Giant cytoplasmic vacuoles reshape membrane and nuclear mechanics to orchestrate YAP/TAZ-dependent cell survival

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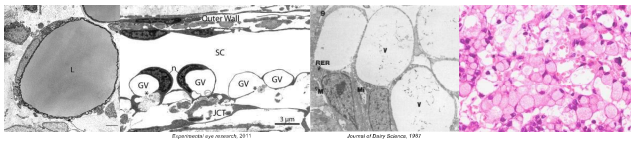
Abstract

Cellular morphology is closely coupled with the mechanical properties that regulate cellular behavior, function, and fate. While cytoskeletal organization and external mechanical forces are recognized as primary determinants of cellular mechanics, how internal organelles contribute to such physical properties remains unclear. Here, we report that the formation of giant vacuoles profoundly alters both the mechanical and transcriptional states of mammalian cells, promoting their survival and immune evasion. Mechanistically, vacuolized cells exhibit high plasma membrane tension and nuclear envelope stretching independent of the actin cytoskeleton, thereby facilitating YAP/TAZ nuclear translocation. This promotes phosphorylation of Akt and surface accumulation of CD24 to increase cell survival and potentiate the antiphagocytic role. Notably, vacuole-mediated mechanotransduction is recapitulated in human signet ring cell carcinoma cells (SRCC), a tumor type histologically diagnosed by mucin-filled vacuoles. Together, these findings suggest a previously unrecognized role of large cytoplasmic vacuoles as mechanical regulators that activate YAP/TAZ, providing a physical mechanism underlying anoikis resistance and immune escape.

Introduction

A long-ignored giant organelle in mammalian cells



Cells of higher organisms contain various functional organelles with characteristic morphologies. These organelles compartmentalize the cell interior and are dynamically remodeled or newly formed as adaptive responses to changes in the cellular environment. The formation of large intracellular vacuoles has been observed across diverse mammalian species. However, the functional and structural outcome of vacuole formation have remained unknown.

Results

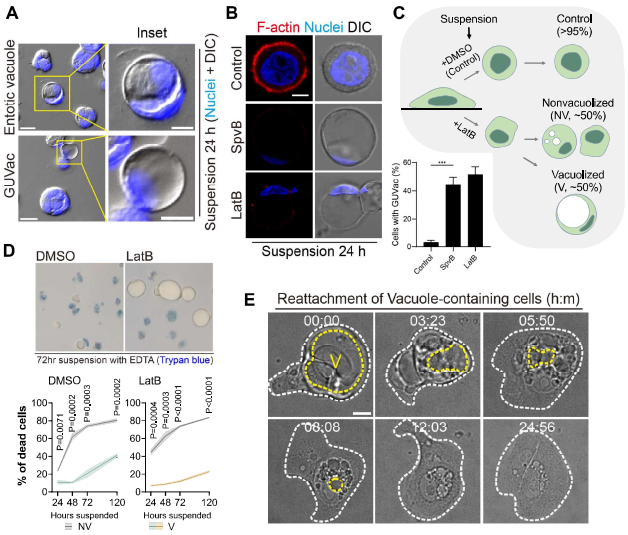


Figure 1. Cells with large cytoplasmic vacuoles resist cell death upon ECM detachment.
Disruption of the actin cortex during suspension culture induces large cytoplasmic vacuole formation (A and B), which confers prolonged cell survival upon ECM detachment (D). Schematic summary represents the experimental design and outcomes (C). Vacuolized cells remain viable and proliferative when returned to normal culture conditions (E).

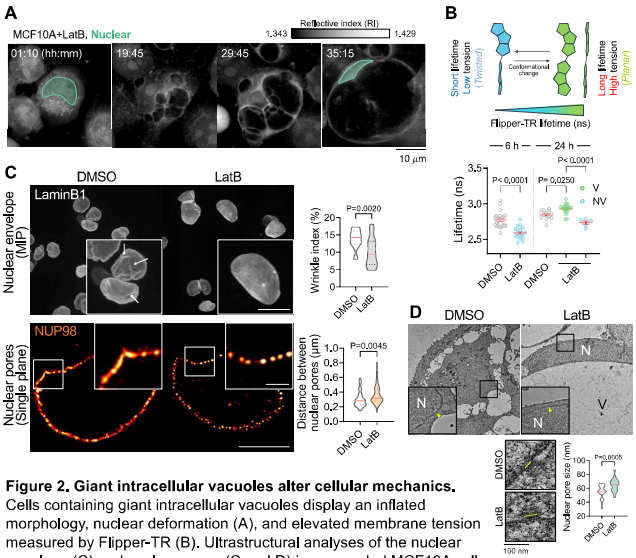


Figure 2. Giant intracellular vacuoles alter cellular mechanics.
Cells containing giant intracellular vacuoles display an inflated morphology, nuclear deformation (A), and elevated membrane tension measured by Flipper-TR (B). Ultrastructural analyses of the nuclear envelope (C) and nuclear pores (C and D) in suspended MCF10A cells reveal that vacuoles stretch the nuclear envelope and increase nuclear pore size.

* Abbreviations: V, Vacuolized; NV, Non-vacuolized cells

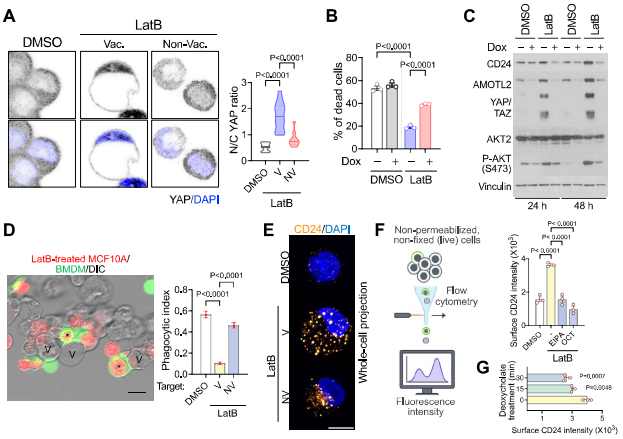


Figure 3. Vacuole-induced mechanical changes restrict both intrinsic and extrinsic cell death.
Vacuolized cells exhibit enhanced nuclear translocation of YAP (A). Genetic inhibition of YAP/TAZ suppresses the Akt pro-survival pathway and increases cell death in vacuolized populations (B and C). Vacuole formation also facilitates the evasion of phagocytic clearance (D) by promoting YAP/TAZ-mediated CD24 expression (B) and its surface retention via high membrane tension (E-G).

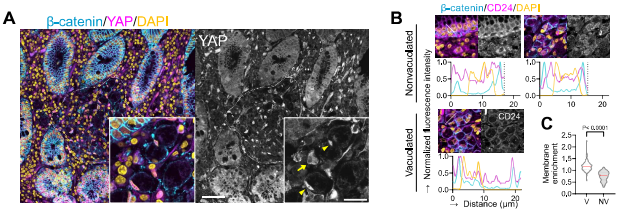


Figure 4. Human gastric signet ring cell carcinoma (SRCC) tissues recapitulated unique protein redistribution by large vacuole *in vivo*.
Human gastric SRCC tissue staining recapitulates YAP activation (A) or CD24 membrane localization (B and C) *in vivo*, potentially promoting a more malignant cancer phenotype.

Conclusion

- ✓ New mechanistic insights into how organelles alter cellular responses in physiological contexts
- ✓ Identification of large cytoplasmic vacuoles as regulators of cell mechanics orchestrating survival and immune evasion
- ✓ Extending the functional significance of mechanotransduction