A Nonapoptotic Cell Death Process, Entosis, that Occurs by Cell-in-Cell Invasion

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Outline
- Introduction/Background
- Overview
- Results
- Discussion

Introduction- LS

Overview

MCF10A Cell Internalize into Their Neighbors following Detachment

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Cell Internalization Occurs Independent of Apoptotic Processes

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Rho and ROCK Are Required in Internalizing Cells

MCF7 Cells Undergo Entosis
- Cell engulfment was observed in a variety of nontumorigenic cell lines and in four of nine tumor cell lines.
- MCF7 displayed the highest percentage.

Cadherins Are Required for Entosis
- EDTA/EGTA chelates calcium ions → cadherin inhibiting
- MCF10A: expresses high levels E- and P-cadherin
- MCF7: expresses high levels of E-cadherin

Adherens Junctions Track Internalization
- LS
- Dense plaque of these proteins at the points of maximum width between the cells (see arrow)

Adherens Junctions Track Internalization
- Closest contact between cells was at the extreme end of the finger-like projections.
Entosis Results in Lysosomal Cell Death

TUNEL: labels DNA fragments, indicative of cell death
Y27632: inhibits ROCK

LAMP1: integral lysosome membrane protein, marked by LysoTracker red
Cathepsin B: lysosomal protease

Internalized Cells Can Be Released

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Release:
00:00:00
00:55:00
06:20:00
06:12:00
07:00:00

Division:
00:00:00

Internalized Cells Can Die by Alternative Mechanisms

ConA: inhibitor of vacuolar H+/ATPase, inhibits lysosome functions

Does ConA alter % of internalized cells?

Human Metastatic Breast Tumors Show Evidence of Entosis

- LS

Entosis in metastatic breast carcinomas

Human Primary Breast Tumors Show Evidence of Entosis

Panel of 20 primary breast carcinomas
4 with most cell-in-cell structures
Discussion

- Apoptosis
  - Caspase 3
  - Scramblase
  - Phosphatidylserine exposure
  - Adherens Junctions
  - Caspase Activation
  - Dying cells

Discussion

- Entosis
  - Phagocytic ingestion
  - Cell Invasion
  - Internalized cells are still alive

Discussion

- Rho dependent
- Actin polymerization
- Myosin II activation
- Intercellular engagement: counterbalancing force
- Absence of basement membrane: unbalanced forces
- Adherens junction formation

Implications

- Provide nutrients for tumor cells
- Promote tumorigenesis by facilitating cell fusion and the development of aneuploidy
- Tumor Suppressor

Discussion – Application to Nature

- Apicomplexa
- Widely reported in human tumors
  - Breast, lung, endometrial stromal, etc.
- Could be a stress response to remove a tumor