MedicalXpress

Skin deep: Fruit flies reveal clues to wound healing in humans

April 5 2013

A person's skin and a fruit fly's exoskeleton, called a "cuticle" may not look alike, but both coverings protect against injury, infection, and dehydration. The top layers of mammalian skin and insect cuticle are mesh-works of macromolecules, the mammal version consisting mostly of keratin proteins and the fly version predominantly of the carbohydrate chitin. Yet the requirement of an outer boundary for protection is so ancient that the outermost cells of both organisms respond to some of the same signals. And because of these signaling similarities, the fruit fly *Drosophila* melanogaster serves as a model for wound healing.

A presentation today at the Genetics Society of America's 54th Annual *Drosophila* Research Conference in Washington D.C. April 3-7 describes a new way to study wound healing in flies that suggests new targets for wound-healing drugs. About 177 million people a year suffer from a wound, an opening that breaks the skin and usually damages the tissue underneath, which may be surgical, traumatic as a burn or laceration, or may be a chronic condition, as with people who have diabetes or those with immune system diseases.

Michelle T. Juarez, PhD, an assistant medical professor at the Sophie Davis School of Biomedical Education at the City College of New York, presents the doctoral research on wound healing of Rachel A. Patterson, from the University of California, San Diego (UCSD). William McGinnis, PhD, distinguished professor of the section of cell and developmental biology at UCSD, completes the research team. He has been investigating the "biological armor" of the fly for many years.

A desire to understand more about wound healing in people inspired the trio, particularly Ms. Patterson. "My fiancé is a firefighter and a member of the U.S. military. Maybe one day our work will influence his medical treatment if he sustains burns or injury wounds," she said.

The fly is an excellent model to dissect skin repair at a cell and molecular level. "Many of the key molecules and proteins involved in *Drosophila* wound healing are involved in mammalian wound healing. The genetics of *Drosophila* is not as complicated as mammalian genetics, so it's easier to attribute specific biological functions to individual genes," explained Ms. Patterson. During healing, molecular signals bind to receptors on the cells that line a wound, influencing the cell division, growth, and migration that restores the barrier.

To study the biological function of wound healing, the researchers needed to develop a "clean puncture wounding" protocol to damage the epidermis of fly embryos without allowing bacteria to infect the breach, which would complicate the study. Researchers study fly embryos rather than adult flies because it's easier and the embryos offer a wider range of genetic mutations than adult flies. The first step was to collect fly eggs, which contain developing embryos, and bleach them to remove the shells. Next they impaled the embryos with microneedles, like using a toothpick to spear an olive.

Key to the technique was injecting trypsin, a member of a family of enzymes called serine proteases, which control cell-to-cell signaling. Trypsin activates genes involved in wound healing throughout the embryo, and it also amplifies the response in the affected cells, revealing new players in the choreography of healing. "We took advantage of trypsin as a powerful wounding tool to pinpoint which genes are 'turned on' versus which genes are 'turned off' after wounding," Ms. Patterson said.

Researchers then looked at which genes were turned on and off at 30, 60, and 120 minutes post-stabbing that illuminate events as the borders of a small, clean wound close. The researchers were surprised to discover that an immune response begins as soon as the cuticle has been breached, with signals that prepare the embryo should bacteria or fungi enter soon after the injury.

Using microarray technology to assess gene action, the researchers surveyed 84 genes that are turned on and 78 genes that are turned off as the fly embryo responds to wounding.

At all three time periods, the embryo's innate immune response kicked in, releasing the same types of antimicrobial peptides (short proteins) that an adult fly uses to fight infection. At 120 minutes, genes whose protein products repair the cuticle with new chitin, the meshwork composing the fly exoskeleton, respond. (The human version of this step, which may occur over several days, actually produces new cells because the cuts are larger.) Finally the fly embryo activates genes that color the cuticle.

The genes that aren't accessed as an embryo's wound heals are also telling. The fly cells at the wound site ignore genes involved in replicating DNA, maintaining chromosome structure, and cell growth and division. Overall, tracking the expression of the 162 genes revealed that the embryo temporarily halts development to repair the wound and keep infection at bay. Their findings made perfect sense; the organism concentrates its activities on addressing the immediate problem, healing the wound.

Like many biological processes, wound healing is fine-tuned. "A balance of gene activation and inhibition is required for efficient healing," said Dr. Juarez. Otherwise, a problem such as an ulcer, a chronic non-healing wound, or a thickening of the fly's cuticle can persist, she added.

The experiments revealed activities of eight genes that hadn't been suspected to participate in wound healing. These genes are expressed at very low levels or not at all in most cells, but are called into action when an injury breaks the cuticle.

Having identified these eight new genes that are activated in cells near puncture wounds in flies, researchers can now explore if genes in humans play comparable roles. "I think one amazing application of our studies may be to build a better bandage – containing compounds to promote wound healing," said Dr. Juarez.

"Perhaps our results can be translated to existing human therapies by incorporating specific, regulated serine proteases and antimicrobial peptides at the sites of diabetic ulcers or skin grafts for more efficient wound healing," Ms. Patterson said.

Ms. Patterson also suggests that this fly research may lead to broader discoveries regarding human skin diseases. Further examination of the roles of serine proteases in wound healing may inform treatment for chronic skin diseases, including psoriasis, severe dry skin, and eczema where levels of these enzymes are known to be abnormal.

More information: www.dros-conf.org/2013/

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