from humans in terms of evolution, which must be taken into account when attempting to generalize these results. However, the principles could be used to inform further studies, as has been done for RAD51 – a great deal of what is known about the function of RAD51 comes from studies of bacteria and yeast. These revealed a remarkably conserved mechanism for repairing DSBs [19]. The function of BRCA2 also seems to be reasonably well conserved because a *BRCA2*-like gene in *U. maydis* was shown to have an important role in DNA repair and maintaining genomic stability [9]. As more *BRCA2*-like genes are characterized, it is likely that other informative model systems will become available that will provide considerable insights into the normal cellular function of BRCA2 and the consequences of its loss in cancer development.

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Getting connected: actin-based cell-to-cell channels in plants and animals

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It has been known for more than one hundred years that plant cells are interconnected by cytoplasmic channels called plasmodesmata. This supracellularity was generally considered to be an exotic feature of walled plants containing immobile cells that are firmly enclosed within robust walls. Unexpectedly, intercellular channels in mobile animal cells have been discovered recently. These are extremely dynamic and sensitive to mechanical stress, which causes their rapid breakage and retraction. Both plasmodesmata and nanotubular cell-to-cell channels are supported by the actin cytoskeleton and exclude microtubules. In this article, we discuss the relevance of cell-to-cell channels not only for intercellular communication but also for the development and morphogenesis of multicellular organisms. We also suggest possible parallels between the cell-to-cell transport of endosomes and intracellular pathogens.

Since Eduard Tangl discovered cell-to-cell channels in 1879 (named plasmodesmata by Eduard Strasburger in 1901) [1], higher plants have been considered to be supracellular organisms. This challenges the current version of the 'cell theory' that is based on a long-standing dogma that cells are physically separated and structurally independent entities [2]. Recent progress in plant cell biology not only confirms this unique feature of immobile,

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walled plant cells but also reveals the molecular basis of the complex cell-to-cell channels that selectively transport proteins and RNA molecules through plant tissues [3,4]. The concept is emerging that plasmodesmata are gateable structures that are supported by actin- and myosin-based forces. Furthermore, microtubules seem to be excluded from these cytoplasmic cell-to-cell channels that are formed and maintained between neighbouring plant cells [3–7]. One characteristic feature of plasmodesmata is that their transport is selective, which enables the passage of large macromolecules but specifically excludes some smaller molecules [3]. This highly controlled sieve-like role of plasmodesmata seems to be regulated by the actin cytoskeleton, although the mechanisms remain elusive and are the subject of intense study.

In sharp contrast to immobilized plant cells, the motile cells of animals are considered to be structurally isolated, as predicted by the current version of the cell theory [2]. Therefore, the report that animal cells generate minute cell-to-cell channels that connect them with supracellular assemblies [8] (Figures 1,2) is surprising and deserves further discussion. Performing 3D live microscopy, Gerdes and colleagues [8] observed highly delicate and dynamic cell-to-cell channels that facilitate the selective transfer of endosome-based vesicles but impede the free flow of molecules that are much smaller. These nanotubular communication channels are enriched with actin filaments but lack microtubules. The effective depolymerization of actin filaments with latrunculin B inhibits the transport of endosomes within these cell-to-cell channels and prevents their formation. Actin polymerization is essential for the *de novo* formation of these intercellular communication channels that seem to be closely associated with the transport of endosomes that have myosin motors co-localized on them. It will be important to test whether other myosins that are known to be associated with endosomes also localize to these channels. Myosin-associated endosomes can be seen to enter nanotubes from one end and to leave them from the opposite end. Moreover, this transport

