Bioelectric signaling controls tissue shape and structure FREE

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which kept them ramrod straight and impeded any radial growth that could effectively short-circuit parts of the p-i-n junctions.

As proof of concept, the researchers built an InP solar cell, partially shown in the figure, composed of 4 million nanowires 180 nm in diameter and 1.5 μm tall, arranged in a square array in which the wires are spaced about 500 nm apart. The device converted about 14% of the incoming light into electric power—nearly triple what had been produced in earlier InP arrays and a new record for nanowire solar cells. The current density delivered by the array is nearly as great as that produced by conventional InP thin-film cells, despite the nanowires' surface packing fraction of just 12%.

The enhanced optical absorption of the device arises from the ability of the nanowires, with diameters below the wavelength of visible light, to confine incoming rays into guided electromagnetic modes. Like miniature antennae, the nanowires concentrate incoming electromagnetic waves. Important to their success is that the spacing between wires is well matched to the wavelength at which the solar intensity peaks.

"Although the new design's efficiency remains below that of silicon cells, it's an impressive achievement that will bring validation to the nanowire community—and probably draw more people into the field," comments Stanford University's Michael McGehee. "But it's certainly not high enough to launch a product," he cautions.

There is a straightforward path to higher performance, at least in principle. One can break the Shockley–Queisser limit, which establishes the maximum conversion efficiency of a solar cell having a single bandgap, by chemically altering the nanowires' growth to emplace multiple materials on top of each other. The different constituent materials absorb different parts of the solar spectrum. That's on the to-do list, Borgström says, noting that it's much easier to pull off in a nanowire architecture than in thin films, which can suffer more from lattice strain at the interface between materials.

"When we reach 30% efficiency, then we'll have a commercially interesting product," he says. Interesting indeed: Solar cells are already a $100 billion industry that is growing at more than 30% a year.

Mark Wilson

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Bioelectric signaling controls tissue shape and structure

Manipulating those signals in just the right way may have applications in regenerative and cancer medicine.

The human body contains trillions of cells, all working in concert. During development, they divide and differentiate to form complex multicellular structures, and they stop dividing when those structures are complete. In the adult body, cells routinely die and are replaced by new ones. Damaged and wounded tissues heal, up to a point. Each cell is somehow able to sense just what to contribute to an organism far larger than itself.

Biologists and biophysicists studying those processes have long focused on the molecular messengers that cells

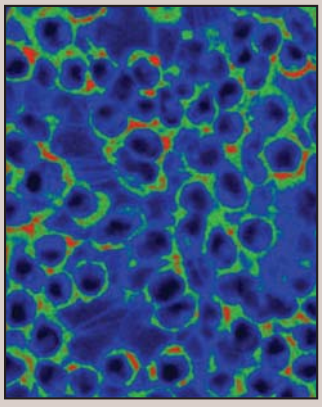

Figure 1. With fluorescent dyes whose spectral properties and spatial distribution are influenced by local electric fields, researchers can measure transmembrane voltages in cell populations (shown here), tissues, and whole organisms. (Adapted from ref. 1.)

send to one another to orchestrate their activity. More recently they've found that mechanical forces are also involved (see PHYSICS TODAY, April 2007, page 20). Now Michael Levin and colleagues at Tufts University are exploring new realms of the little-understood area of bioelectric signaling.[1] They've found that manipulating an organism's internal electric signals can alter its growth in powerful and often surprising ways. And their approach suggests that questions in areas of biology and medicine traditionally viewed as disparate—morphogenesis and development, regenerative repair, and even cancer—may really fall under a single umbrella of cell communication and information.

Electric instructions

That biological systems respond to electricity is not a new idea. In 1771 Luigi Galvani discovered that electric sparks could cause a dead frog to twitch its legs. Of course, we now know why that is: Nerve cells convey pulses of electricity that are carried by ions throughout the body, including to muscles to stimulate their movement.

In fact, all cells—not just those in nerves and muscles—can participate in electric signaling. Proteins embedded in a cell membrane shuttle hydrogen, sodium, potassium, and other ions into and out of the cell. Some of the proteins, called ion pumps, work actively (and consume energy) to move ions against their concentration gradient. Other proteins, called ion channels, passively allow ions through, but they can close and reopen in response to various stimuli (see PHYSICS TODAY, December 2003, page 27). As a result, two cells with the same genes and membrane proteins can be in very different electric states. Together, ion pumps and channels establish a transmembrane voltage difference, V_{mem}, which can influence other cells and contribute to voltage gradients on larger spatial scales.

