Intercellular bridges for cell-cell communication

Takayuki Kohno

Department of Biochemistry, Cancer Research Institute, Sapporo Medical University School of Medicine, Sapporo, Japan.

ABSTRACT

In multicellular organism, intercellular communication is essential for maintenance of life activity. The intercellular communication includes direct and indirect crosstalk such as gap junction and ligand-receptor interaction, respectively. Recently, a new type of cell-cell communication for intercellular exchange of signaling molecules via a nanotube bridge structures, referred to as a tunneling nanotubule (TNT), between nearby cells was identified. In this review, we introduce current understanding of TNT having received a lot of attention as a novel direct cell-cell communication method.

Key words : TNT, Tunneling nanotubule, Cell-cell communication, Intercellular bridge, Cytoneme

INTRODUCTION

Most of monocellular organisms can live out their life cycle by themselves. By contrast, intercellular informational exchange is essentials for survival in multicellular organisms. There are many different ways to crosstalk between cells, including direct cell-cell communication between two adjacent cells and indirect communication between nearby non-contact cells. Between two adjacent cells with close proximity, channels such as i) cell-cell-adherens junction between homophilic cells via cadherin and desmosome, ii) cell-matrix adherens junction between heterophilic cells via integrin and hemidesmosome, and iii) gap junction via connexin are formed. Among these cell-cell connection structures, only gap junction can passively or actively exchange intracellular components such as inorganic ions, ATP, hydrophilic small molecules, and phospholipids. It was known that two adjacent cells can be synchronized through a gap junctional communication to crosstalk changes in concentrations of intracellular components [1),2)].

Between non-contact cells, information is transmitted from a cell secreting extracellular signal molecules such as cytokines, growth factors and hormones to target cells by binding of the signal molecules to their specific receptors expressed on the surface of the target cell. Exosomes, extracellular vesicles related to antigen presentation, are also released into extracel-

CORRESPONDENCE TO : Takayuki Kohno,
Department of Biochemistry, Cancer Research Institute, Sapporo Medical University School of Medicine, South 1, West 17, Chuo ku, Sapporo 060-8556, Japan.
Email : kohno@sapmed.ac.jp
TEL : 011-611-2111 (ext 2380)
FAX : 011-611-2299

lular circulation, enabling intercellular communication without direct contact through their acquisition by recipient target cells. These signal transduction mechanisms are unidirectional but effective ways to transmit signals to multiple cells. Synaptic structures composed of nerve and immune cells are categorized as a signal transduction mechanism in non-contact cells. However, signaling factors released by the cells are delivered to the target cells with absolute precision in signal transduction at the synaptic stage, due to a closed environment of extracellular space around synapses.

Recently, a new route of cell-cell communication via intercellular bridges is identified [3]. This bridge connects between neighboring cells each other and thus called tunneling nanotubule (TNT). The similar mechanisms of cell-cell communication have been known and called filopodial bridges [4], cytonemes [5], and long tubulovesicular extensions [6]. TNT is observed in many types of cells including nerve and immune cells[3,7], and involved in intercellular transfer of intracellular ions such as calcium, small molecules such as ATP and glucose, cell surface and cytoplasmic proteins, subcellular vesicles, and organelles between connected cells. It was strongly suggested that proteins known so far as intercellular protein transfer (IPT), such as GPI-anchored proteins including CD55 and CD 59, CCR5 and P-glycoproteins, are transferred by a direct intercellular material exchange between cells via TNT [8]. Thus, it was demonstrated that cells are communicate with nearby cells by direct material exchange via TNT.

Structure and properties of TNT

TNT is a long, thin and vulnerable tube with 50-200 nm in diameter and about 100 μm in length composed from plasma membrane. Both ends of the TNT are fused to the plasma membrane of each cell. TNT is observed in immune cells including dendric cells, macrophages and NK cells as well as many other cells such as neuronal and epithelial cells, and typically formed between the same type of cells [3,9]. There are diverse structures of TNT thus far reported, including linear, nonlinear and branched forms [3,9,10,11]. TNT which contains membrane-like structure inside the tubule has been identified [10].

Most of TNTs contain actin cytoskeleton [10]. This suggests that TNT originates from filopodial protrusion. In fact, it has been observed that a filopodial protrusion can extend from one cell and then fused to another cell or a filopodial protrusion extended from another cell to form the TNT [3,4]. However, detailed molecular mechanism underlying formation of long filopodial protrusion and its extension until it reaches a target cell remained to be elucidated. Aside from this, it was reported that there is another type of TNT which is formed when two tightly connected cells are moved apart in an opposite direction, keeping a region connected [9,10,11]. There is a distinct barrier between two cells to separate their cytoplasms in this type of TNT. This TNT is present predominantly in immune cells but the mechanism of the TNT formation also remained to be elucidated. In macrophages, formation of the TNT containing microtubules is observed [11]. The TNTs containing microtubules are typically thicker in diameter than those without microtubules. Thus, the TNT containing microtubules are able to transduce larger intracellular components such as mitochondria. The mechanism of formation of the TNT containing microtubules is also unclear. Since TNT was only defined as the structure which forms intercellular bridge thus far, many different TNTs with a variety of distinct structures will be reported.

