Dispatches

Cell Spreading: The Power to Simplify

A eukaryotic cell spreads over a substrate in distinct stages, with the earliest events characterized by passive adhesion and cell deformation. Recent work suggests a common physical mechanism can explain the early stages of cell spreading for a wide range of cell types and substrates.

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Despite outward similarities, cell motility and cell spreading are mechanistically different phenomena. Both processes involve the deformation of the plasma membrane and the formation of cell–substrate attachments; however, cell motility is an active process in which a crawling cell must expend metabolic energy on a host of purposeful reactions. In contrast to crawling, the minutes after a cell in suspension encounters an adhesive surface are characterized by passive adhesion and spreading, akin to the manner in which a liquid initially adheres to a surface [1] (Figure 1). While the later stages of cell spreading do involve the mechanisms of cell crawling such as actin polymerization and myosin contraction, it is the earlier events that determine if a cell will adhere to a surface in the first place. A new report by Cuvelier *et al.* [2], published recently in *Current Biology*, contributes to our understanding of early cell attachment with data suggesting the possibility of a universal mechanism for early spreading and a model that appears to capture the underlying physics.

Cuvelier *et al.* [2] used reflection interference microscopy to follow the dynamics of cell spreading on coverslips in time-lapse imaging. Reflection interference microscopy is an established imaging technique that produces image contrast at points of contact between cells and glass substrates [3]. The group measured contact area as a function of time for different cell types and different adhesive coatings on glass coverslips. The results showed two similarities among the experiments: first, early spreading was isotropic; and second, when plotted on log–log axes, the spreading curves all exhibited the same slope. The first observation is consistent with published data showing that cells spread radially from the point of first contact [4]. The second observation is new and holds clues to the physical mechanism of early cell spreading.

Physicists often examine the slope of data in log–log plots to inquire about the physical mechanisms that underlie a trend, independent of the data's magnitudes. The slope in a log–log plot becomes an exponent of the independent variable in a linear plot and so data that can be described by a single slope are said to follow a 'power law'. Cuvelier *et al.* [2] found that the same slope of ½ described the evolution of contact radius over time for HeLa cells, a sarcoma cell line and red blood cells, regardless of whether they were spreading on serum-coated glass, the extracellular matrix protein fibronectin or through homotypic associations of E-cadherin. Thus the results suggest a common physics despite the obvious molecular differences in these experiments. Some experimental details, such as the specific amounts of receptor and ligand on the cell and substrate, do affect the strength of adhesion and the time to complete spreading, but they do not change the physical processes at work.

Cuvelier *et al.* [2] are able to explain the ½ power-law relationship with a rather simple physical model. Their model balances the energy gained through cell adhesion to a surface with the energy dissipated by deformations in the cell's actin cortex. The energy argument is analogous to that which explains the rate at which a liquid drop deforms on a flat surface, only the spreading of a liquid drop does not follow a ½ power law. Only by confining energy dissipation in their model to a layer as thin as the actin cortex were Cuvelier *et al.* [2] able to recover the correct power law. The authors extended their model to suggest that passive spreading slows once the contact area expands such that the entire droplet must

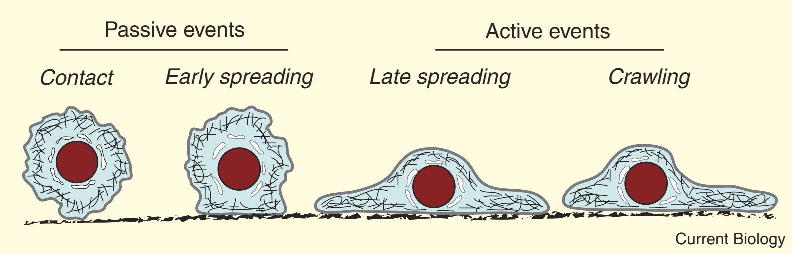

Figure 1. Cell spreading and attachment.

The early stages of cell spreading attachment do not require the cell to expend metabolic energy, while the later stages involve the active processes of actin polymerization and mysosin contraction that are essential for polarized cells to crawl. Recent work by Cuvelier *et al.* [2] suggests the same dynamic process accounts for early spreading by many cell types over a wide range of substrate conditions. The physics of early spreading are captured by a simple model balancing substrate adhesive power with the energy dissipated as the actin cortex deforms.

deform to spread further. The later stages of spreading, however, are also known to involve active mechanisms such as actin polymerization and myosin contractions [4–6], so the full process is too complex to be described by a single theory.

In earlier studies of the dynamics and metabolic requirements of cell spreading, inhibitors of energy metabolism were found to have no affect on early cell attachment and deformation [7–9]. These studies further showed that cells are truly adherent after early spreading because they resist detachment by fluid shear forces [9]. The quantitative arguments of Cuvelier *et al.* [2] explain these results, and require that the actin cortex relax as a viscous liquid during early cell spreading. Indeed, the group only saw a deviation from the ½ power law when they used cytochalasin to disrupt the actin network.

The ability of an adherent cell to spread has important consequences. Studies dating back to the pioneers of cell culture established that substrate contact area can determine whether or not a cell proliferates [10], becomes quiescent [11,12] or dies [13]. While it is likely that active mechanisms provide the feedback that controls these responses to spreading, the results of Cuvelier *et al.* [2] are important to explain how a cell gets a 'foothold' on a surface in the first place. A universal model for early adhesion may have application to understanding the formation of stable contacts between blood cells and endothelium *in vivo* [14], and may aid in the rational design of tissue engineering surfaces in which cells are seeded in spatially defined patterns [15]. The results suggest that cells of different types can adhere to the same surface so long as the surface provides for non-specific associations between cell and substrate.

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Brain Stimulation: Feeling the Buzz

A recent study demonstrates that artificially generated patterns of brain activity are surprisingly easy to sense. Brain areas that differ substantially in their functional specialization are remarkably similar in their ability to support this awareness.

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Few demonstrations of the link between brain and mind are as compelling as experiments in which behaviors are evoked or modified by perturbing brain activity. More than a hundred years have passed since Fritsch and Hitzig [1,2] pioneered what remains one of the most effective ways to do this: by passing an electrical current into the brain. By stimulating the motor cortex and eliciting body movements, they showed for the first time that artificially activating different parts of the brain could elicit reproducibly different behaviors. In the modern era, brain stimulation has been used to probe the organization of a wide range of higher brain functions, including perception [3–6], attention [7] and learning [8]. As brain stimulation has entered this cognitive realm, its effects have been demonstrated by inference, not by direct observation. Drawing the correct conclusion about how and where brain stimulation interacts with cognitive processing depends more than ever on the design and control of experiments, and even these may not fully constrain the possible interpretations [7,9,10].

Life might be easier if we could know what subjects are feeling during brain stimulation, in addition to simply observing what they are doing. For human subjects, who can put those feelings into words, this is relatively easy. The