CELL BIOLOGY

Stretching Is Good for a Cell

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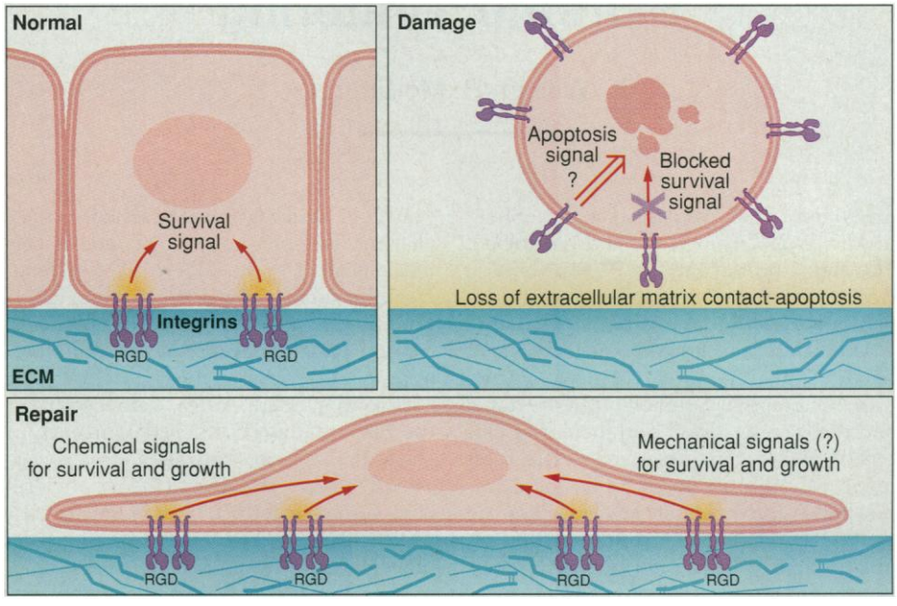
Cells in tissues are attached to one another and to the fibrillar protein meshwork known as the extracellular matrix (ECM). Most cells require this attachment and subsequent spreading on the ECM substrate for proper growth, function, and even survival. Without it, they often die by undergoing apoptosis, or programmed cell death (*1*). This dependence of cell growth and survival on substrate attachment is known as anchorage dependence; the apoptosis resulting from lack of anchorage has been named "anoikis." Only the cells circulating in the blood are designed to survive without attachment and spreading. (Some tumor cells acquire this ability and leave their original tissue site to form metastases.) On page 1425 of this issue, Chen *et al.* (*2*) report a significant advance in the understanding of how anchorage dependence works.

Cell adhesion is mediated by cell surface receptors; one class of these, the integrins, are the primary receptors for ECM. Originally discovered as a mechanical link between the cell surface and ECM (and, in some instances, the surface of a neighboring cell), integrins also link the external ECM "cytoskeleton" to the intracellular actin cytoskeleton. This linkage takes place in cultured cells at specialized membrane structures called "focal adhesions," which are thought to function similarly in intact tissues. Focal adhesions consist of a cluster of ECM-bound integrins that serve as a membrane attachment site for actin fibrils inside the cell. Many accessory cytoskeletal proteins concentrate at focal adhesions, as do various signaling proteins (*3*).

The presence of these signaling molecules reflects the fact that integrins do more than simply link structural elements. The integrins also trigger a number of signaling pathways, some of which are primarily related to cell adhesion, whereas others are shared by growth factor receptors. The focal adhesion kinase (FAK) pathway is used by several integrins and appears to participate in the control of anchorage dependence. Thus, a form of FAK that does not require integrin and cell attachment for its activity can render cells independent of anchorage (*4*). Moreover, integrins also activate many signaling molecules already known to be associated with growth factor signaling. These include the Ras–Raf–mitogen-activated kinase pathway, protein kinase C, and phosphatidylinositol 3′-kinase (*5*). Some integrins activate Shc, an adapter that serves as a link in various growth factor pathways (*6*). Indeed, integrins cooperate with growth factors to enhance mitogenic signaling (*7*).

The biochemical signals originating from ECM-bound integrins would seem to provide an adequate explanation for anchorage-dependent survival and growth of cells. However, Chen *et al.* propose something different; their results indicate that cells forced to extend themselves over a large surface survive better and proliferate faster than cells with a more rounded shape. The fact that spread (flattened) cells thrive, whereas rounded cells do not, has been shown before. Thus, small beads coated with an integrin-ligand peptide can bind and activate integrin-specific signals but, owing to their small size, do not induce spreading and fail to rescue detached endothelial cells from anoikis (*8*).

The new feature of the work by Chen *et al.* is that they were able to equalize the surface area to which the cells were attached, while varying the shape (degree of spreading) of the attached cells. They accomplished this with a clever use of microfabricated surfaces. In the key experiment, these investigators created a pattern of adhesive ECM dots on an otherwise nonadhesive surface that allowed cells to attach either to a single circular dot or onto several smaller dots. By varying the size and spacing of the small dots they were able to make the cells spread wider, while keeping constant the total area of contact with the ECM. Their rationale was that if chemical signals from the integrins were the predominant factor, the cells should survive and grow equally whether attached to one large dot or several small dots with the same combined area; the same amount of integrin engagement should generate the same amount of signal. What they found instead was that the cells spreading on the multiple small dots had less tendency to undergo apoptosis and thrived compared with the more rounded cells on the single dots. In addition, when the attachment was mediated by one set of integrins, the anti-apoptotic effect of spreading was clearer than when other integrins were involved. This reflects the fact that different integrins, while causing equal attachment and spreading, differ in their signaling pathways.



