# Calcium-mediated effect plays key role in cell disposal, researchers discover

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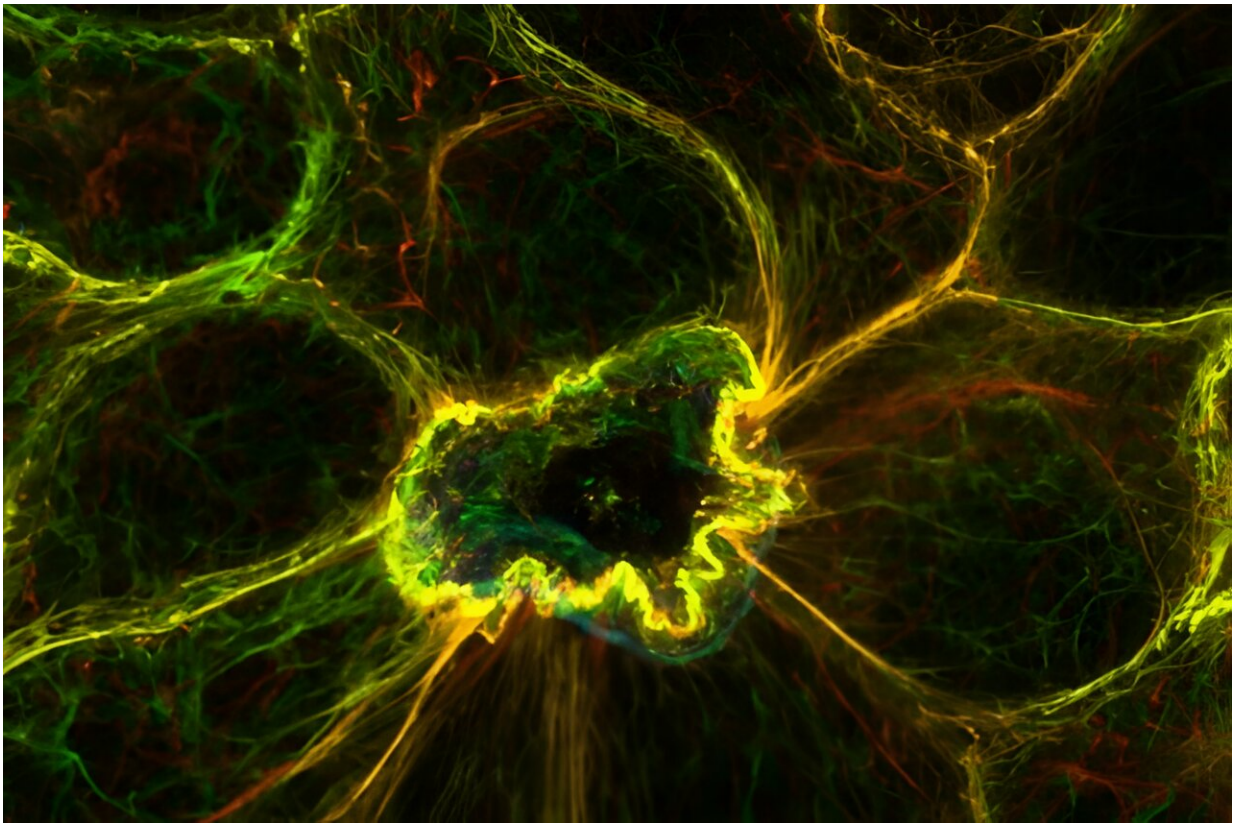


An apoptotic, or dying cell, characterized by its wavy membrane, lies within a cultured sheet of epithelial cells. Credit: Yuma Cho and Junichi Ikenouchi, Kyushu University

A research team from Kyushu University in Japan has recently

discovered a calcium-based mechanism that plays a key role in the disposal of dead cells, shedding light on how our bodies protect themselves from injury and disease. In their study, published in *Current Biology*, the team unveiled how calcium ion levels are essential for the efficient removal of dying or apoptotic cells from epithelial tissues (cells lining the body surface), using genetically engineered epithelial tissue cultures, molecular markers, and advanced imaging techniques.

