Why patients with epidermolysis bullosa suffer extreme pain

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For patients suffering from epidermolysis bullosa (EB), a hereditary skin disease, even a gentle touch is extremely painful. Now Dr. Li-Yang Chiang, Dr. Kate Poole and Professor Gary R. Lewin of the Max Delbruck Center for Molecular Medicine (MDC) in Berlin-Buch have discovered the causes underlying this disease. Due to a genetic defect, individuals with EB cannot form laminin-332, a structural molecule of the skin that in healthy individuals inhibits the transduction of tactile stimuli and neuronal branching. According to the findings of the MDC researchers, this explains why EB patients are more sensitive to touch and experience it as painful.

Even the slightest touch causes a stinging sensation like being stabbed with pins; the body is covered with blisters and the skin is inflamed in many places. Young patients with epidermolysis bullosa are often called "butterfly children" because their skin is as fragile as a butterfly's wing. Because of the severe pain associated with the disease, EB sufferers hardly have any chance to lead a normal life. Even walking is a torment because of the pressure on the soles of the feet.

Due to a genetic defect, the patients' outer skin layer (epidermis) separates from the underlying skin layer (dermis), and blisters (bullosa) are formed. EB patients are deficient in laminin-332, a structural molecule normally found between the skin cells in the extracellular matrix which serves as a kind of cellular "glue" between the two skin layers.

The new findings of the MDC researchers show that in healthy individuals, laminin-332 has other important functions as well: It inhibits touch transduction and prevents the branching of the sensory neurons that are receptive to tactile stimuli in the skin.

At their endings, sensory neurons have mechanosensitive ion channels. These are proteins in the cell membrane through which charged particles can flow into the cell in a controlled manner. Upon touch, pressure on the extracellular matrix actuates a tether mechanism on the ion channels, thus opening the channels and allowing the charged particles to flow through. This excites the neuron, thus enabling the stimulus to be perceived.

Unsuppressed mechanotransduction

In experiments using cell cultures, the MDC researchers found that physical stimuli trigger ion currents in all neurons not surrounded by laminin-332. In neurons growing on laminin-332, by contrast, the number of responsive cells was much reduced. "To a great extent, laminin-332 blocks the tether mechanism that opens the ion channels, thus impeding stimulus transduction. Because patients with epidermolysis bullosa are deficient in laminin-332, the transduction of the stimulus is unsuppressed. Their sensory neurons are excited much more strongly, and thus they react much more sensitively to mechanical stimuli," Professor Lewin explained.

Furthermore, in the skin tissue of EB patients the MDC researchers found that sensory neurons showed much more branching than in the skin of healthy individuals. "From cell-culture experiments we know that laminin-332 inhibits neuronal branching. Without laminin-332 this inhibition does not take place. Presumably, this effect also contributes to the increased perception of tactile stimuli," Professor Lewin said.

In further studies the researchers hope to find drug targets for therapy. However, much has already been achieved: "Because the causal mechanisms are now understood, we can focus on the patient's pain situation and on administering more efficient pain therapies," he added. "We recommend that in treating the disease, neurologists should be consulted in addition to dermatologists.

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