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Tunneling-nanotube

A new way of cell-cell communication

Yan Zhang

Laboratory of Neurobiology and State Key Laboratory of Biomembrane and Membrane Biotechnology; College of Life Sciences; Peking University; Beijing, China

Tunneling-nanotubes (TNTs) are a kind of cell-cell communication when cells are under stress. We hypothesize that insulted cells use TNTs as a highway to transfer materials and energy to healthy cells. TNTs transfer cellular compartments, such as endoplasmic reticulum (ER), mitochondria, Golgi and endosomes. Some cytotoxic particles, such as intracellular and extracellular amyloid β (Aβ), scrapie prion protein (PrP^{Sc}) and human immunodeficiency virus (HIV)-1, are suggested to transfer with TNTs as well. p53, epidermal growth factor receptor (EGFR), Akt, phosphoinositide 3-kinase (PI3K) and mTOR are important for TNT induction. However, currently our understanding of TNTs is greatly limited. Further studies need to be done to improve our knowledge of the mechanisms and physiological functions of TNTs.

Key words: tunneling-nanotube, physiological functions, p53, EGFR

Abbreviations: Aβ, amyloid β; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; HIV, human immunodeficiency virus; PI3K, phosphoinositide-3-kinase; PrP, prion protein; TNTs, tunneling nanotubes

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Correspondence to: Yan Zhang;
Email: yanzhang@pku.edu.cn

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Tunneling-nanotubes (TNTs) are thin membranous, freely hovering channels between cells with a diameter of 50–200 nm that mediate communication in many types of cells.[1] In our recent study, we found that TNTs can be induced in rat hippocampal astrocytes and neurons by H_2O_2 or serum depletion. When two populations of cells are co-cultured, it is the stressed cells that always develop TNTs to the unstressed cells, not vice versa, indicating that induction of TNTs is initiated from the insulted cells, not by the target cells, suggesting that the ability to develop TNTs is a potential defense response to stress. We hypothesize that TNTs are a general machinery for cell-cell communication. As a form of membrane continuity, TNTs may be efficient communication tunnels facilitating information and material exchange. TNTs are important structures to transfer cellular contents or energy from the insulted cells to other cells when cells are under stress.[2] Consistent with the previous reports in references 1 and 3, our data show that TNTs transport cellular substances uni-directionally suggesting that TNTs mediate selective and targeted interaction between cells. TNTs transfer endoplasmic reticulum (ER), mitochondria, Golgi and endosomes.[2] Some pathogens, including scrapie prion protein (PrP^{Sc}) and human immunodeficiency virus (HIV)-1, are suggested to "hijack" TNTs for their cell to cell spreading.[4-7] We report that intracellular and extracellular amyloid β (Aβ) can be transferred through TNTs at the speed 2–8 times to ER, mitochondria, Golgi and endosome. Noticing that transfer velocity of cytotoxic intracellular Aβ is much faster than cellular organelles, it is possible that cytotoxic or transmissible particles, such as PrP^{Sc} and HIV-1, can hijack TNTs as their spreading highways.[2]

Our study suggests that p53 is important for TNT development. In addition, we find that among the genes activated by p53, epidermal growth factor receptor (EGFR) is also critical to TNT development. Akt, phosphoinositide-3-kinase (PI3K) and mTOR are involved in TNT induction.[2] We propose that insults induce p53 activation, which then in turn upregulates EGFR expression and activates Akt/PI3K/mTOR pathway. p53 activation or EGFR or Akt/PI3K/mTOR

induces M-Sec overexpression, which can trigger F-actin polymerization[8] and contributes to TNT development from the initiating cell membrane.[2]

There are many questions unsolved in the development and functions of TNTs: (1) Are there any attractive molecules in or secreted by the target cells to guide the growth direction of TNTs? (2) Are there any receptors or binding partners of the attractive molecules on the initiating cells and how do they mediate the growth of TNTs? (3) Since the mature TNTs are freely hovering channels,[2,3] do their "growth cones" attach to the culture bottom or not? (4) How does the membrane protruding develop from the initiating cells? (5) When membrane protruding reaches the target cells, how does it merge with the target cell membrane? (6) Similar cell-cell communication projections were described in Drosophila imaginal discs in vivo in 1999.[9] However, do TNTs really exist in vivo and how do we prove it in live animals? (7) Are there any specific markers for labeling TNTs? (8) What are the physiological functions of TNTs during cell-cell communication? (9) What is the relationship between TNT induction and apoptosis and cancer formation? (10) How do TNTs selectively transfer materials to another cell and how do virus-like particles "hijack" TNTs? The answers to the above questions are critical to understand the mechanisms and physiological functions of TNTs.

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