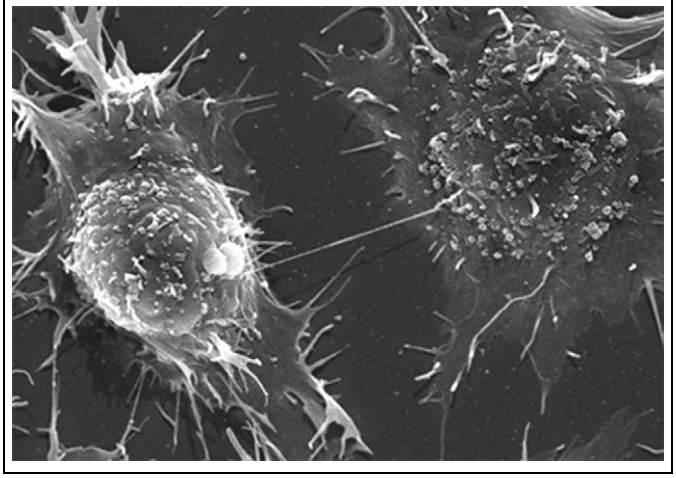

Figure 1. Scanning electron microscopic image showing a tunnelling nanotube (TNT) tensed at the nearest distance between two PC12 cells without contact with the substrate. Several emerging filopodia are also visible. Reprinted, with permission, from Ref. [8]. © (2004) American Association for the Advancement of Science (www.sciencemag.org).

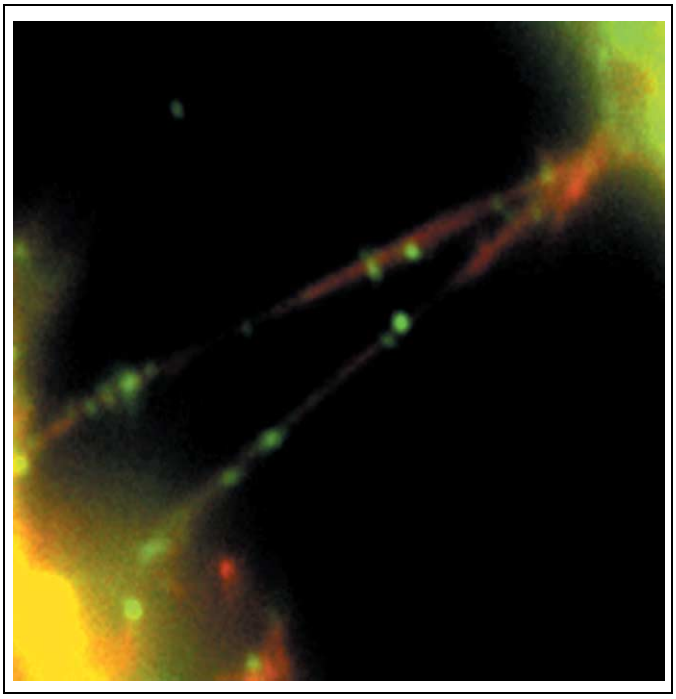

Figure 2. Tunnelling nanotubules (TNTs) as vehicles for the transport of endosomes. Immunolabelling showing myosin-Va-labelled endosomes (green) within actin-based (red) TNTs of PC12 cells. Reprinted, with permission, from Ref. [8]. © (2004) American Association for the Advancement of Science (www.sciencemag.org).

is independent of exocytosis and endocytosis events, which confirms the direct exchange of endosomes through cytoplasmic cell-to-cell channels. Consequently, the channels have been termed 'tunnelling nanotubes' (TNTs).

TNTs: direct devices for the transcellular spread of argosomes, melanosomes and pathogens?

Such direct connections between animal cells could explain several mysteries of cell-to-cell transport, namely morphogen-gradient establishment by argosomes, the transfer of lysosome-based melanosomes from melanocytes to keratinocytes, and the spread of bacteria and viruses across animal tissues. Argosomes are endocytic vesicles that are enriched with morphogens and that are transmitted through epithelia [9]. Three different indirect pathways for the cell-to-cell spread of argosomes have been considered [10], although direct cell-to-cell transfer through TNTs is the most exciting possibility. Similar cell-to-cell transfer of melanosomes has been envisioned, but never shown, to be accomplished by ill-defined melanosome secretion from the tips of filopodia that emerge from melanocytes and the subsequent endocytic uptake of the melanosomes by keratinocytes [11]. Again, TNTs might provide an attractive explanation. Finally, infectious bacteria such as *Listeria* use the actin-polymerization machinery [12] not only for intracellular motility but also for their cell-to-cell spreading by inducing filopodia-like protrusions [13] that seem to extend deep into neighbouring cells in which they are taken up in a process called paracytophagy [13–15]. Considering the discovery of TNTs, this model could be complemented by another scenario in which the tips of *Listeria*-induced actin-based

