Mini-Review

Cell-cell nanotubes

Tunneling through several types of synapses

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Abbreviations: HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus; MTOC, microtubule organizing centre; TNT, tunneling nanotube

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Nanotube can be generally seen as a nanoscale cylindrical structure. Membrane (or tunneling) nanotube (TNT) is a cytoplasmic tunnel between two cells. Such direct cell-cell channel is used for a physical transport of biochemical cargo, whereas nanotubular networks between cells may be a novel principle of communicative and integrative biology. Recently, TNTs and their networks were discovered in plant cells and then they were reported also in animal cells. Just the reverse, a notion of plant synapse has been also proposed only recently, long after the corresponding notion of neuronal synapse in animals. However, both TNTs and synapses seem to be closely related and evolutionary conserved structures through different types of cells. Accordingly, this mini-review aims to demonstrate that TNTs may represent one of the deep functional similarities between neuronal, immune, viral and plant synapses.

Introduction

Synapse can be defined as a stable adhesive junction between two cells across which information is relayed by directed secretion.¹ The concept of the synapse as a nexus of communication between neurons is now well over 100 years old. It is only recently, however, that the several counterparts have been identified as the immune (or immunological) synapse,¹ ² the viral (or virological) synapse³ and even the plant synapse.⁴ In spite of their differences, there seems to be at least three deep functional similarities and the fundamental communicative mechanisms the neural and immune synapses have in common: molecular networks,⁵ receptor assemblies⁶ and natural nanotubes⁷ including ion channels, microtubules and recently discovered TNTs⁸ ¹⁰ Among them, TNTs seem to be the most common and intriguing feature of all types of synapses, including the viral and the plant ones (Fig. 1).

Neuronal Synapse

Chemical synapses¹¹ enable cell-to-cell communication via secretion of neurotransmitters. At most interneuronal chemical synapses, neurotransmitters are stored in synaptic vesicles and are released after synaptic vesicle fusion at the active zone. This event is triggered by an action potential followed by a rapid influx of calcium into the presynaptic terminal. Such chemical signaling is controlled by voltage-gated ion channels in presynaptic membrane and ligand-gated ion channels in post-synaptic membrane. In their own turn, synaptic vesicles containing neurotransmitter use microtubules and actin filaments to reach the active zone. In addition to the vesicle-based synaptic secretion, a variety of molecules and even organelles can be directly transmitted from
target to the effector cell across the synapse by TNT (Fig. 1). When TNTs from neighboring cells meet, they appear to coalesce and to form a cytoplasmic bridge between the cells. Both immune and neuron cells have been observed transferring proteins to one another through these nanotunnels, and viruses have been seen to travel from cell-to-cell using the TNTs as well.

**Immune Synapse**

Immune cells establish dynamic adhesive cell-cell interactions at a specific contact region, termed the immunological synapse. Although the immune synapse was first described in terms of directed secretion of cytokines between T-cell and antigen-presenting cell, it was the landmark discovery of micrometer-sized segregated clusters of proteins at this intercellular contact that led to the common use of the concept, and triggered an ongoing major research effort in imaging immune responses.

Intriguing features of the immune synapse are the formation of regions of plasma membrane fusion and the intercellular exchange of proteins and membrane fragments between the conjugated cells. It is intriguing similarity between neurons and immune cells when observed that long TNTs readily form between immune cells and a variety of other cell types. Neither the immunologists nor the neuroscientists know the function of these nanotubular highways, but finding out is a new goal for immunology and neuroscience alike. These TNTs might, for example, constitute a previously unknown mechanism for immune cell communication by allowing directed secretion of cytokines between cells far apart. It has been also found that a population of immune cells could use such nanotubular highways to transmit calcium signals across vast (for cells) distances of hundreds of microns within seconds. Although these data indicate intercellular transport of molecules through the structure, the transport of receptors at the surface of TNT cannot be ruled out.

