ISSUE 1/2026

JANUARY 2026

PRESCRIPTION

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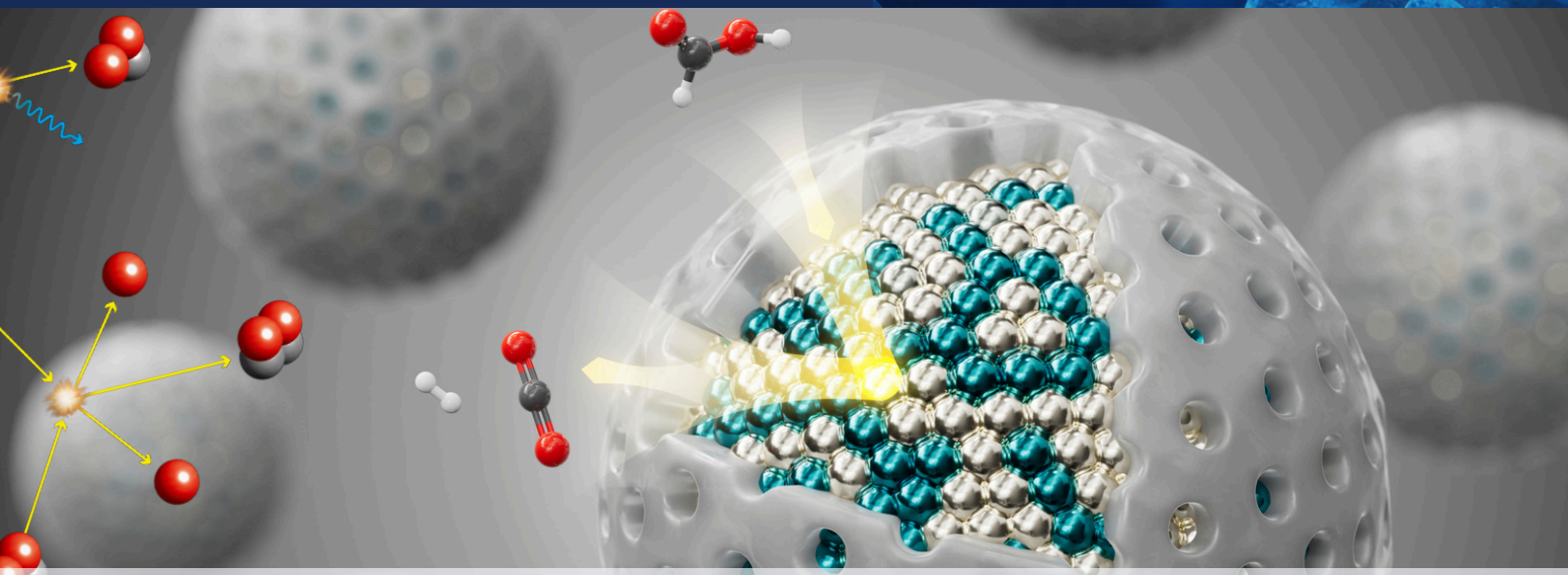


Calcium Gatekeepers Within: Turning the Tide on Breast Cancer Chemoresistance

By Dr. Aisyah Hasyila Jahidin

Breast cancer remains one of the most common and challenging diseases worldwide. Despite remarkable advances in early detection and treatment, many patients still face relapse, a painful reminder that some tumours have learned to fight back.

Why does this happen? The truth is that cancer cells are remarkably adaptive. When exposed to chemotherapy, they do not simply die; they change. They reprogramme their inner systems to withstand treatment, a phenomenon known as chemoresistance. It is one of the biggest obstacles standing between today's therapies and long-term cures.

IN THIS ISSUE

Most of us think of calcium as the mineral that builds strong bones. But inside our cells, calcium acts as a vital messenger, regulating whether a cell should live, divide, or die. When this signalling system becomes disrupted, cells can gain survival advantages, and in cancer, that can mean the difference between remission and relapse.

Our research focuses on a lesser-known part of this story, the lysosome. A small bubble-like structure inside cells once thought to be just a waste bin, is now recognised as a critical command centre. It senses nutrients, manages stress, and even decides when the cell should recycle itself through a process called autophagy. Hidden within its membrane are calcium channels, molecular gates that release tiny pulses of calcium to keep the system in balance. Two of these channels, the two-pore channels (TPCs) and transient receptor potential mucolipin 1 (TRPML1), have emerged as key players in cancer's survival strategy.

In our recent work, we explored how TPC1 and TPC2 influence breast cancer cell behaviour. These channels help move calcium inside the cell and can affect how cancer cells grow, migrate, and respond to stress. We found that silencing these channels alters how breast cancer cells behave under challenging conditions. This suggests that even subtle shifts in lysosomal calcium signalling may shape how tumours adapt and survive. Although still at an early stage, our findings point to the exciting possibility that targeting TPCs could make cancer cells more sensitive to treatment.