filopodia fuse with the plasma membrane of adjacent cells to create TNTs and enable the free passage of *Listeria* into these cells. In support of this model, actin-propelled *Mycobacterium marinum* has been reported to spread to adjacent cells, using actin-based dynamic filopodia as transfer structures, without first leaving the cytoplasm [16]. Similarly, like argosomes and melanosomes, intracellular pathogens are closely linked with the endocytic machinery and the endosomes of host cells. Because both endocytic compartments and pathogens use actin polymerization for propulsion through the cytoplasm [17,18], it is tempting to propose that these forces help to push out the plasma membrane locally, leading to the formation of narrow evaginations that, in turn, develop into long processes that are reminiscent of actin-based filopodia. In addition to bacteria, viruses such as vaccinia also show this ability [19]. Moreover, plant viruses are also known to produce long tubular protrusions on the surface of protoplasts [20] but it is not known whether actin and myosin are relevant to this phenomenon. Furthermore, plant viruses have the inherent ability to 'hijack' plant plasmodesmata for their cell-to-cell spread [3,4,7] with the help of so-called 'movement proteins'. It is intriguing to note that these unique proteins are also targeted to prokaryotic cell–cell junctions, where they induce the formation of tubular structures [21], in the same way that they are targeted to the plasmodesmata of higher plants. The most recent discovery is that tobacco mosaic virus does not pass through plasmodesmata as single virus particles, as widely assumed, but instead passes through as intact membrane-associated replication complexes [22]. These membrane-bound compartments are highly motile before they dock at plasmodesmata for their cell-to-cell transfer. Intriguingly (as is the case for endosomes, phagosomes and lysosomes), F-actin and myosin are essential for the intracellular and intercellular transport of these replication complexes. This fits well with reports that virus replication complexes are associated with endosomal compartments [23,24].

Even whole nuclei have been reported to be transferred from cell to cell in *Polysiphonia* (a marine red alga) that has been infected with another red alga, *Choreocolax* [25]. This unique process was accomplished by a direct fusion of nucleated cellular fragments with the host plasma membrane. Similarly, viruses are known to induce the fusion of animal cells to produce heterokaryons and multinucleate syncytia [26,27] that resemble fusing myotubes in the process of muscle generation [28].

Actin-based protrusions of the cell periphery

Besides pathogen-induced cell-periphery protrusions, animal cells also routinely generate actin-based dynamic protrusions on their surfaces, including microspikes, microvilli, stereocilia and filopodia [12]. The characteristic feature of all of these dynamic membrane protrusions is that actin polymerization provides the driving force for them [12]. Obviously, the protrusions can be rapidly extended and retracted, which gives an impression of 'tasting' the environment [29]. In accordance with this view, dynamic filopodia are abundant at the leading edges of expanding neuronal cones [30,31], they accomplish cell-to-cell recognition and initiate synaptic contacts during synaptogenesis [32], and they are sensitive to mechanical stress and environmental factors [33]. Larger and more-permanent protrusions such as microvilli and stereocilia are equipped with robust F-actin bundles. Actomyosin-generated forces that are exerted between this central actin bundle and the peripheral plasma membrane maintain the integrity of these structures [33] (Figure 3). This situation resembles the current model of actomyosin-based organization of plasmodesmata [3,4,6,7]. However, delicate and dynamic TNTs either lack or have extremely delicate central F-actin bundles, which makes them highly sensitive to both mechanical stress and chemical fixation. This delicate nature might be a plausible explanation of why TNTs avoided the attention of previous studies and were revealed only because of recent progress in cytological techniques that enabled more-sophisticated *in vivo* studies.

