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Review

Emerging physiological and pathological implications of tunneling nanotubes formation between cells

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ABSTRACT

Cell-to-cell communication is a critical requirement to coordinate behaviors of the cells in a community and thereby achieve tissue homeostasis and conservation of the multicellular organisms. Tunneling nanotubes (TNTs), as a cell-to-cell communication over long distance, allow for bi- or uni-directional transfer of cellular components between cells. Identification of inducing agents and the cell and molecular mechanism underling the formation of TNTs and their structural and functional features may lead to finding new important roles for these intercellular bridges in vivo and in vitro. During the last decade, research has shown TNTs have different structural and functional properties, varying between and within cell systems. In this review, we will focus on TNTs and their cell and molecular mechanism of formation. Moreover, the latest findings into their functional roles in physiological and pathological processes, such as signal transduction, micro and nano-particles delivery, immune responses, embryogenesis, cellular reprogramming, apoptosis, cancer, and neurodegenerative diseases initiation and progression and pathogens transfer, will be discussed.

Contents

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1. Introduction

Direct cell-to-cell communication is a critical requirement for development, tissue regeneration and conservation of normal physiology of multicellular organisms. Plants share their cytoplasmic contents through intercellular channels called plasmodesmata, whereas animal cells possess analogous gap junctions and tunneling nanotubes (TNTs) (Lee, 2014; Wang and Gerdes, 2012). In 2004, for the first time, Hans-Hermann Gerdes as a researcher at EMBL Germany reported a novel cell-to-cell communication channels that called tunneling nanotubes (Rustom et al., 2004). This name is taken from both their original discovery diameter size (50–200 nm), and also their tunneling ability in the extracellular matrix (McGowan, 2011). TNTs also called as intercellular nanotubes (ICNs) (Hurtig et al., 2010) or membrane nanotubes (MNTs) (Zhang and Zhang, 2013). They are thin tube structures which protruding from one cell and connecting with another to form a nanotubular network with the surrounding cells (You et al., 2014). These intercellular bridges are not empty membrane tubes, but filled with cytoskeletal filaments, like actin, microtubules and motor proteins. In most cases, TNTs houses F-actin in smaller tubes (<100 μm) and both F-actin and microtubules in thicker (>100 μm diameter) nanotubes (Rustom et al., 2004; Sowinski et al., 2008; Wang et al., 2010). F-actin depolymerization drugs, such as Cytochalasin B/D and Latrunculin B, inhibit TNT formation (Bukoreshtliev et al., 2009; Wang et al., 2011; Wittig et al., 2012).

Different studies reported the presence of TNTs between cells in vivo and in vitro. So far, TNTs have been observed in vivo between myeloid cells in mouse cornea (Chinnery et al., 2008; Seyed-Razavi et al., 2013), between neural crest in chicken embryo (McKinney et al., 2011; Teddy and Kulesa, 2004), and between human mesothelioma cells (Lou et al., 2012b). Moreover, there are many different types of cells (Table 1) which are able to communicate in vitro using TNTs, and their functions are impressive by these nanotubes (Austefjord et al., 2014; Wang et al., 2012b,c). The heterogeneous morphology and composition of TNTs suggests that TNTs may form in different ways (Austefjord et al., 2014; Gerdes et al., 2007; Onfelt et al., 2004). Studies have also been shown that TNTs are transient structures, having variable lifetimes ranging from a few minutes to less than 60 min for T cells, neuronal cells and for more PC12 cells and even up to several hours for normal rat kidney (NRK) and for a few percent of PC12 cells (Bukoreshtliev et al., 2009; Gurke et al., 2008). Moreover, these nanotubes are diverse according to their lengths and thickness (Table 1), and displayed a pronounced sensitivity to light excitation, mechanical stress and chemical fixation, leading to the rupture of many TNTs between cells. So far, the longest and thickness TNTs were reported for ARPE-19 and human lung carcinoma A549, respectively (Austefjord et al., 2014).

