

Review Article

Non-chemical and non-contact cell-to-cell communication: a short review

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Abstract: Cell-to-cell communication is the basis of coordinated cellular activity and thus fundamental for the functioning of biological systems. In a recently published research article by Chaban et al. (Am. J. Transl. Res., 5(1), 69-79), the authors report on interesting new experimental findings supporting a neuro-hormonal independent, non-diffusible cell-to-cell signaling. Our paper aims to (i) discuss some critical notions used by the authors to describe their findings, and (ii) briefly review related experimental work performed so far but not discussed in the original work of Chaban et al. In our opinion, the research on principles of non-chemical and non-contact cell-to-cell communication has the potential to offer new fundamental insights into biological processes. With this paper, we want to encourage future research on this topic by discussing critical issues and giving an overview of the current state of research.

Keywords: Cell-to-cell communication, physical signaling

Introduction

Cell-to-cell communication serves as the basis for functional coordination between unicellular organisms, as well as between cells in multicellular organisms. The signaling pathways associated are based on different mechanisms, such as, for example, direct cell-to-cell contact, release of soluble factors or vesicles, or electrical signals [1-6].

We read with great interest the article by Chaban et al. [7] in this journal about new experimental findings supporting a cell-to-cell signaling *independent* on the exchange of chemical substances or electrical signals. The authors state that their “findings demonstrate that apoptotic and cancerous cells are capable of exerting a non-diffusible, non-neuronal influence over distance on nearby, but physically disconnected cells”, and that “the findings here are the first to our knowledge to support physically disconnected, non-diffusible cell-to-cell signaling”. However, we see the need to refine these statements as well as to provide additional information about the context of the

research concerning this topic performed to date.

Taking the article of Chaban et al [7] as a starting point, our main objectives are to clarify that (i) the term “physically disconnected cells” does not describe their experimental situation accurately, and show (ii) that their findings are not the first concerning experimental evidence of possible non-chemical and non-contact cell-to-cell communication. In general, we aim to encourage future research on this topic by discussing critical issues and giving an overview of the current state of research. In the following we explain our objectives in detail.

“Non-physical” or “non-contact” cell-to-cell communication?

Chaban et al. equate the term “non-physical” with “non-contact”. Yet, from a physical point of view this equalization is not justified since these terms refer to two characteristics that are independent. Cells that are not directly in contact with each other, i.e. the “non-contact” condition, may be physically connected at the same

time by exchange of physical signals. Likewise, cell-to-cell signaling (also in a non-contact condition) can also be based on volatile, i.e. chemical, communication, which has already been demonstrated to take place between several prokaryotic as well as eukaryotic microorganisms (e.g. yeast [8-10], *Escherichia coli* [11, 12], *Bacillus licheniformis* [13], *Candida albicans* [14], *Trichoderma* [15], *Serratia rubidaea* [16], *Chlamydomonas reinhardtii* [17]) and plants [18-21]. For example, Volodyaev et al. [22] recently showed that yeast cell cultures of the *Saccharomyces cerevisiae* can have an effect on each other (i.e. stimulation of budding and culture growth) mediated by volatile carbon dioxide (CO₂) as a factor of cell-to-cell interaction. When the authors separated the cultures by metal, glass and quartz glass plates, the effect disappeared, indicating the solely involvement of volatile communication in the causation of this effect.

