People & Ideas

Benny Geiger: A force in the study of focal adhesions

Geiger researches the composition and function of cell adhesions.

Focal adhesions are protein clusters that form where integrins attach to the extracellular matrix. But, says Benjamin Geiger, from the Weizmann Institute in Israel, focal adhesions are not simply a cellular footprint; they are also sensory devices that transmit information about the properties of the extracellular milieu to the cell interior. Geiger should know; he's spent most of his career energetically studying how adhesion sites sense and communicate these signals to the cell.

A night owl, Geiger says he gets some of his most useful work done in the peace of the night. His tireless efforts have generated many novel insights about what proteins are found in focal adhesions (1, 2) and what they do there (3, 4). Along the way, he's also helped to develop new technologies to probe cell adhesion sites (4, 5). We reached him late one evening at his lab to talk about some of the things that keep him up and energized all night.

FAMILY BONDS

Early in your career, you identified the cytoskeletal adaptor protein vinculin…

When I went to La Jolla from Israel in 1977 to start my postdoc with Jon Singer at UC San Diego, the field of cytoskeletal research was just starting to explode, almost out of nowhere. Major questions emerging at that time were: how is this intracellular machinery affected by the outside world, and how is it participating in sensing the environment in which cells are located? We and others started to look into the mechanism by which cytoskeletal filaments link to the membrane, for which we needed high-resolution technologies for localizing molecules, such as immuno-electron microscopy.

I was looking for the glue that connects actin to the membrane in specific regions of the cell. One candidate for this job was the protein α-actinin, but, when we tried to localize it, we saw that it wasn't really located close enough to the membrane to be the direct link. While I was purifying α-actinin, I got as a by-product an unknown protein with a molecular weight of approximately 130 kilodaltons. To figure out what this protein might do, I prepared antibodies to it and used immunofluorescence microscopy to find where it was located within cells. And when I did this—I really remember this moment of discovery—I saw a most beautiful array of arrowhead-shaped structures all around the cells that were all localized at the ends of actin fiber bundles. We chose to call it vinculin because "vinculum" means bonds that link things together, and we thought it might do this kind of job in cells—which actually was more or less correct.

> "I saw a most beautiful array of arrowhead-shaped structures."

Did you consider staying in the United States or going to another country to continue your career?

I was born in 1947, just a few months before the formal birth of the state of Israel. Growing up there in the fifties and sixties had a major effect on my development and thinking, giving me a strong sense of belonging and commitment to my life in Israel. I don't think it affected my attitude toward science in any way, but I admit that it's difficult for me to see myself doing science anywhere else.

When I returned to Israel, I joined the faculty of the same department where I had done my PhD. Returning to the Weizmann Institute was a natural choice for me, due to the openness of the Institute to multidisciplinary research. All along I was interested in working at the interface between biology, chemistry, and physics; as a graduate student, I had worked in Ruth Arnon's lab studying Tay-Sachs disease using advanced immunochemical approaches. When I returned to Israel, I wanted to apply multidisciplinary approaches to study cell adhesion and migration, so I chose to come to the Weizmann Institute to start my own lab.

PHOTO COURTESY OF WEIZMANN INSTITUTE PHOTOLAB

Benny Geiger

INNER BONDS

What molecules connect the actin cytoskeleton to the cell membrane?

There are around 180 or so molecules that have been reported to localize in adhesion sites or to affect their structure and function. Collectively, we refer to these adhesion-associated molecules as the adhesome. It will be a major future challenge to figure out how such a complex molecular network works at the whole system level.

I must add that we would not have such a comprehensive view of the complexity of the adhesion site without the contributions of multiple research groups. Fortunately, the cytoskeletal and adhesion research communities are not only very productive but also very friendly and cooperative. A good example of this spirit is the activity of the Cell Migration Consortium of the NIH, which just celebrated ten years of activity.

Text and Interview by Caitlin Sedwick
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What properties do these adhesions have?