Since the late 1950s, researchers have identified correlations between V_{mem} and cell division. Fully differentiated cells in tissues that have stopped growing (such as nerves, muscles, and most organs) have relatively high transmembrane potentials of 50–90 mV. Cells that divide rapidly or that have more plastic identities—embryonic cells, stem cells, and cancer cells—typically have V_{mem} values of less than 30 mV. Furthermore, V_{mem} was observed to vary throughout the cell cycle in a way that appeared to be causal: Altering the ionic concentrations of cells *in vitro* to lower or raise their V_{mem} induced the cells to start or stop dividing.

But the prevailing wisdom was that it would never work to tinker with V_{mem} *in vivo*. The transmembrane potential, it was thought, was an essential component to cell health, and to alter it in a living organism would either be lethal or give uninterpretable experimental results. Levin was skeptical: "I always thought that if V_{mem} bears instructive information, then we ought to be able to dissociate that from its housekeeping functions. Remarkably, that turned out to be the case."

Viewing voltages

Before they could study the effects of changing V_{mem} *in vivo*, Levin and colleagues needed to develop the tools to do it. "For 50 years the community has focused on tools and techniques for studying gene function and chemical gradients," says Levin. "Very little had been done to help us study the role of voltage gradients." All the early measurements of V_{mem} had been done by pricking individual cells with tiny electrodes, a laborious technique that wasn't suitable for looking at V_{mem} patterns across tissues or whole organisms.

Instead, the Tufts researchers use a technique adapted from the study of electric signaling in nerve cells: fluorescent "reporter" dyes whose spectral characteristics or spatial distributions respond to local electric fields. Using a

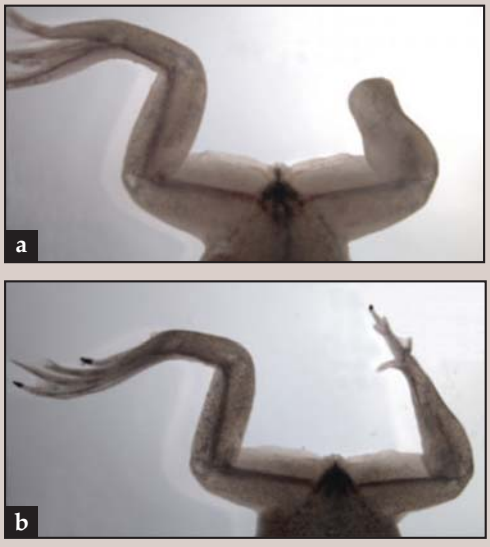

Figure 2. Frogs' legs don't normally regenerate: Cutting off the developing leg of a tadpole **(a)** yields a frog with a missing leg. **(b)** But when the tadpole is given a suitable bioelectric trigger, the missing limb can regrow. (Adapted from ref. 1.)

combination of two dyes optimized for studying resting voltages (rather than the rapidly varying nerve signals), they obtain images like the one in figure 1.

The researchers also needed tools to manipulate V_{mem}. An externally applied electric field was one possibility, but the complexity of living tissue makes it too difficult to control how the field is distributed *in vivo*. Instead, they tune V_{mem} the same way the cells do: with ion pumps and channels. They can do that genetically or pharmacologically—by treating cells with either messenger RNA or small biomolecules to change the number of membrane proteins. Importantly, they always have more than one way to induce the V_{mem} change they want to study, to make sure the effects they see are really due to V_{mem} and not to the specific reagents or ions.

A leg up

Among their findings was that bioelectrical signals often serve as triggers that set off chains of events more complex than the signals themselves. For example, tadpoles past a certain stage in their development don't normally regenerate lost body parts. A tadpole whose tail is amputated won't grow a new one, and a tadpole whose developing leg is cut off will grow into a frog missing a leg (figure 2a). But when Levin and colleagues treated the cells at the site of each amputation to lower their V_{mem}, the tail or leg was able to grow back (figure 2b).[1,2] The regenerated appendages contained muscles that moved and nerves that were sensitive to touch, and the new legs had toes and toenails. The applied change in V_{mem} contained no information about those structures. Nonetheless, the cells at the site of the wound were triggered to form structures that they already knew how to make, even though, without the researchers' interference, they'd never be called upon to make them.