We welcome that Chaban et al. mention in their paper the possible involvement of volatile communication in their experimental setup. Volatile compounds might be able to establish a communication channel between the cultures placed in the inner and outer chamber of the “flask-in-flask” device used. However, to the best of our knowledge, volatile communication between neuronal cells has not been described in the literature so far. Thus, although the possibility of volatile communication involved in the experiments presented by Chaban et al. could not be ruled out and should be further investigated, in our opinion the experimental setup of the authors should be primarily regarded as an investigation of a non-chemical and non-contact cell-to-cell communication featuring a *physical* communication channel. As reviewed by Reguera et al. [6] there are at least three physical cell-to-cell communication channels: *sound*, *electric current* and *electromagnetic radiation*. Since the cell cultures of the experiment performed by Chaban et al. are not in direct contact with each other and since signaling based on electrical currents needs a direct connection between the cells or an exchange via a medium, this type of signaling can be excluded as a possible cause of the observed effect. In addition, sound is fairly unlikely to be the physical communication signal in the experimental setup of Chaban et al. since sound would be greatly damped by the used setup involving different damping media

(i.e. water, plastic). Thus, these physical conditions highlight the involvement of electromagnetic radiation, rather than electrical current or sound.

Research performed so far into non-chemical and non-contact cell-to-cell communication

Experimental evidence for a non-chemical and non-contact cell-to-cell communication can be traced back almost 100 years ago and has also been reported by many recent studies, as reviewed in detail by Rahn [23], Salkind [24], Wainwright [25], Gurwitsch [26], Popp et al. [27], Nikolaev [28], Trushin [29, 30], Cifra et al. [31], and Reguera [6].

Intensive research started in the 1920s with the work of Gurwitsch [32-36] whose 200 or more experiments revealed that when pointing the tip of an onion root (inducer) to another onion root (receiver), separated by quartz glass, the receiver root surprisingly shows an increased rate of mitosis (approx. 20-25%). Since this effect was absent when using ultraviolet (UV)-opaque glass, he concluded that electromagnetic radiation in the UV range was responsible. He termed this type of radiation “*mitogenetic radiation*”. In 1927 Frank & Gurwitsch [37] reported the successful spectroscopic detection of UV radiation in the range of 193-237 nm originating from frog muscles. Gurwitsch’s research stimulated many other researchers in the 1930s and early 1940s to replicate and extend their experiments, leading to both successful and unsuccessful replications (see reviews by [26, 29, 31, 38]). The research showed that there is indication for a non-chemical, electromagnetic cell-to-cell signaling which can be experimentally detected when investigating the effect of inducer cells on receiver cells, where the inducer cells have to be in the mitotic state or in a stressed condition (induced by e.g. chemical, thermal, mechanical or electrical treatments). The radiation emanated from stressed cells was termed by Gurwitsch as “*degradation radiation*” [26]. One limitation of Gurwitsch’s work is that it does not completely meet modern scientific requirements for proper experimental investigations, i.e. it lacks proper statistical analysis and complete control over confounders. However, new analyses of Gurwitsch’s data revealed that most of the results were statistically significant using modern statistical test

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(personal communication, Prof. Belousov [Faculty of Biology, Lomonosov Moscow State University, Moscow], Dr. Stefanov [Institute of Biophysics, Russian Acad. Sci., Moscow]). Unfortunately, these analyses were not published. Thus, Gurwitsch's work is primarily of historical significance and should be regarded as an initial approach for experimental investigation of a new topic. Unfortunately, in the 1940s-1950s, World War II and a shift in the focus to biochemistry halted research into this topic.

In the 1960s-1980s the research group of Kaznacheev [39, 40] continued to investigate the topic by performing a large number of experiments with different cell cultures. They used a specially designed device to perform the experiments consisting of two flasks, which were connected by a window of either quartz glass or a UV-opaque glass plate (with a depth of about 0.2-2 mm). An "inducer" cell culture was placed in one flask and a "receiver" culture in the other. It was investigated how the treatment of the inducer culture with different stressors (e.g. viruses, chemicals or UV-radiation) affects the receiver culture. For example, experiments using inducer cell cultures consisting of monkey kidney tissue treated with adenoviruses demonstrated that the receiver cell culture also shows morphological signs of infection in 72% of performed trials (total number of trials: 170) after 2.3 days of contact [39]. The observed effect was termed the "mirror cytopathic effect" [41]. After analyzing all experiments done, Kaznacheev concluded [39, 40] among other things that the effect (i) was at its strongest when cultures from the same species were used, (ii) seems to be caused by an electromagnetic interaction between the cultures in the UV range, and interestingly, as highlighted by [31], (iii) its strength showed an annual modulation (month with most successful experiments: August), possibly related to environmental factors [31, 40]. Although the work of Kaznacheev's group improved the experimental quality, compared to the work of Gurwitsch, the statistical analysis and the controlling of confounders could have been performed better.