Matrix adhesions don't just function as a physical scaffold linking cells together but also function as the sensory organs of a cell. They can distinguish between matrices of different chemical composition, which may interact with different integrins, and in addition they can sense physical features of the extracellular matrix: adhesions are different if they form on a smooth surface as opposed to a rough one or on a soft surface as opposed to a rigid one. This ability to distinguish the physical properties of the environment is really opening up exciting possibilities for the regulation of cell activity, structure, and fate.

> "Matrix adhesions... function as the sensory organs of a cell."

NEW LINKS

How are the activity and structure of adhesion sites changed by cells' interactions with their environment?

Information about the molecular mechanisms underlying adhesion-mediated signaling is rather scarce and mostly indirect. I'll nevertheless share with you what we think are the basic design principles. Let's start by putting a force on an adhesion: if I apply force to an adhesion site, you might intuitively expect the adhesion to break. Actually, though, the opposite occurs. In studies carried out in collaboration with Sasha Bershadsky we showed that, if you pull on an adhesion, it is reinforced. This could be a mechanism for stabilizing matrix adhesion, rendering it resistant to mechanical perturbation, yet the molecular basis for this phenomenon is unclear. What we do know is that there are many mechanosensitive proteins in the adhesion site, which can change their conformation and, consequently, activity under mechanical stress. If, for example, you pull on the extracellular matrix protein fibronectin, specific binding sites that under relaxed conditions are buried within the three-dimensional structure of the molecule become exposed. Then, within the adhesion itself, mechanical forces can change the conformation of integrins and associated molecules like talin, vinculin, and p130Cas (and possibly additional adhesome components), thereby affecting their function. Our main current challenge is to figure out how the entire adhesome network is modulated by external and cytoskeletal forces and how this process activates the signaling machinery of the cell.

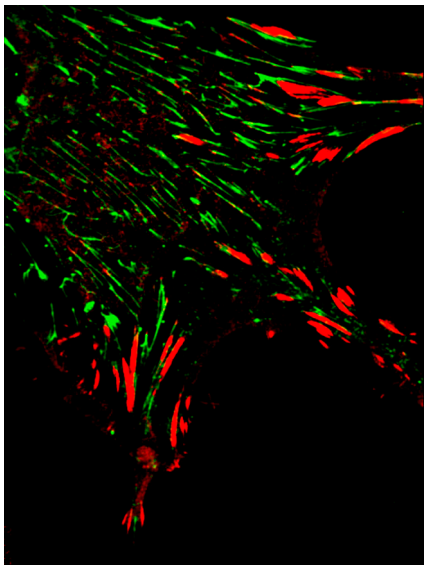

IMAGE COURTESY OF DR. TOVA VOLBERG

Focal adhesion–associated vinculin (red) and fibronectin (green) are clustered in separate types of integrin adhesions.

PHOTO COURTESY OF DR. TOVA VOLBERG

Geiger's lab takes an outing in the northern Negev Desert.

What other projects are you excited about right now?

My work has taken me in some completely unexpected directions, most of which are associated with long-term collaborations with different people. For example, we've worked with Lia Addadi to study new properties of adhesive matrices, focusing on their effect on adhering cells, particularly bone-degrading osteoclasts; with Zvi Kam, novel approaches for quantitative, high-content, automated microscopy were developed; and Joachim Spatz introduced us to the power of high-precision nanofabrication of cellular environments. In a recent collaboration with Ohad Medalia, we've combined light microscopy with cryo-electron tomography to reveal the internal nano-architecture of focal adhesions, and our collaboration with Paul Kaufman, an ophthalmologist, highlighted the involvement of the cytoskeleton in maintaining intraocular pressure, suggesting that cytoskeletal drugs might be effective anti-glaucoma drugs.

Finally, I've been fortunate to work with an amazing group of students, postdocs, and support staff, with whom my interactions have been not only productive but also extremely pleasant.

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