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EDITORIAL

From cell-cell adhesion and cellular oscillations to spectacular views inside the cell – 50 years of research with *Dictyostelium*

Early pioneering research

Günther Gerisch studied biology in Berlin, Göttingen and Tübingen. He did his first scientific work in the lab of K.G. Grell in Tübingen on cell differentiation and phototaxis in the alga *Pleodorina californa*. In the late 1950s, as a graduate student in the lab of Wolfhard Weidel at the Max Planck Institute for Biology in Tübingen, Günther started to work on *Dictyostelium* and wrote his doctoral thesis on "Zellfunktionen und Zellfunktionswechsel in der Entwicklung von *Dictyostelium discoideum*". He then moved to Freiburg and worked until 1969 at the Zoological Institute of the University of Freiburg.

Based on his thesis work, between 1959 and 1962 Günther published a series of papers, in which he described precise and reproducible conditions for growth and development of *Dictyostelium* cells in shaken cultures. Long before liquid growth media were available (Watts and Ashworth's description of the first axenic medium was published in 1970), Günther grew *Dictyostelium* cells in high-density suspensions of bacteria in a simple phosphate buffer (Gerisch, 1959). In the absence of nutrients the bacteria could not grow, but served as food for the amoebae, so it was possible to get exponentially growing cultures of *Dictyostelium* cells that inversely correlated with decreasing bacterial density. Günther showed that up to a defined bacterial density, cells remained vegetative and afterwards started developing to become aggregation competent (Gerisch, 1960, 1961a). Washing the amoebae free of bacteria and resuspending them in simple buffers allowed him to find out optimal conditions of oxygen supply, salt composition and pH for cell development (Gerisch, 1962). He also found out that cells adhered to each other in suspension, that the aggregates could rapidly dissociate when transferred to a glass substratum, but this did not occur after 5 h starvation in suspension. Similarly, EDTA inhibited aggregate formation in suspension if added during the first 4 h of starvation, but not later on (Gerisch, 1961b, c).

Thus, with this first series of experiments, Günther laid down conditions that facilitated a biochemical and physiological analysis of *Dictyostelium* growth and development and at the same time he discovered developmental changes in cell adhesion which could be easily discriminated by using the divalent cation chelator EDTA.

A successful strategy for identifying cell adhesion molecules

Careful analysis of the EDTA effects on cell adhesiveness had led Günther to propose that the observed developmental differences were of a qualitative and not just quantitative nature (Gerisch, 1961b). Therefore he started a systematic study of cell adhesion with the purpose of identifying the cell surface components that were responsible for the EDTA-labile and the EDTA-stable forms of cell-cell adhesion. By raising antibodies against membrane fragments, he first characterized the antigenic properties of *Dictyostelium discoideum* and *Polysphondylium pallidum* membranes, showing that there were species-specific differences in the carbohydrate composition of the cell membranes in addition to intra-specific developmental differences, the latter finding confirming previous work by Gregg, Sonneborn and their coworkers (Gregg and Trygstad, 1958; Sonneborn et al., 1964). This work was also influenced by Otto Lüderitz, Director at the local Max Planck Institute for Immunology and a specialist on bacterial surface lipopolysaccharides, who was a collaborator during the time in Freiburg.

After his return to Tübingen as a group leader at the newly founded Friedrich Miescher Laboratory of the Max Planck Society, with the help of students that had joined his lab (in particular Hartmut Beug), Günther designed a semi-automatic agglutinometer for standardized quantitative measurement of cell-cell adhesion in microliter volumes and generated highly polyspecific sera against crude membranes of vegetative

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or aggregation-competent cells. By using monovalent antibodies with appropriate controls and by absorbing the antibodies with membrane fractions from cells at different developmental stages, his group identified two antigenically distinct mechanisms for cell-cell adhesion and showed that the first, which was named "contact sites A", was responsible for the developmentally regulated EDTA-resistant form of adhesion, and the second ("contact sites B") mediated the EDTA-labile adhesion (Beug et al., 1970; Beug et al., 1973a, b).