The shape is the thing.

One striking feature of the endothelial cells used in this study is how malleable the shape of these cells is to instructions from the ECM. By plating the cells on tiny adhesive squares, the investigator produced square cells, whereas cells presented with round spots for attachment assumed a round shape; and so on with more complex patterns. Some cells—free-floating

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cells, such as red blood cells, and yeast—can determine their own shape by their cytoskeleton or other intrinsic signals (9). Endothelial cells, and presumably other adherent cells, clearly differ in that their shape is determined by the properties of the surrounding ECM and by adjacent cells.

The results of Chen *et al.* indicate that after the ECM controls cell shape, cell shape in turn controls survival and growth. This relation makes sense in situations such as tissue regeneration. For example, if an epithelial or endothelial cell layer is damaged, there will be fewer cells covering the damaged area, the remaining cells will be able to spread, and this would stimulate them to proliferate until the tissue gap is filled.

A highly speculative, but tantalizing, possibility raised by these and earlier results from the same laboratory is that cell shape might directly control gene regulation. The authors have shown that tugging on an integrin outside the cells can cause deformation and movement of the nucleus (*10*). It will be interesting to see whether such a physical connection might alter the regulation of growth and survival genes without chemical intermediates.

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PLANETARY GEOLOGY

Extreme Cratering

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In March 1995, geologists E. M. Shoemaker [U.S. Geological Survey (USGS), Flagstaff, Arizona] and J. C. Wynn (USGS, Reston, Virginia) were invited to accompany an expedition sponsored by the Zahid Corporation (a heavy equipment dealer) of Saudi Arabia. Their mission: to venture into The Empty Quarter of southern Arabia and recover the "lost" iron meteorite craters of Wabar. First described to the West by St. John Philby in 1933 (*1*), these craters had by 1961 been mostly buried by the shifting desert sands. Traveling in Humvees and through 55°C daytime heat, the geologists were simply taking the extreme measures necessary to study that most extreme of geologic events, the hypervelocity collision of planetary objects. Shoemaker described the results of his adventure at Lunar and Planetary Science Conference XXVIII, held 15 to 19 March 1997 in Houston, Texas. This meeting, although broad in scope, is the preeminent annual meeting for the presentation of new results on impact cratering: terrestrial studies, planetary observations, theoretical models, experimental tests, and simulations.

There is little doubt in the planetary community as to the importance of major impacts in the evolution of life on Earth. The best established and most studied example is, of course, the demise of the dinosaurs at the end of the Cretaceous Period (65 million years ago), which is linked by abundant trace element, isotopic, mineralogic, and microfossil evidence to the 200- to 300-km-diameter Chicxulub crater in the Yucatán (*2*). It was of some interest, then, when geochemical and petrological analyses of drill cores from a large near-circular structure near Morokweng, South Africa, were reported at the same meeting (C. Koeberl, University of Vienna). The site had already been suspected of being an impact (*3*), and the drill cores turned up a thick layer of impact melt rocks with high abundances of iridium and other platinum-group elements. The samples of impact melt rock have a remarkably uniform composition, which is characteristic of large melt bodies formed by wholesale fusion of country rock, and the platinum-group elements are sufficiently abundant to indicate mixing of 2 to 5% chondritic meteoritic component into the melt. Unannealed relics in quartz show remnants of planar deformation features, the signature indicator of shock passage. Most intriguing of all are the age dates from zircons that grew from the melt, which are, within the errors, indistinguishable from that of the Jurassic-Cretaceous (J-K) boundary (≈145 million years ago).

The size of the original Morokweng impact crater is uncertain, owing to deep erosion, but diameter estimates range from a merely devastating 70 km to a truly Chicxulubian 340 km (*3*). Stratigraphic evidence of impact debris (ejecta) at the J-K boundary has not yet been reported (*4*), but greater attention to defining and studying this boundary is clearly in order.

An ejecta horizon from a different (and much older) era, the late (or neo) Archean, has been discovered in the Transvaal of South Africa (reported by B. M. Simonson, Oberlin College). This distinctive ejecta layer, the Monteville, consists of spherules up to 1 mm in diameter that display inward-radiating fibrous quench and devitrification textures: that is, the spherules are frozen impact melt spray (or condensed vapor). Similar textures are seen in spherules from the Cretaceous-Tertiary boundary and, indeed, from even older Archean units in South Africa and Australia (*5*). What makes these spherules notable is that they are petrologically similar to impact spherules found in layers preserved in Neo-Archean strata of the Hamersley Basin of Western Australia. The Monteville and one of the Hamersley layers, the Wittenoom, are also of a very similar age (≈2.55 billion years ago), based on radiometric dating of volcanic tuffs in the stratigraphic vicinity of the layers and of carbonates within the Wittenoom, and both appear to have been deposited under high-energy wave conditions, possibly impact-induced tsunamis. Furthermore, independent geologic evidence suggests that the South African and Western Australian provinces in which the spherule layers are found were once part of a single continental landmass (*6*).

Thus, this work suggests that the Monteville and one of the Hamersley spherule layers are contemporaneous, and more significantly, that a new technique exists for establishing the stratigraphic succession of ancient terrestrial rocks. Ejecta horizons have been pressed into service as stratigraphic markers for some time on the moon and planets, more or less by default. The terrestrial spherule layers represent a new tool for establishing the intercontinental correlation of geologic time, which for early Precambrian geology would be a tremendous boon.

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