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EDITORIAL

Cell-to-cell communication: current views and future perspectives

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Introduction

Multicellular organisms rely on complex and tightly regulated communication between individual cells embedded in a dense extracellular matrix. Through the course of evolution, diverse mechanisms underlying this communication have appeared. These include communication via direct cell–to-cell contact (e.g., Delta/Notch signalling), the release of soluble factors (e.g., hormones, cytokines) that activate target cells locally or distantly through surface receptors and the direct transfer of signals through gap junction channels that span the plasma membranes of adjacent cells. During the last decade in particular, exciting progress has been made in the understanding of intercellular communication and new signalling pathways between mammalian cells have been discovered: exosomes, which are small vesicles released by cells that can be taken up by other cells; cytonemes, which are long thin membrane protrusions of cells implicated in the long-distance signalling of morphogens; tunnelling nanotubes, which are recognized as thin membranous bridges connecting distant cells that facilitate the intercellular transfer of various cellular cargo; and bioelectrical signalling in which slow changes in the resting potential of cells provide signalling cues for the regulation of cell proliferation, migration and differentiation. A second advance in our understanding of cell-to-cell communication has resulted from the development of new technologies. These are primarily imaging methods suitable for recording cells in living organisms (e.g., 2-photon microscopy) but also include micromanipulation tools (e.g., laser nanosurgery) that permit the perturbation of cells or substructures therefrom, in a natural tissue environment. This Special Issue represents a sample of various areas related to cell-to-cell interactions and in which significant advances have led to new concepts of cell–cell communication. The first part focuses on selected mechanisms of signalling pathways between cells and the second part highlights the power of advanced technology that has provided a breakthrough or shows great potential for applications regarding the analysis of cell-to-cell communication in vivo. In the following, we will briefly introduce the review articles published in this Special Issue.

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Mechanisms of intercellular signalling

The first article addresses the secretory pathway of mammalian cells, through which many signalling molecules are released. The article by Prydz et al. (2012) makes it clear that an increasing number of secretory processes bypass the Golgi apparatus and seem to play important roles in the communication between organelles, cells and tissues. Hervé and Derangeon (2012) in their article have focused on gap junction channels, the most direct cell-to-cell communication routes that connect the cytoplasm of adjacent cells. They convincingly argue that these channels are not just passive conduits, as has been thought for a long time but are gated pores that are able to open and close in response to biological stimuli. Furthermore, they discuss the concept that mutational alterations of these channels are associated with many diseases and, therefore, the modulation of gap junction channels represents a potential pharmacological target. In their article on exosomes, Schneider and Simons (2012) report on these small exo-vesicles that are released by most cell types. Only recently has their role been recognized in the targeted delivery of molecules destined for intercellular communication and signalling. The authors focus in their review on the cell biology and function of neuronal exosomes and discuss the evidence for pathogenic intercellular protein transfer mediated by these vesicular carriers. Kragler (2012) introduces in his article the membrane-lined microchannels termed plasmodesmata (PD), which traverse the cell walls of plant cells and some algal cells. These channels were discovered more than a century ago and enable transport and communication between cells. Kragler starts his review with a concise overview of the structure and function of PD, at a suitable level for readers not familiar with plant biology and then summarizes recent insights suggesting that the intercellular transport of macromolecules through these channels is a regulated process depending on the tissue, developmental stage and nature of the transported macromolecules. In this context, Kragler highlights the transfer of homeodomain transcription factor and micro- and messenger RNAs and discusses the implication of this transfer in the formation of differentiation patterns during plant development. The next two articles focus on two recently identified communicative routes that are found in mammalian cells and that have structural and functional similarities with PDs. One of these structures, the cytoneme, takes the form of long thin filopodial protrusions with a specialized signalling role during developmental processes. In their article, Gradilla and Guerrero (2013) discuss the implications of cytonemes in cell-to-cell signalling during developmental processes and put forward the concept that the extension of cytonemes correlates in space and time with morphogen gradient formation in vivo. The second structure related to PDs is composed of tunnelling nanotubes (TNTs), which are thin membranous tubes that connect remote cells over long distances. Tunnelling nanotubes facilitate the intercellular transport of various cellular cargos ranging from molecules to organelles. Kimura et al. (2012) focus in their article on the induction and/or formation of TNTs. They survey the molecules/factors that have been implicated in this process. In addition to M-Sec and HIV Nef as prominent TNT inducers, they discuss molecules and conditions associated with the inductive processes, such as the Rho family of small GTPases, pathogen infection, inflammation and oxidative stress. Bukoreshtliev et al. (2012) discuss, in their review, the current views and understanding of mechanical cues in cellular signalling and communication. They summarize many of the known mechanisms by which cells are able to sense mechanical cues and to integrate this information into a cellular and multi-cellular response. Several examples from the literature are included in this broad and well-structured review illustrating the deep involvement of mechanical forces in fundamental cell–to-cell communication pathways. In the last contribution of the first part, Adams and Levin (2012) introduce the fascinating field of bioelectrical signalling elicited by ion-channel-dependent changes in the resting potential of the plasma membrane of cells. The authors explain how, in embryonic and regenerative pattern formation, bioelectrical cues serve as mediators, e.g., of positional information and large-scale anatomical polarity. On the practical side, they highlight available technologies that researchers can employ to identify and dissect ionic signalling by endogenous voltage gradients as mediators of cell–to-cell communication.

Advanced methods for studying intercellular signalling

The following examples illustrate the power of new technologies to address cell-to-cell signalling in a three-dimensional (3D)-like or natural 3D environment. Page et al. (2012) discuss, in their review, 3D cell culture approaches currently used to mimic a tissue-like environment. These include multicellular spheroids produced by various methods and 3D scaffold-based systems composed of synthetic or naturally derived biomaterials that simulate the extracellular matrix of tissue. The authors highlight examples where 3D culture approaches have led to diverse cell responses (e.g., gene expression profiles) as compared with "standard" 2D culture systems. Such 3D culture models might become excellent "easy to handle systems" for studying cell–cell communication under "close to in vivo" conditions. In their article, Colombelli and Solon (2012) present recent advances in the field of force sensing and biomechanics from laser-ablation-based studies performed in vitro and in vivo. They review the way that this technique has assisted in the analysis of the molecular mechanisms underlying mechano-sensitivity and of the role of these forces in tissue remodelling and the collective behaviour of cells during morphogenesis. The last two articles of this part focus on two in-vivo-imaging methods with highly promising potential for studying cell–to-cell interactions. Osswald and Winkler (2013) discuss the power of two-photon microscopy for imaging cell–to-cell interactions in the brain of living organisms over a wide range of time spans. They survey the application of this technique in studies of cellular, vascular and molecular interactions in healthy brain and neurological diseases. A strong focus in their article is on brain tumor formation, progression and response. The authors illustrate recent advances in this field by providing supplementary videos acquired through a chronic cranial window. Finally, Pampaloni et al. (2013) introduce light-sheet-based fluorescence microscopy (LSFM) as the method of choice for imaging 3D cell cultures over extended periods of time. They explain LSFM in an easily understandable and practically orientated manner and emphasize its strength (deep penetration into the specimen, high imaging speed and minimal photodamage). In extension of their previous work with

LSFM showing reconstruction during the first 24 h of embryonic development in zebrafish at the single cell level (Keller et al. 2008), they here discuss potential application of LSFM for the analysis of in-vivo-like cellular spheroids. Many inspiring images acquired from these cultures are provided in their article.

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