Also killing of target cells requires a transient interaction between the killer and the target cells. This interaction takes place at a specialized intercellular contact, also called the immune synapse, where the encounter causes proteins to segregate into micrometer-scale domains. For example, two killer cells were captured as they prepared to destroy a diseased cell. Poisonous lytic proteins clustered at the synapses between the T-cells and their target, carried there by microtubules. The lytic proteins should be injected into the target cell through the center of the synapse structures, which may also protect the T-cells from poisoning themselves. While the physiological role and consequences of immune synapse formation are beginning to be understood, these studies have given rise to a new research topic in the biology of lymphocyte interactions: synaptic transfer of proteins between lymphocytes.

**Viral Synapse**

Human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1) can spread directly between T-cells by forming a supramolecular structure termed a virological synapse. The viral synapse resembles the immune synapse; each is a specialized contact between a lymphocyte and another cell that contains organized protein microdomains, and each involves repolarization of the T-cell microtubule cytoskeleton. However, formation of the viral synapse is not triggered by T-cell receptor mediated antigen recognition.

Secretion at the viral synapse takes the form of virus transfer from the presynaptic to the postsynaptic cell. A tantalizing observation probably relevant to this event is the reorientation of microtubule organizing centre (MTOC) in the infected cell proximal to the site of cell-cell contact. It has been shown that when a HTLV-1 infected T-cell meets an uninfected T-cell, the MTOC of the infected cell becomes polarized toward the uninfected cell. Complexes of HTLV-1 core (Gag) and the RNA genome of the virus accumulate at the point of cell contact and are then transferred to the uninfected cell.

HIV-1 and HTLV-1 may “hijack” the lymphocyte secretion machinery to send virus to the site of cellular contact in a manner analogous to directed cytotoxic granule secretion at the immune synapse. The movement of HIV-1 across the viral synapse then appears to take place by viral budding at or near the site of cell-cell contact followed, most likely, by virion fusion with the target cell plasma membrane. It has been proposed that HIV also hijacks TNT communication to spread HIV through an intercellular route between communicated cells. The authors demonstrate that HIV infection of human macrophages results in an increased number of TNTs, and show HIV particles within these structures. It has been reported that prions also hijack TNTs for intercellular spread.

**From Plant Synapse to Nanotubular Networks**

Plant synapse has been proposed since actin cytoskeleton-based adhesive contacts between plant cells resemble the neuronal and immune synapses found in animals. Cell-Cell Channels book summarizes reviews recent developments in cell-to-cell trafficking of macromolecules in plants and animals. It is worth noting that the viral infection of plant cell protoplasts (that lack cell walls) leads to the formation of TNT-like tubules which can extend at least 20 μm outward from the cell surface. Such tubules are induced by viruses also in walled cells organized into intact plant tissues. Similar TNTs can be induced in vitro using liposome vesicles which show dynamical self-organizing behavior and form nanotubular networks of interactions.

After plant cells, structures with striking similarity have been reported in animal cells. Such contacts are extremely dynamic and sensitive to mechanical stress, causing their rapid breakage and retraction. It has also been found that TNTs are able to establish complex communication networks between various types of cells. For example, Onflet et al. present evidence that TNTs create supracellular structures and facilitate a novel mechanism for intercellular communication in the immune system. TNTs could be created upon disassembly of the immune synapse, as cells move apart. Thus, nanotubular networks could be assembled from transient immune synapses. Such networks are also suggested to represent novel way to spread drug resistance in tumor cells. Accordingly, several works propose a novel biological principle of cell-to-cell interaction based on membrane continuity and intercellular transfer of organelles.
Tunneling nanotubes at synapses

Conclusions

The increasing number of results suggests that TNTs are widely involved in the key stages of biochemical signaling. This phenomenon is quite general being present in multiple cell types. Apparently, TNTs emerge as basic and evolutionary conserved participants in rather different biochemical pathways. This mini-review also indicates that TNTs may constitute rather novel universal structural and biochemical mechanism of intercellular communication over both short and long distances. Similar to universal structural and biochemical mechanism of intercellular communication over both short and long distances. Similar to universal structural and biochemical mechanism of intercellular communication over both short and long distances.

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