Multicellularity versus supracellularity

In contrast to the TNTs that have been reported for cells in culture, ring canals (also known as intercellular bridges) of *Drosophila* germlines [34] are structurally supported by prominent F-actin bundles, as is the case for larger tubular protrusions of the cell periphery such as filopodia and stereocilia. As with plant plasmodesmata, this feature makes them robust enough to survive fixation, which enables *in vitro* studies to be carried out. In fact, ring canals are one of the best-studied cell-to-cell channels. Another similarity between ring canals and primary

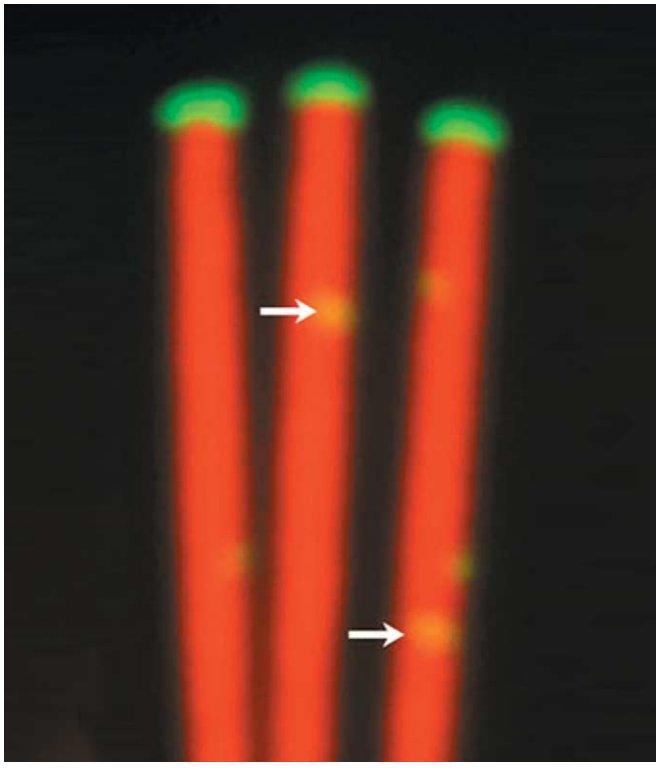

Figure 3. Immunolabelling showing punctated myosin XVa labelling along stereocilia of rat auditory hair cells. The prominent accumulation of myosin XVa is obvious at the tips of the hair cells (arrows). The red fluorescence represents F-actin labelled with rhodamine phalloidin. Reprinted, with permission, from Ref. [33]. © (2004) The Rockefeller University Press.

plasmodesmata is that they are formed by incomplete cytokinesis. Unfortunately, plasmodesmata are firmly embedded in cell walls, which precludes their biochemical characterization.

Importantly, plant cells also generate secondary plasmodesmata [35]. These are not based on incomplete cytokinesis but, instead, on the *de novo* formation of cell-wall tunnels in a process that might be accomplished by tubular extensions tunnelling through cell walls. This process might be initiated from both of the neighbouring plant cells, which resembles the formation of TNTs from two opposite filopodia-like protrusions in animal cells, as shown by Rustom *et al.* [8]. In future studies, it will be a major challenge to determine which processes enable the formation of tunnels through cell walls in plants. In this respect, it might be relevant that cell-wall pectins, which are abundant in cell-wall domains that are traversed by plasmodesmata [6], can be rapidly internalized into plant endosomes by actin-dependent endocytosis [36].

Irrespective of how cell-to-cell connections in plants and animals are formed, it is obvious that cells have an inherent tendency to fuse together in a process that is strictly actin-based and associated with the endosomal system. On an aside, one might now expect to find similarities between the fusion of both plant and animal gametes, in addition to the formation of filopodia-like shmoos of mating haploid yeast cells during sexual reproduction. Interestingly, in this respect, viruses can induce cell-to-cell fusions in both eukaryotes and prokaryotes [27,37]. Therefore, one might speculate that the virus-induced fusions of hypothetical proto-cells and/or early cells were crucial for both the origin and the sexual reproduction of contemporary eukaryotic cells [38]. Further *in vivo* studies might reveal that actin-based cell-to-cell channels are a regular feature of all multicellular organisms. The potential importance of this is indicated by the discovery of another type of transcellular transport pathway that is integrated into a so-called 'vesiculo–vacuolar organelle'. This organelle is a complex network of vesicles and vacuoles that interconnect nearly all cells of the venular endothelium, thus facilitating the cell-to-cell passage of diverse macromolecules [39]. Interestingly, the vesiculo–vacuolar organelle is also directly connected to endosomes, in this case to those related to caveolae.