Levin envisions applications to regenerative medicine. A long-term goal of bioengineering is to use stem cells to build new, living limbs and organs to replace those lost to injury or disease. But reproducing tissues in all their intricacy remains a difficult challenge. Finding the right bioelectrical triggers could, potentially, bypass the need for bioengineers to fully understand the structures they seek to replace.

Heads or tails

In the tail and leg experiments, body parts always grew in the right places: An amputated tail was never replaced by a leg, or vice versa. But in other experiments, the researchers found that bioelectric cues could influence not only whether a new structure grew but also what the new structure was. They discovered that a certain V_{mem} range in frogs is specific to eye formation.[3] When they tuned V_{mem} out of that range at the site of the developing eyes, it kept the eyes from forming properly. But they could induce fully formed eyes to grow on any part of the frog's body by tuning V_{mem} there into that range.

Other strange results came from their experiments on planarian flatworms. Unlike frogs, planarians under natural circumstances are highly regenerative—decapitated planarians can even grow new heads. Levin and colleagues found that planarian regenera-

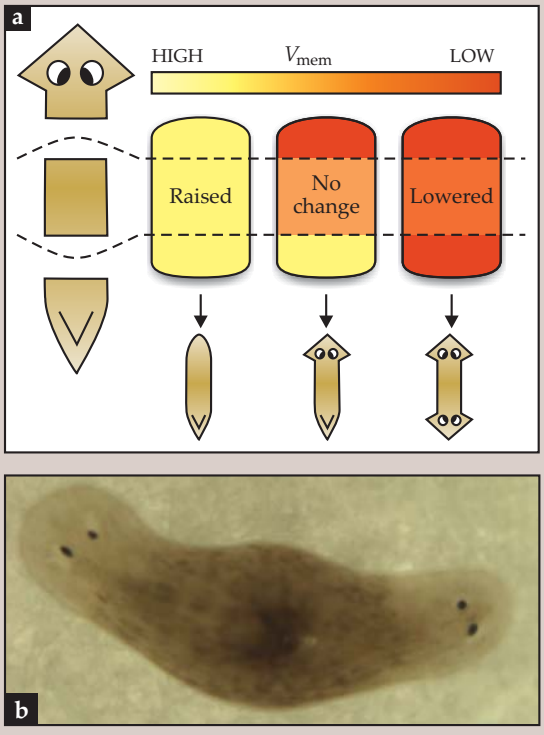

Figure 3. Planarian flatworms can regrow new tails and even new heads. The regeneration is guided by a head-to-tail gradient **(a)** in the transmembrane electric potential V_{mem}. Interfering with that gradient by raising or lowering V_{mem} can produce worms with two heads **(b)** or with none. (Adapted from ref. 1.)

tion is guided by a V_{mem} gradient from head (low) to tail (high).[4] By manipulating that gradient, as shown in figure 3, they could produce planarians with two heads or with none. Other V_{mem} manipulations could alter the size and shape of the new heads and tails.[5]

Cancer is, in a sense, a disease of cell orchestration gone wrong—of cells losing track of what structures they're supposed to form and instead proliferating out of control. So perhaps it's not surprising that bioelectric signaling is involved. Indeed, it's long been known that tumor cells have lower transmembrane potentials than healthy cells. Levin and colleagues found, in an experiment on frogs, that V_{mem} measurements could predict where tumors would form before the tumors were detectable by other means. And manipulating V_{mem} could alter a tumor's behavior: Raising V_{mem} could, in some cases, turn cancer cells into healthy cells, and lowering V_{mem} could induce otherwise healthy cells to metastasize and spread throughout the body, just as cancer would. But there's more to the latter effect than meets the eye: It wasn't the metastasizing cells' own V_{mem} that the researchers lowered, but that of other, distant cells, which then triggered the metastasis-like behavior through a combination of electric and chemical signaling.[6]

Cracking the code

Right now, bioelectric signaling is still as mysterious as it is powerful. Because large-scale V_{mem} measurements are so new, there's a scarcity of data on how V_{mem} varies in different tissues and under different circumstances. Larger bioelectric data sets, analogous to those that already exist for gene and protein levels, could be mined for important clues.

Levin—a computer scientist by training—views multicellular organisms as sophisticated information-processing systems. In his effort to crack the bioelectric code, he's looking to extend methods from cognitive science and artificial intelligence to systems beyond neural and gene regulatory networks. "Biology is not only ruled by chemicals and gene products," he explains. "This new electrical layer is a fascinating and untapped field for fundamental discoveries."

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