Molecular mechanism of protrusion formation

Small GTP-binding proteins are classified into 5 families: the Ras, Rho, Rab, Arf/Sar and Ran families, and regulate wide variety of biological events, including cell proliferation, differentiation, gene expression, cell motility, intracellular vesicular traffic, and nuclear transport. Rho, Rac and Cdc42, all of which belong to the Rho family small GTP-binding protein, are re-

lated to reconstitution of actin cytoskeleton [12]. Among these proteins, activation of Cdc42 is involved in protrusion formation, and the filopodial protrusions formed via activation of Cdc42 contribute to promotion of cell motility. In practice, expression of active form of Cdc42 in the cells resulted in formation a number of short filopodial protrusions throughout the plasma membrane followed by enhanced cell motility [13]. Meanwhile, significant extension of one or several filopodial protrusion was observed in TNT. This was structurally distinct from the short filopodial protrusion formed by expression of active form of Cdc42. Thus, it was suggested that this type of TNT was formed via a different molecular mechanism from that of known Cdc42 activation. It has been demonstrated that activation of Ral-exocyst pathway mediated by M-Sec is important for TNT formation [14]. M-Sec was originally identified as an essential factor for long filopodia formation although the molecular mechanism related to extension of the protrusions required for TNT formation has not been cleared yet. Although there are many different types of TNT, formation of long filopodia is at least necessary for formation of all of the TNTs. For extension of actin filaments, it is required to linearize actins aggressively by suppression of actin depolymerization, promotion of convergence of actin cross-linking proteins and/or inhibition of actin branching [15]. An increasing attention has been drawn to the difference in regulatory molecular mechanisms between formation of long filopodia required for TNT formation and formation of short filopodia involved in promotion of cell motility.

Among Rho family GTPases, Cdc42 is first activated by inflammatory cytokines such as TNFα and IL-1 to induce actin reorganization. Subsequently, the cytokines induce Rac activation and promote cell motility. In this process, activation of Cdc42 doesn't induce formation of long filopodial protrusion. Viral infection can also induce actin reorganization. However, significantly extended filopodial protrusion was observed in the cells infected by viruses [4]. This protrusion is extended until it reaches another cell and forms a filopodial bridge-like structure, which is thought to be the same structure as TNT, between infected and uninfected cells. Viral particles can be transduced to the other cells via the filopodial bridge. These observations suggest the possibility that viruses transmit a signal which induces extension of TNT in infected cells. It is thought to be reasonable for viruses to infect to the other cells through the TNTs since viruses can avoid to be contacted with and attacked by immune cells.

Physiological significance of TNT formation

Cells having tubular TNTs can share the information on changes in calcium concentration with cells connected each other through a TNT [7]. TNTs are excellent mediators to transmit information toward neighboring cells when the cells are exposed to a limited number of exogenous stimuli. However, it has not been reported that a signaling molecule which is activated by a cell can transactivate the other factors in the other neighboring cells via a TNT. Although TNT can transport organelles such as mitochondria and late endosomes [11], physiological significance of the TNT-mediated intercellular transport has also been unclear. On the other hand, it has been demonstrated that certain pathogens such as retroviruses including HIV-1 [4, 10] and prion [16] can be spread via TNTs. It is clear that TNT plays an important role for viral infections but not clear whether the TNT-mediated infection pathway is all or a part of the route to intercellular viral infections.

In plant cells, plasmodesmata are formed for intercellular communication across the cell walls. The structure and function of plasmodesmata are largely different from those of gap junction but rather similar to those of TNT. In terrestrial plants, plasmodesmata are tubes with 30-60 nm in diameter and have desmotubules, a tube of appressed endoplasmic reticulum with approximately 20 nm in diameter, passing through them. Plant cells can synchronize each other by sharing intracellular components

through the plasmodesmata, allowing for collective regulation in the cells [17]. Some of plant viruses can infect into adjacent cells via the plasmodesmata. The plasmodesmata must be a highly informative model to understand the role, structure and formation mechanism of TNTs.

Conclusion

Intercellular communication is essential for the cells to function in a collective and organized way to make up a complete individual organism. TNT can surely and directly transduce intracellular components involved in signal transductions, by intercellular bridging, from a cell to neighboring cells that are not connected via gap junction. Although presence of TNTs implies communications through ligand-receptor interaction and gap junction are not enough for the cells to survive in an organized way, advantages of TNT-mediated cell-cell communication have not been well demonstrated. Progress in research related to function of TNTs such as mechanisms underlying formation of a long filopodial protrusion, connection between filopodial protrusions, significance of intercellular transport of signaling molecules and organelles, and function of TNTs will disclose physiological advantages of the TNTs.

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