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Ring-Around-the-Cell

Breaking down bone is a tough job. Yet, our bones undergo remodeling every day of our lives, as old material is cleared away so that new bone can form. In diseases such as osteoporosis, an imbalance in this process is responsible for the characteristic bone loss. New research at the Weizmann Institute of Science, which recently appeared in the on-line journal *PLoS ONE*, has revealed, in unprecedented detail, how the roving cells whose job is to digest bone seal off their work area as they get down to business.

The cells, called osteoclasts, have some unique features not seen in any other cell type. Osteoclasts move around the bone until they reach a site where they sense that their services are required, at which point they undergo a transformation called polarization. The polarized osteoclast sticks itself tightly to the bone, while an impermeable ring forms around the cell perimeter. This ring functions to keep the bone-eating acids and enzymes produced between the cell and the bone confined to the demolition site.

How does this ring form? To solve the mystery, Prof. Benjamin Geiger, Dean of Biology, and Prof. Lia Addadi of the Structural Biology Department, together with doctoral students Chen Luxenburg and Dafna Geblinger, and with the assistance of Dr. Eugenia Klein (electron microscopy unit), Prof. Dorit Hanein and Karen Anderson of the Burnham Institute, San Diego applied two different observation methods to samples of stripped-down, polarized osteoclasts: electron microscope imaging that allowed them to see fine details of the ring structure, and a light microscope method in which specific features glow. Because each method captures different information at a different scale, combining them was tricky, but the two together gave them a much more extensive picture than either alone.

They found that the ring is composed of dot-like structures called podosomes, anchored to the cell membrane. When the osteoclast is on the move, these little dots amble randomly around the cell, but when the cells prepare to dissolve the bone, they make a beeline for the edge. Scientists had been unsure how podosomes were involved in ring formation or, if they did form the ring, whether they somehow fused together or kept their individual shapes. The research team's findings showed clearly that the ring is made of individual podosomes held together by interconnecting protein filaments they throw out to each other. "The podosomes are like folk dancers," says Geiger. "As soon as the music starts up, they join hands and form a tight circle. From afar, a circle of dancers looks like a blur, but now we have managed to make out the individual dancers."

Addadi points out that isolated podosomes look, from above, like a tent with rope-like lines radiating from a central pole. "In effect," she says, "the podosomes may be more than just seals. They appear to act as highly connected nodes of communication between the inside and outside of the cell, enabling the cell to adjust its activity according to the condition of the bone underneath." ❙

Prof. Lia Addadi's research is supported by the M.D. Moross Institute for Cancer Research; the Clore Center for Biological Physics; the Ilse Katz Institute for Material Sciences and Magnetic Resonance Research; the Helen and Martin Kimmel Center for Nanoscale Science; and the Helen and Milton A. Kimmelman Center for Biomolecular Structure and Assembly. Prof. Addadi is the incumbent of the Dorothy and Patrick Gorman Professorial Chair.

Prof. Benjamin Geiger's research is supported by the Clore Center for Biological Physics; the Leo and Julia Forchheimer Center for Molecular Genetics; the Mario Negri Institute for Pharmacological Research - Weizmann Institute of Science Exchange Program; the Edith C. Blum Foundation Inc.; and the estate of Lore. F. Leder, Manchester, VT. Prof. Geiger is the incumbent of the Professor Erwin Neter Professorial Chair of Cell and Tumor Biology.

Doubly Safe Activation

"Dual key" activation, in which two people must act in concert to launch a weapon, is often installed to safeguard highly destructive arms. New research at the Weizmann Institute of Science shows that cells may employ this strategy as well before launching certain potent weapons of the immune system.

Interferons, which were discovered 50 years ago, are the body's first line of defense against viral attack. They are produced in cells that have been invaded by viruses, and from there, they spread out to warn other cells to prepare for the impending onslaught. These signaling molecules are associated with the symptoms – fever and inflammation – of viral infections such as the flu. Three main interferon families have been identified, and they are known by the Greek letters alpha, beta and gamma. Interferons alpha and beta are very similar: They have nearly identical modes of action and even attach to the same receptor on the cell wall. Interferon gamma is different from these two. It has its own receptor and, in addition to its immediate antiviral actions, is involved in a number of crucial activities in the immune system, including a step known as antigen presenting, which enables the immune system to tailor antibodies to a specific enemy, and the activation of certain immune cells that engulf and destroy pathogens.

But new findings published recently in the *Proceedings of the National Academy of Sciences* (PNAS), show that the third type of interferon often doesn't act alone. The Weizmann Institute team headed by Prof. Menachem Rubinstein of the Molecular Genetics Department, which included Dr. Vladimir Hurgin, Dr. Daniela Novick and Dr. Ariel Werman, together with Prof. Charles Dinarello of

the University of Colorado, USA, found that another molecule that's produced inside cells, interleukin 1- alpha (IL-1 alpha), must be present for initiating many of the basic activities of interferon gamma.

While molecules have been known to work together in this way, the collaboration between interferon gamma and IL-1 alpha came as something of a surprise to scientists: Although the molecules are produced in two independent systems, they match like two halves of a key: IL-1 alpha doesn't affect alpha or beta interferons, and interferon gamma seems to work specifically with IL-1 alpha. They were also surprised because interferons, which form the basis of a number of drugs (mainly alpha and beta), have been widely studied, yet the connection between these two molecules had not been seen before. Rubinstein's explanation is that previous interferon experiments had been performed with cells that produced their own IL-1 alpha in the lab culture, and thus scientists had missed its effect.