Other experiments, often using a "dish-in-dish" setup similar to that one used by Chaban et al., were performed in the 1980s [42-44], 1990s [45-56], and the research continued in the

21st century [28, 57-69]. In the following, we will give a brief review of some of these research works.

Bat'yanov [44] published in 1984 a study showing that optically coupled mitochondria (isolated from rat liver by centrifugation) interact. The sender mitochondria caused decrease in the oxygen consumption of the receiver mitochondria. Both cultures were separated by a quartz cuvette system with two chambers and a wall thickness of 1 mm. The experiment was carried out in uniform daylight and room temperature. Unfortunately, the paper does not report if the cultures were properly shielded against a possible interaction based on volatile chemical compounds.

Albrecht-Buehler [55] published 1992 a study showing the ability of two groups of hamster cells to adopt their orientation through a sheet of glass. The effect disappeared when thin metallic films were used.

In 1993, Galantsev et al. [53] showed that mammary tissue cultures (explants) of lactating albino mice can interact even when separated by a quartz glass wall (0.1 mm thick). When the sender cell culture was treated with different substances (oxytocin, epinephrine or norepinephrine), the level of thiobarbituric acid-reactive substances in the sender as well as in the optically connected two receiver cell cultures changed. The authors stated that chemiluminescence due to lipid-peroxidation might be the physical factor behind the observed effect.

In a study of 1994, Shen et al. [52] demonstrated that neutrophils (isolated from pig blood) stimulated to undergo respiratory burst are able to activate a second population of neutrophils that were chemically separated but optically coupled. The activation in the receiver population was registered as an increase in low-level chemiluminescence and superoxide (O_2^-) production (measured by the reduction of ferricytochrome c and by O_2^- spin-trapping).

Wainwright et al. [47] reported 1997 about a study investigating the interaction of optically coupled cultures from two different species. The bacterium *Pseudomonas corrugate lux* (genetically modified *Pseudomonas* with a gene (*lux*) that encodes bioluminescence) was used as a receiver, and the fungus *Gaeumannomyces*

graminis var. *tritici* (a natural antagonist) as a sender. The experiments were conducted in a special designed system comprising an inner and outer vial. The inner vial was made of either normal or quartz glass. The bacterium culture, in a late-exponential phase, was placed in the inner vial, the fungus in the outer one. As a result, light emission from bacteria grown in the quartz glass vial was higher than in case grown in the vial of ordinary glass. In order to check if a possible volatile communication took place, Wainwright repeated the experiments with hermetically shielded inner vials. Under this condition, no (photon) emission changes (of receiver) were observed. At the first glance, this could be interpreted as evidence against a possible physical (optical) cell-to-cell communication and an evidence for a chemical volatile one. However, the authors tested the possibility that simply the lack of fresh O₂ prevented the growth-stimulatory effect of the sender culture. Indeed, when the inner vials were filled with O₂ and then hermetically shielded, an increase in light emission was observed when the bacteria were placed in the vial of quartz glass. Interestingly, the effect vanished when using ordinary glass. These experimental results are in strong favor for a physical cell-to-cell communication. Despite the clear results, Wainwright et al. could only observe the effect in 2 out of 7 experiments performed. They hypothesized that “some as yet unknown factor or factors” might interfere with the effect.

