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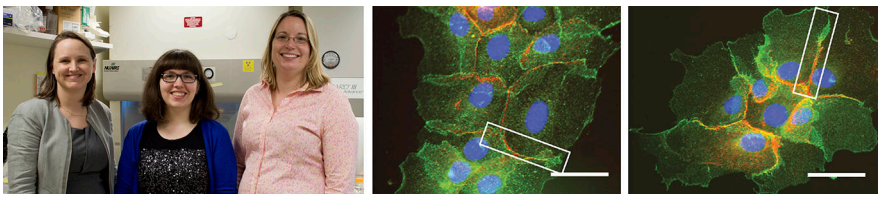
SUN protection for the skin

A component of the nuclear envelope–spanning LINC complex maintains the integrity of epidermal cell adhesions.

Focal Point



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(Left to right) Megan King, Rachel Stewart, Valerie Horsley, and colleagues reveal that, by organizing both the cytoskeleton and intercellular adhesions, nuclear envelope–spanning LINC complexes help balance forces across cells and tissues. In a wild-type keratinocyte colony (center), nuclei (blue) are moved by actomyosin-based forces toward adherens junctions (green) in the colony interior. These forces are resisted by the microtubule cytoskeleton. In keratinocytes lacking the inner nuclear membrane LINC complex component SUN2 (right), microtubules are disorganized, allowing nuclei to move even closer to adherens junctions. Microtubule disorganization also disrupts the distribution of desmosomes (red), which, in *Sun2* knockout mice, causes a loss of epidermal integrity and hair loss.

LINC complexes, consisting of inner nuclear membrane SUN proteins and outer nuclear membrane KASH proteins, connect the nucleus to the cytoskeleton, transmitting forces that control the nucleus's position within the cell. But how LINC complexes affect the cytoskeleton, and thus the balance of forces across cells and tissues, is less well understood. Stewart et al. now demonstrate that the LINC complex component SUN2 organizes the cytoskeleton of epidermal keratinocytes, thereby controlling the localization and stability of the desmosomal adhesions that maintain epidermal integrity (1).

LINC complexes interact with the actin, microtubule, and intermediate filament cytoskeletons (2), as do various types of intercellular adhesions. Nuclei may therefore be physically linked to cell–cell contacts. In epithelial cells, for example, nuclei are drawn toward cadherin-based adherens junctions (3). Rachel Stewart, a Yale University graduate student co-mentored by Megan King, who studies the function of LINC complexes, and Valerie Horsley, an expert in mammalian skin development, found that nuclei also move toward the adhesions formed between cultured keratinocytes (1). "We immediately thought that this had to involve the LINC complex," King says.

Stewart et al. therefore generated keratinocytes lacking the LINC complex protein SUN2, expecting that their nuclei would no longer move toward intercellular adhesions. "But instead we got the opposite result," King continues. "The nuclei moved closer to the adhesions." The researchers discovered that nuclei are pushed toward nascent cell–cell adhesions by actomyosin contractility. These forces are normally opposed by the microtubule cytoskeleton, but, in the absence of SUN2, keratinocyte microtubules were highly disorganized, allowing nuclei to be pushed closer than normal to intercellular contacts.

> **"We think that…the nucleus integrates mechanical forces across the tissue."**

Stewart and colleagues then turned their attention to how the loss of microtubule organization in SUN2-deficient keratinocytes affected their intercellular adhesions. Microtubules are particularly important for the formation and maintenance of desmosomes, strong adhesions required to maintain the integrity of tissues, such as the skin, that are subject to mechanical stress (4, 5). "Desmosomes form in keratinocytes lacking SUN2," Horsley explains, "but they're in the wrong place and they're not mechanically stable." In the absence of SUN2, desmosomes were no longer distributed evenly around the sites of cell–cell contact and, when keratinocyte monolayers lacking SUN2 were subjected to mechanical stress, they fragmented much more easily than wild-type monolayers.

The researchers then examined whether they could see similar effects on desmosomes and epidermal integrity in vivo. *Sun2* knockout mice have previously been reported to have no phenotypic abnormalities, presumably due to functional redundancies with other SUN family proteins (6). Stewart et al. noticed, however, that the animals went temporarily bald, losing their hair 16 days after birth before growing a new coat a few weeks later.

SUN2 was highly expressed in the hair follicles of wild-type mice during this time period. But in the protein's absence, follicles became bent and the animals' hair shafts broke. Crucially, desmosome distribution was perturbed in these abnormal follicles, and large gaps appeared between the follicle epidermal cells, suggesting that the adhesions were unable to withstand the forces associated with hair growth. At later time points, SUN1 was up-regulated in *Sun2*-null epidermis, likely explaining why normal follicle morphology and hair growth were restored in older mice.

Thus, by organizing the cytoskeleton and coordinating intercellular adhesions, LINC complexes are required to maintain epidermal integrity. "We think that, through its interactions with the cytoskeleton, the nucleus integrates mechanical forces across the tissue," Horsley says.

"The positions and shapes of nuclei vary tremendously throughout the skin," adds King. "It's really interesting to think about what that might mean mechanically." The researchers now want to investigate how the LINC complex organizes microtubules and to develop biosensors that can monitor how mechanical forces are spread across the nucleus, cytoskeleton, and intercellular adhesions.

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