Interferon gamma and IL-1 alpha have a synergistic effect on each other, activating around 500 genes, including those that bring about the fever and muscle aches. Rubinstein: "The antiviral activity of interferon gamma comes at a high cost. We think this is the reason the body uses a 'dual key' system – to provide an extra level of security before paying that price." ❙

Prof. Menachem Rubinstein is the incumbent of the Maurice and Edna Weiss Professorial Chair of Cytokines Research.

One Membrane, Many Frequencies

Modern hearing aids, though quite sophisticated, still do not faithfully reproduce sound as hearing people hear it. New findings at the Weizmann Institute of Science shed light on a crucial mechanism for discerning different sound frequencies and thus may have implications for the design of better hearing aids.

Research by Dr. Itay Rousso of the Weizmann Institute's Structural Biology Department, which recently appeared in the *Proceedings of the National Academy of Sciences* (PNAS), suggests that a thin structure in the inner ear called the tectorial membrane responds to different frequencies. This membrane communicates between the outer hair cells – which amplify sound in the form of mechanical vibrations – and the inner hair cells – which convert these mechanical vibrations to electrical signals and pass them on to the brain via the auditory nerve. If certain genes for this membrane are missing or damaged, total deafness ensues.

Rousso and research student Rachel Gueta, together with researchers at the Ben-Gurion University of the Negev, wanted to explore the mechanical properties of the tectorial membrane. Using an atomic force microscope, which probes surfaces with a fine microscopic needle, they tested the resistance of the gel-like membrane at various points to assess precisely how rigid or flexible it was. To their surprise, the scientists found that the level of rigidity varies significantly along the length of the membrane: One end of the membrane can be up to ten times more rigid than the other.

These differences occur in the part of the membrane that is in direct contact with the outer hair cells. Observation under a scanning electron microscope revealed that this variation is due to changes in the way the protein fibers are arranged: At one end, they form a flimsy, net-like structure that allows the membrane to be flexible; on the rigid side the fibers are densely and uniformly packed.

The more rigid a tectorial membrane is, the higher the frequency at which it can vibrate. Thus, the flexible end of the membrane, which should respond to low-frequency vibration, is found near the hair cells that transmit low frequencies, and the rigid end near hair cells that transmit high ones. This spatial separation, say the scientists, translates into the ability to distinguish between sounds of different frequencies.

The new understanding of the mechanics of hearing may assist in the development of better hearing aids. Rousso, meanwhile, plans to continue exploring how variations in membrane rigidity affect hearing. He intends to test tectorial membranes under different physiological conditions to further understand how we hear such a wide range of frequencies (the highest is a thousand times the lowest), as well as to shed light on the causes of certain hearing problems. ❙

Dr. Itay Rousso's research is supported by the Clore Center for Biological Physics; the Helen and Martin Kimmel Center for Nanoscale Science; the Jeans-Jacques Brunschwig Fund for the Molecular Genetics of Cancer; the Estelle Funk Foundation; and the President's Fund for Biomedical Research. Dr. Rousso is the incumbent of the Robert Edward and Roselyn Rich Manson Career Development Chair.

It's Only a Game of Chance

The validity of a leading theory that has held a glimmer of hope for unraveling the intricacies of the brain has just been called into question. Dr. Ilan Lampl of the Weizmann Institute of Science's Neurobiology Department has produced convincing evidence to the contrary. His findings recently appeared in the journal *Neuron*.

Cells in the central nervous system tend to communicate with each other via a wave of electrical signals that travel along neurons. The question is: How does the brain translate this information to allow us to perceive and understand the world before us?

It is widely believed that these electrical signals generate spiked patterns that encode different types of cognitive information. According to the theory, the brain is able to discriminate between, say, a chair and a table because each of them will generate a distinct sequence of patterns within the neural system that the brain then interprets. Upon repeated presentation of that object, its pattern is reproduced in a precise and controlled manner. Previous experiments had demonstrated repeating patterns lasting up to one second in duration.

But when Lampl and his colleagues recorded the activity of neurons in the brain region known as the cortex in anaesthetized rats and analyzed the data, they found no difference in the number of patterns produced or the time it takes for various patterns to repeat themselves, compared with data that was randomized. They therefore concluded that the patterns observed could not be due to the deterministically controlled mechanisms posited in the theory, but occur purely by chance.

The consequence of this research is likely to contribute significantly to the ongoing debate on neuronal coding. Lampl: "Since the 1980's, many neuroscientists believed they possessed the key for finally beginning to understand the workings of the brain. But we have provided strong evidence to suggest that the brain may not encode information using precise patterns of activity." ❙

Dr. Ilan Lampl's research is supported by the Nella and Leon Benoziyo Center for Neurological Diseases; the Carl and Micaela Einhorn-Dominic Brain Research Institute; the Alhadeff Research Award; the Chais Family Foundation; the Clore Foundation; the Grodetsky Family Foundation; the Dr. Pearl H. Levine Foundation for Research in the Neurosciences; the Henry S. and Anne S. Reich Research Fund for Mental Health; and Mr. and Mrs. Gerald M. Lushing, Beverly Hills, CA. Dr. Lampl is the incumbent of the Carl and Frances Korn Career Development Chair in the Life Sciences.