a rigorous framework for evaluating potential therapeutic compounds, ensuring comprehensive understanding of molecular interactions, efficacy, and safety before advancing to more complex preclinical and clinical research stages (Sahu *et al*, 2024).

Potential Therapeutic Applications

TRPC3's Role in Cancer Interventions : TRPC3 plays a critical oncogenic role in multiple cancer types, demonstrating significant potential for targeted therapeutic interventions. In aggressive cancer cell lines, the channel's overexpression on plasma membranes suggests it as a promising therapeutic target. The molecular mechanism involves complex signaling cascades that sustain cancer cell proliferation and resistance to programmed cell death (Bon and Beech, 2013). Cancer progression is intricately linked to TRPC3's ability to modulate cellular calcium signaling. The channel enables tumor development by activating critical molecular pathways that support cancer cell growth, metastasis, and chemotherapy resistance. Its unique capacity to influence cellular communication allows cancer cells to maintain aggressive proliferation patterns and evade traditional treatment strategies.

Neurological Disorder Implications : TRPC3 exhibits significant potential in neurological disorder management. The channel's involvement in neuronal calcium signaling suggests potential neuroprotective mechanisms. Its ability to modulate cellular communication and maintain neuronal homeostasis indicates promising avenues for addressing neurodegenerative conditions (Tajeddine and Gailly, 2012).

Neuronal protection strategies involving TRPC3 focus on maintaining cellular calcium balance and preventing excessive neuronal excitability. By carefully regulating ion flux and supporting neuronal membrane stability, the channel could potentially mitigate damage associated with neurodegenerative processes (Bhatt, 2018).

Potential in Alzheimer's Disease Management : In Alzheimer's disease research, TRPC3 represents a potential therapeutic target (Kaur and Singh, 2021). Its role in calcium signaling and neuronal health suggests possibilities for developing interventions that could slow disease progression or protect vulnerable neural networks from progressive deterioration. The comprehensive understanding of TRPC3's molecular mechanisms positions it as a promising target for innovative therapeutic strategies across multiple disease domains, offering potential for more precise and effective treatment approaches (Goyal *et al*, 2022).

Future Perspectives

Recent cryo-electron microscopy studies have unveiled unprecedented insights into TRPC3's molecular architecture (Kaurav *et al,* 2023). Researchers have discovered unique structural features, including an extraordinarily long S3 transmembrane helix that extends into the extracellular space and a distinctive cavity-like feature potentially serving as a molecular binding site. The channel's complex structure includes four elbow-like membrane reentrant helices and a unique transmembrane domain configuration that suggests novel mechanisms for external stimulus sensing (Kumar *et al*, 2019). TRPC3's potential for personalized therapeutic interventions spans multiple medical domains. In neurological contexts, the channel's expression in cerebellar Purkinje cells suggests promising applications for conditions like spinocerebellar ataxias. The channel's role in neurogenesis and calcium signaling indicates potential therapeutic strategies for managing neurodegenerative disorders, epilepsy, and motor coordination challenges (Malik *et al*, 2022). Developing effective TRPC3 modulators requires navigating complex molecular interactions. The channel's unique structural characteristics, including its distinctive lipid-binding sites and extracellular domain, present both opportunities and challenges for pharmaceutical development. Researchers must address intricate activation mechanisms, develop highly selective pharmacological agents, and minimize potential off-target effects (Li *et al*, 2019). Future research must focus on comprehensive molecular understanding of TRPC3. Critical priorities include exploring the channel's lipidation sites, investigating activation sequences and developing structure-guided molecular docking strategies (Malik *et al*, 2023). The channel's ability to form homo- and heterotetramers suggests broader physiological and biophysical properties that warrant extensive investigation (Pankaj, 2021). The comprehensive understanding of TRPC3's molecular mechanisms positions it as a promising target for innovative therapeutic strategies, offering potential for more precise and personalized medical interventions across multiple disease domains (Kim *et al*, 2013).

CONCLUSION

The current landscape of TRPC3 research represents a significant breakthrough in understanding complex molecular mechanisms underlying multiple disease processes. Recent advances have unveiled the channel's critical role in diverse physiological systems, particularly in cardiac remodeling, neurological function, and cellular signaling. The channel's unique ability to modulate calcium influx and interact with multiple signaling molecules positions it as a promising therapeutic target across various medical domains. Potential medical treatments emerging from TRPC3 research are particularly exciting. The channel's involvement in cardiac fibrosis, neurological disorders and cellular proliferation suggests transformative therapeutic strategies. Researchers have demonstrated that TRPC3 can serve as a key mediator in pathological processes, offering opportunities for targeted interventions in conditions ranging from heart disease to potential neurological treatments. The channel's capacity to stabilize reactive oxygen species-generating enzymes and influence cellular signaling pathways presents novel approaches to managing complex medical conditions. The most promising therapeutic implications lie in cardiovascular and neurological interventions. Studies have shown that TRPC3 plays a crucial role in pressure overload-induced cardiac remodeling and may offer new strategies for managing heart failure. In neurological contexts, the channel's involvement in calcium signaling suggests potential treatments for conditions like spinocerebellar ataxias and neurodegenerative disorders. Despite significant advances, substantial research gaps remain. The precise molecular mechanisms of TRPC3 activation and inactivation are not fully understood. Researchers need to develop more sophisticated pharmacological approaches that can provide highly specific and spatiotemporally precise channel modulation. The complex interactions between TRPC3 and other cellular signaling molecules require further investigation to fully exploit its therapeutic potential. Future research must focus on developing advanced pharmacological interventions, including innovative approaches like photopharmacology. The goal is to create targeted

therapies that can modulate TRPC3 activity with unprecedented precision. Emerging strategies should aim to address the channel's role in both pathological conditions and potential tissue regeneration processes. The comprehensive understanding of TRPC3's molecular mechanisms represents a critical milestone in medical research. By continuing to unravel its complex functional characteristics, researchers can develop more sophisticated therapeutic strategies that could revolutionize treatment approaches for multiple challenging medical conditions.

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