In 1999, Musumeci et al. [70] used *Sacharomyces cerevisiae* yeast cultures to show that the putting of a sender cell culture in optical contact with a receiver cell culture of the same age but with stopped cell division due to previous temperature treatment, an increase in the cell density of the receiver cell culture is observed. Both cell cultures were in the exponential growth phase. The quartz cuvette with the sender culture was sealed with a lid to prevent volatile signaling. Musumeci et al. pointed out that the cell cycle phase is an important parameter in these kinds of experiments. They argue that the negative result of Quickienden et al. [43] could be attributed probably to the fact that their receiver cell culture was not in the exponential phase, but in the lag or stationary phase, making the detection of the effect difficult.

The most recent studies were performed by one of the authors (DF) who detected an inter-

cellular communication between *Paramecium caudatum* colonies when separated with quartz glass and significantly different effects between inducer and receiver populations when separated by glass barriers [67, 68]. The author used the same “dish-in-dish” setup as Chaban et al., performed a proper statistical analysis and minimized the impact of confounders. That not only cell cultures but also whole organisms exert an influence on each other when separated was shown for example by Burlakov et al. [71] who showed that when loach (*Misgurnus fossilis* L.) embryos of different developmental stages were kept in different quartz cuvettes so that only optic contact between the groups was possible, significant developmental abnormalities were registered in the embryos. The authors concluded that an optical communication took place.

In parallel to the studies about non-chemical, non-contact cell-to-cell communication, other studies focused on identifying the physical signaling factor. In general, two such factors were identified: electromagnetic radiation (in the UV, visible and near-infrared (NIR) spectral region) and sound. That cell cultures emit sound was demonstrated by Matsushashi et al. [72] who detected that *Bacillus subtilis* cells emit sound with peaks at approx. 8-10, 18-22 and 27-43 kHz. In two cell samples peaks at 9, 14, 18, 29, 32 and 34 kHz were observed. Interestingly, they reported that “there were no positive results with heat-killed *B. subtilis* cells” and “no significant sound production by *B. carbo-niphilus*, *Escherichia coli* or *Saccaromyces cerevisiae*” could be detected [72]. Other studies documented ultra-weak photon emission (UPE) in the UV-NIR range from cell cultures (see review [27, 73-76]), possibly involved in optical cell-to-cell communication. Focusing on electroexcitable cells, several experiments show that these cells are able to generate non-thermal electromagnetic radiation in the spectral region of millimeter [77], infrared [78] and also visible [79-81] waves when stimulated to depolarize its membrane.

Since the “flask-in-flask” device used by Chaban et al. is made of plastic (personal communication) it is in principle possible that the observed effects can be attributed to a cell-to-cell communication based on electromagnetic radiation.

Summary, conclusion and outlook

In conclusion, we hope that this overview about the research on non-chemical and non-contact cell-to-cell communication so far will encourage researchers to further explore this fascinating topic of physical cell-to-cell communication, in that they (i) critically examine the accumulated research literature about this topic in detail, and (ii) continue their research into seemingly non-chemical and non-contact cell-to-cell communication by extending the experimental protocol. Such extensions would be the use of various “dish-in-dish” setups made of different materials (e.g. normal or quartz glass, different kind of plastics) and incorporating different (e.g. optic and electromagnetic) shielding options as well as investigating how specific parameters like cell cycle state, incubation time, ambient light condition and other environmental factors might have an impact on the experimental results. In addition, the possible role of volatile (chemical) and (ultra) sound communication should be further investigated by repeating the experiment while completely hermetically shielding the cell cultures from each other. Finally, as effects on cell division rates were observed [35, 67] and as biomolecules (e.g. hormones) are known to have similar effects too, we will have to test for interactions and hierarchical relations between chemical cell signals and radiation-based cell signals.

In our view, this important research topic on physical cell-to-cell signaling should be highlighted and included into mandatory university courses on biophysics. It should as well become an integrated part of textbooks on cell signaling.

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Disclosure of conflict of interest

None.

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