In the long run these adhesion studies were influential in two respects: (1) they favored a paradigm shift from a view in which cell adhesion was the sum of non-specific interactions between adjacent membranes to a view in which adhesion depended on specific interactions between discrete cell surface constituents; (2) they paved the way to make the immunological approach the method of choice for identifying cell adhesion molecules (CAMs) of other organisms, from sea urchin embryos to mammalian cells. Crucial for the success of this strategy, in addition to the quantitative assay and the homogeneity of the cell culture that could be dissociated without protease treatment (conditions that were difficult to meet with mammalian cells), was the production of a large batch of polyspecific serum. This could be used over several years (traces of it exist even today) and helped to refine the methods for purifying and characterizing the membrane glycoprotein responsible for the EDTA-stable adhesion: csA or gp80 (Müller and Gerisch, 1978). This was one of the first cell-cell adhesion proteins to be identified in any organism, and one of the best characterized in terms of structure and function.

Basics of cellular oscillations and the regulation of *Dictyostelium* development

Concomitantly with the studies on cell adhesion, Günther started a careful analysis of another feature of *Dictyostelium* development that intrigued him: during aggregation on agar, cells moved toward aggregation centers in a periodic manner that generated self-propagating waves and spirals (Gerisch, 1965). This behavior had been already described by other investigators (Arndt, 1937; Bonner and Dodd, 1962; Shaffer, 1962). By comparing the chemotactic behavior of wild-type and some mutant cells in an aggregation field, Günther determined the frequency of wave formation and the speed of wave propagation, identifying three cyclic phases: (1) a phase of chemotactic responsiveness, (2) a phase of chemotactic activity and (3) a refractory phase (Gerisch, 1968, 1971).

With Benno Hess, he then established conditions for reproducing and manipulating spontaneous periodic cellular oscillations in suspended cell cultures. By using cuvettes, in which cells could develop and which allowed recording of cell shape changes, they showed that periodic light scattering changes could be linked to the periodic activity in aggregating cell layers as well as to changes in the redox state of cytochrome b. These early attempts resulted in a series of experiments showing that the light scattering oscillations were synchronized with spontaneous oscillations in cAMP and that both could be induced by cAMP pulses (Gerisch and Hess, 1974). Cyclic AMP had been discovered shortly before as the *Dictyostelium* chemoattractant by Konjin and co-workers (Konijn et al., 1967). The finding that secreted cAMP not only induced chemotaxis of neighboring cells, but also induced these cells to release their own burst of cAMP established that the chemoattractant and the signal propagating over an aggregation field were identical and could explain how chemotaxis could assemble cells over distances that were far too large to enable sensing of a simple cAMP gradient. Most of these studies were conducted at the Friedrich Miescher Laboratory in Tübingen with the help of students and collaborators, among those were Dieter Malchow, Ursula Wick and Werner Roos.

In 1975, Günther moved with these collaborators to Basel, as a guest professor at the newly established Biocenter of the local university. In Basel, the studies on cell adhesion led, as mentioned above, to the purification of contact sites A in *Dictyostelium* (Müller and Gerisch, 1978) and related cell adhesion molecules in *Polysphondylium* (Bozzaro and Gerisch, 1978; Bozzaro et al., 1981), while the investigations on cellular oscillations were continued in particular with Dieter Malchow, Werner Roos, Ursula Wick, Bernd Wurster, and Vidia Nanjundiah. The experimental setup for measuring light-scattering changes was used to further explore the biochemical signalling pathways downstream of cAMP stimulation, and this led to the discovery that light scattering oscillations were linked not only to cAMP, but also to cGMP, Ca^{2+} ions and pH periodic changes (Gerisch et al., 1979; Malchow et al., 1978; Wurster et al., 1977). It was also possible to show that the pulsatile production of cAMP, and the underlying periodic activation of adenylyl cyclase, was crucial for regulating gene expression and cell differentiation (Gerisch et al., 1975; Roos et al., 1975, 1977). The EDTA-stable contacts, and the csA glycoprotein, were strongly regulated by cAMP pulses, and thus the cell adhesion and oscillation studies became integrated (reviewed in Gerisch, 1982).

Two technological developments occurred during this time, which would determine much of his future research: the advent of monoclonal antibodies and the amenability of *Dictyostelium* to molecular genetic approaches. Georges Köhler had just established, together with César Milstein, the methodology for producing monoclonal antibodies and had moved in