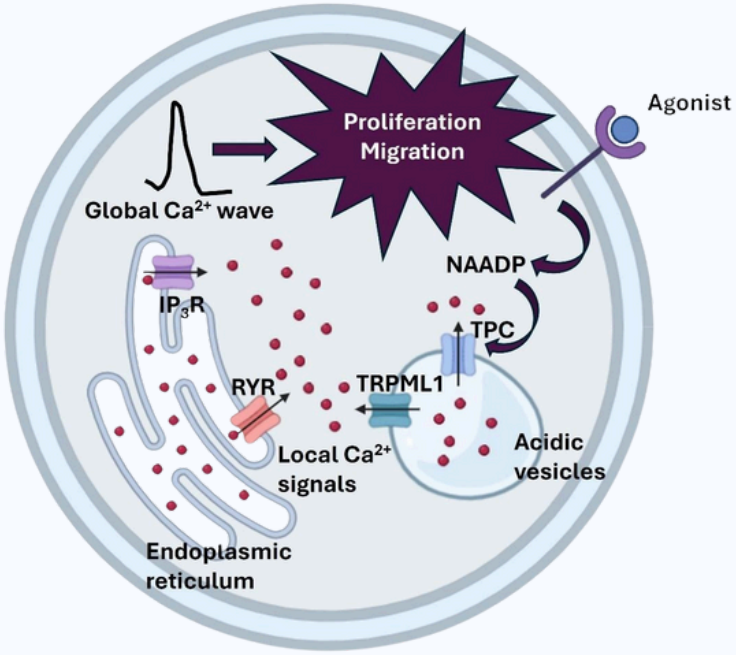
Supporting this, our recent global bibliometric analysis of TPC research revealed a clear rise in interest over the past two decades, with nearly 300 publications worldwide between 2000 and 2022. The study identified strong research clusters centred on calcium signalling, autophagy, and cancer, showing how this once niche field has evolved into a vibrant and growing research area. Importantly, an increasing number of studies now link TPCs to tumour growth, metastasis, and drug resistance, reinforcing the view that endolysosomal calcium channels could serve as promising new therapeutic targets.

Meanwhile, global studies highlight TRPML1 as another calcium channel deeply involved in cancer cell resilience. Studies show that TRPML1 is often overexpressed in breast cancer, especially in cancer stem cells, the small but stubborn population capable of regenerating tumours after treatment. When researchers blocked TRPML1, these cells became more vulnerable to chemotherapy drugs like doxorubicin, undergoing a unique form of cell death called ferroptosis. In animal models, tumour growth was dramatically reduced, especially in triple-negative breast cancers, one of the most aggressive and hard-to-treat types.

To understand how TRPML1 research has evolved, we also analysed the scientific landscape. A recent bibliometric study of global TRPML1 research found about 155 publications from 158 researchers, with strong clusters focusing on autophagy, oxidative stress, calcium signalling, and cancer progression. This pattern mirrors the growing attention toward lysosomal calcium signalling as a whole, confirming that the field is gaining strong traction in cancer biology.

Together, these lines of research reveal how cancer cells may exploit these hidden calcium channels to endure the stress of chemotherapy. Lysosomes, long overlooked as simple recycling bins, turn out to be key players in a cell's decision to live or die. By learning how to fine-tune or disrupt the signals that flow through TPCs and TRPML1, we may one day be able to make standard cancer treatments far more effective.

Much work remains before these insights reach patients, but the idea is profoundly hopeful. Instead of inventing entirely new drugs, we might enhance existing ones by targeting the hidden systems that dictate how cells respond to stress. In the quiet rhythm of calcium signals and lysosomal responses lies a powerful hope, that mastering these microscopic movements could help us outsmart chemoresistance and bring longer-lasting victories against breast cancer.



Endolysosomal (EL) calcium channels mediate oncogenic calcium signalling. NAADP promotes tumorigenesis by inducing EL calcium release through TPCs and TRPML1. The localized NAADP-induced calcium release is further amplified into a global intracellular calcium elevation via the calcium-induced calcium release (CICR) mechanism, involving IP_3Rs and RYRs.
Abbreviations: TPC: two-pore channel; TRPML1: transient receptor potential mucolipin 1; IP_3R: inositol 1,4,5-trisphosphate receptor; RYR: ryanodine receptor; NAADP: nicotinic acid adenine dinucleotide 2'-phosphate.

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Dr. Aisyah Hasyila Jahidin is a Senior Lecturer at the Faculty of Pharmacy, Universiti Teknologi MARA (UiTM). She holds a Ph.D. and Master's degree from The University of Queensland, Australia, and a Bachelor's degree in Biomedical Technology from the University of Malaya, Malaysia. With nearly two decades of academic experience, her research focuses on calcium signalling in cancer and the potential of medicinal plants and natural products as anticancer agents. Dr. Aisyah has secured multiple research grants and published her work in reputable scientific journals. Passionate about mentoring, she strives to inspire future researchers and nurture well-rounded students who uphold the values of excellence, synergy, and integrity.

QUIZ

01

Why do some breast cancers return even after chemotherapy?

A. The chemotherapy was too strong.
B. Cancer cells learn to adapt and resist treatment.
C. The immune system becomes overactive.
D. The treatment targets only healthy cells.

Answer: B. Cancer cells learn to adapt and resist treatment

02

Inside our cells, calcium mainly acts as a

A. bone-building mineral.
B. source of energy.
C. messenger that helps control cell life and death.
D. waste product.

Answer: C. messenger that helps control cell life and death.

03

What surprising new role does the lysosome play in cancer?

A. It works only as a waste bin for the cell.
B. It helps control how cells handle stress and survive.
C. It produces hormones.
D. It repairs DNA damage.

Answer: B. It helps control how cells handle stress and survive