TNTs, as a novel biological tool in cell-to-cell communication over long distance, allow for direct transfer of organelles, proteins, genetic materials, ions and small molecules (Table 1) (Guescini et al., 2012; Lou et al., 2012b; Mi et al., 2011; Rolf et al., 2012; Thayanithy et al., 2014). They are critical requirement for development, and tissue homeostasis and regeneration. Recent studies have been shown the importance role of TNTs in mechanical and signaling processes during embryonic patterning and development (Caneparo et al., 2011). Interestingly, it have also been reported TNTs can contribute in cellular differentiation and reprogramming by providing a highway to transfer cellular components from one cell to a target cell (Koyanagi et al., 2005; Rolf et al., 2012; Takahashi et al., 2013). They are also important in pathological situations. Recently, it appeared that TNTs formation between malignant cells and their surrounding stromal cells may facilitate tumor development, invasion, and metastasis (He et al., 2011; Lou et al., 2012b; Thayanithy et al., 2014). TNTs as a tool for intercellular transmission of cellular contents also help to rapid progression of neurodegenerative diseases. In addition, TNTs use to transfer pathogenic agents including bacteria, viruses, and prions between cells, and therefore contribute to the spread of pathogenic diseases (Dubey and Ben-Yehuda, 2011; Gousset et al., 2009; Roberts et al., 2015; Sowinski et al., 2008).

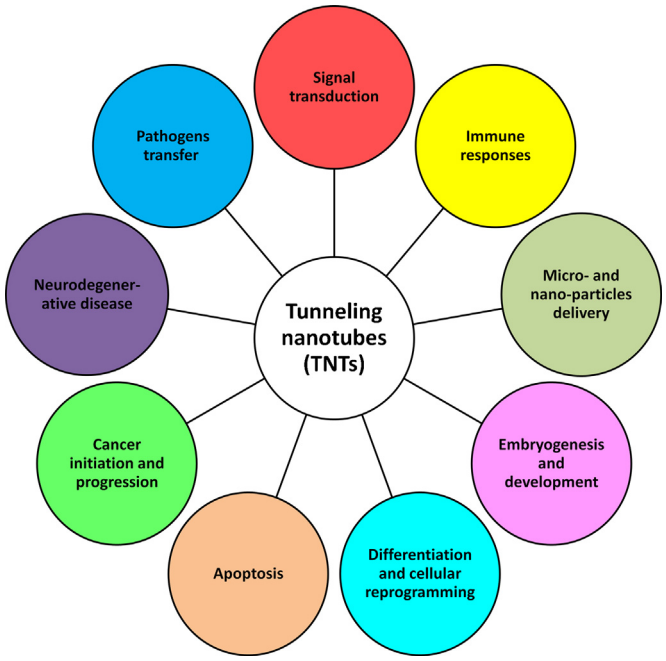

Fig. 1. The functional significance of TNTs formation between cells.

Tunneling nanotubes, as a highway for direct transfer of cell contents to neighboring cells, has lately received particular consideration and thus it has been subjected to a range of investigations to find its characteristics and functions (Fig. 1) in vivo and in vitro. Hence, in this review we describe some of the early findings and characteristics of TNTs along with new discoveries and suggestions regarding their mechanisms of formation and also trafficking by TNTs. Moreover, we summarize the latest findings into their functional roles in physiological process, such as signal transduction, micro and nano-particles delivery, immune responses, embryogenesis, and cellular differentiation, reprogramming and apoptosis. Finally, the potential functions of TNTs in pathological processes, like cancer and neurodegenerative diseases initiation and progression and pathogen transfer, will be discussed.

2. Mechanisms of TNTs formation

The mechanism of TNTs formation is still not fully understood. However, time-lapse recording studies suggested that TNTs form de novo by two different mechanisms. As proposed in the first TNT formation mechanism, filopodial interplay mechanism, the intercellular bridges are established by an outgrowth of a filopodia-like protrusion, which are rich of cytoskeletal filaments, toward a neighboring cell (Fig. 2A) (Abounit and Zurzolo, 2012). In the second mechanism of TNT formation (cell dislodgement mechanism), which is typical for cells of immune system (e.g., macrophages or lymphocytes T), the bridges are appeared when attached cells depart from one another, after which the cells are separated and a nanotube is formed between them (Fig. 2B) (Gerdes et al., 2007; Onfelt et al., 2004; Sowinski et al., 2008). This mechanism is dependent on cell-cell contact duration. For example, it showed that transient contact between lymphocytes T, about 2–3 min, rarely leads to TNTs formation, but increasing duration of cell-cell