Concluding remarks

Rustom *et al.* [8] showed, for the first time, that endosomes can spread from cell-to-cell, using dynamic actin-based protrusions as effective vehicles for this intercellular transport. Although the authors documented the *de novo* formation of TNTs in several animal cell types, it is possible that this feature is specific to cells that are cultivated *in vitro*. However, it would not be surprising if future studies were to reveal that this phenomenon is also valid for cells of intact tissues. This scenario is appealing because the cell-to-cell channels are present not only in higher plants and animals but also in lower plants, fungi, the green alga *Volvox* and even in prokaryotic organisms [21,40,41]. Obviously, there is an inherent tendency for cells, irrespective of whether they are enclosed in robust cell walls, to send out thin actin-based protrusions that can approach each other and, subsequently, fuse together to form actin-based cell-to-cell channels. It is still a mystery why endosomes are attracted into TNTs and transported from cell to cell. It would be exciting to study whether cellular pathogens such as bacteria and viruses can, in a similar way to plant viruses, hijack cell-to-cell channels to spread through multicellular organisms.

Finally, it is known that nearly all of the cells of plant bodies are interconnected and, thus, are merged into supracellular continuity. Future studies might confirm that this phenomenon also occurs in animal cells, which would make this a general principle. By showing that animal cells are interconnected, either temporarily or permanently, by actin-based tubules *in vivo*, the paradigm of higher organisms as multicellular assemblies will yield in favour of viewing them as supracellular units.

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The interaction between FOXO and SIRT1: tipping the balance towards survival

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When overexpressed, the NAD-dependent protein deacetylase Sir2 extends the lifespan of both budding yeast and the nematode worm *Caenorhabditis elegans*. In the worm, this extension of lifespan requires the FOXO transcription factor *daf-16*. Three recent articles focusing on mammalian homologues of Sir2 and FOXO have highlighted the mechanisms that generate this genetic interaction. Mammalian SIRT1 deacetylates FOXO3 and/or FOXO4, thus attenuating FOXO-induced apoptosis and potentiating FOXO-induced cell-cycle arrest. SIRT1 might increase longevity by shifting FOXO dependent responses away from cell death and towards cell survival.

An important discovery has been that single gene mutations can produce large increases in adult lifespan. Loss-of-function mutations in the genes encoding components of the insulin and/or insulin-like growth factor (IGF)-like signalling (IIS) pathway have been shown to extend the lifespan of the nematode worm *Caenorhabditis elegans* [1], the fruit fly *Drosophila* [2] and the mouse [3] (Box 1). When overexpressed, *Sir2* (silent information regulator 2), which encodes a NAD-dependent protein deacetylase [4,5], has been shown to extend the lifespan of budding yeast [6] and *C. elegans* [7]. In *C. elegans*, the extension of lifespan by *Sir2* requires the presence of *daf-16* [7], which is the only *C. elegans* homologue of the FOXO family of forkhead transcription factors [8,9]. FOXO factors are downregulated by the IIS pathway and *daf-16* is also required for the extension of lifespan by reduced IIS activity in *C. elegans* [10]. These genetic interactions suggest that the product of *Sir2* expression interacts with one or more components of the IIS pathway. Three recent articles have shown that the product of the mammalian orthologue of *Sir2* deacetylates and regulates the activity of FOXO family members [11–13].

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FOXO binding and deacetylation by SIRT1

There are seven mammalian members of the Sir2 family, of which the closest to yeast Sir2 is SIRT1 [14]. SIRT1