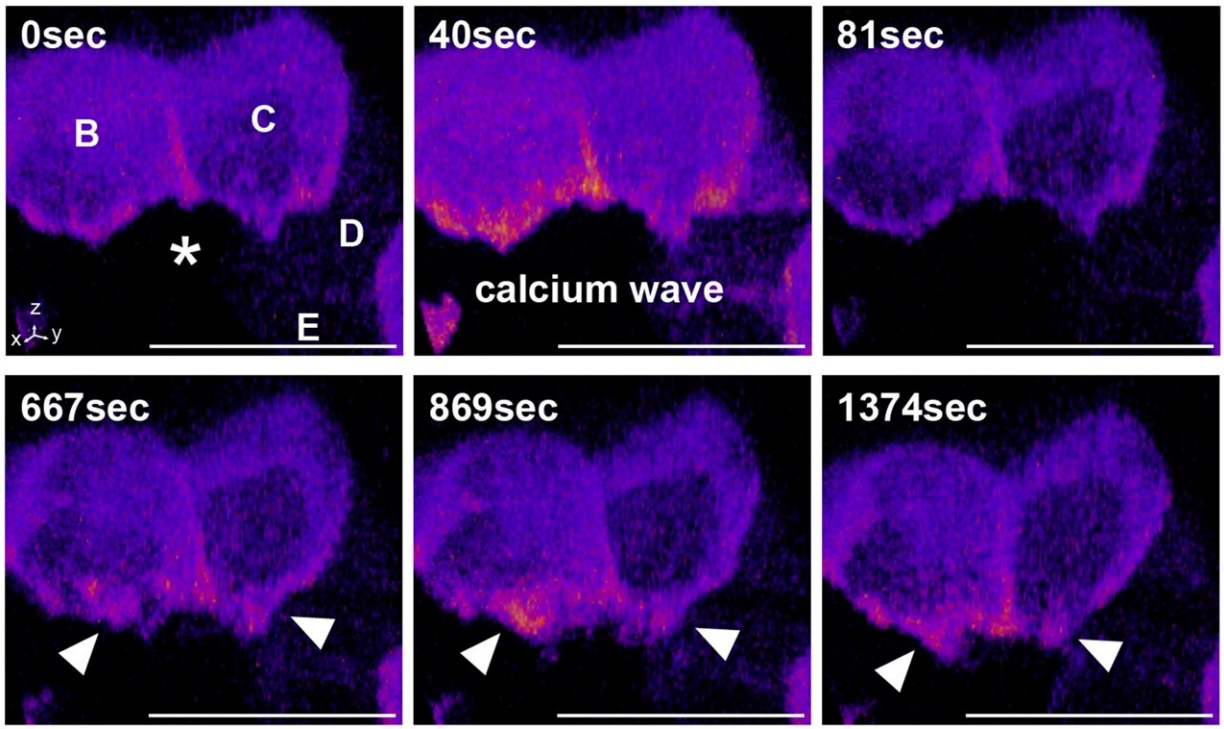
The surfaces of our bodies, including the skin and internal organs, are covered by sheets of epithelial cells that act as vital barriers. When these cells become damaged and die (apoptosis), neighboring cells quickly band together to push them out and seal any gaps through which foreign substances could enter and potentially lead to infections or inflammation. Although this complex process is essential for maintaining a healthy epithelial barrier, the exact mechanism underlying it has not been entirely clear—until now.

The study, led by Professor Junichi Ikenouchi and his colleagues, Dr. Kenji Matsuzawa and Mr. Yuma Cho, the first author, from Kyushu University, also included contributions from collaborators from the University of Tokyo and Health Sciences University of Hokkaido in Japan.

To begin with, the team induced apoptosis in individual epithelial cells using a focused laser and observed the response in the surrounding cells. They then observed how nearby cells reacted by modifying them to express special calcium ion probes called GCaMP6, which allowed them to visualize real-time calcium changes.

Interestingly, they found that the neighbors of the apoptotic cell showed a significant spike in calcium levels, particularly near the membrane regions interfacing with the dying cell. The researchers named this intriguing phenomenon the "calcium response in effectors of apical

extrusion (CaRE)."




In this image, the cell marked with an asterisk was damaged using a focused laser, triggering apoptosis. After an initial increase in general calcium levels around the dying cell (calcium wave), a sustained increase in calcium levels was observed at the interface between the apoptotic cell and the surrounding cells (marked B and D). This new mechanism is essential for expelling the apoptotic cell and preserving the integrity of the epithelium. Credit: Junichi Ikenouchi, originally published in https://doi.org/10.1016/j.cub.2024.08.057

Probing deeper into this newly discovered mechanism, the team next examined the role of IP3 receptors, proteins present inside cells that help regulate calcium ion levels. They found that inhibiting the activity of IP3 receptors or removing their associated genes completely prevented the expulsion of apoptotic cells. Further analysis using advanced electron

microscopy revealed that a specific subset of IP3 receptors, particularly those located near desmosomes, plays a key role in CaRE.

Desmosomes are cell adhesion structures that form strong connections between cells, acting like buttons that hold them together. They are especially important in tissues like skin and organ linings, helping to keep everything intact and functioning properly.

By ensuring neighboring cells adhere tightly, desmosomes play a key role in maintaining the structure and stability of our body's tissues. The team found that the activation of IP3 receptors near desmosomes is necessary for triggering the contraction of a group of proteins known as actomyosin complex, which helps cells change shape and move, facilitating the removal of apoptotic cells.

"Our study sheds light on a newfound role of IP3 receptors in desmosomes, the latter of which were previously thought to be involved only in mechanical connections between epithelial cells," highlights Ikenouchi.

As this study was conducted on cultured cells, the team notes that further analysis of the CaRE mechanism is needed to determine whether the mechanism also functions in living organisms, whether it varies between different organ tissues, and whether other factors also play a role.

Overall, this study advances our understanding of how our bodies maintain a healthy epithelium—something many of us take for granted.

"Our findings provide valuable insights into understanding diseases caused by epithelial barrier disruption, such as atopic dermatitis and inflammatory bowel disease, and may contribute to the development of new preventive measures and treatments for chronic inflammation," concludes Ikenouchi.

**More information:** Yuma Cho et al, A sustained calcium response mediated by IP3 receptor anchoring to the desmosome is essential for apoptotic cell elimination, *Current Biology* (2024). DOI: 10.1016/j.cub.2024.08.057

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