The Force Behind Our Strength: How Mechanical Processes Regulate Muscle Development

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Skeletal muscles grow and regenerate as individual precursor cells – called myoblasts – fuse into long fibers from which mature muscle fibers develop. How they coordinate this process and form functional muscles is not yet fully understood. A research team at the Max-Planck-Zentrum für Physik und Medizin (MPZPM) has now shown that mechanical stress influences the fusion of muscle cells. The results, published in *Nature Communications*, reveal an interaction between the organization of muscle cells, the surrounding intercellular space, mechanical stress, and muscle growth.

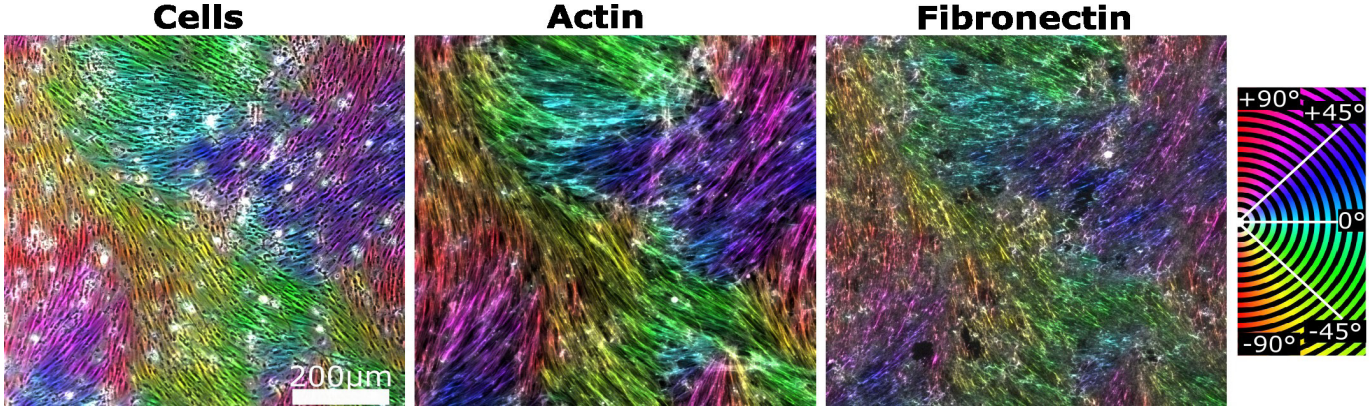
Skeletal muscle attaches our bones and enables us to move or exert force. It consists of long, multinucleated muscle fibers. Their precursors, the myotubes, are formed through the fusion of individual myoblasts.

Previously, research into how this fusion is regulated had focused on understanding molecular signals. More recently, however, it has become clear that cells also respond to physical forces and the mechanical properties of their environment. How such mechanical signals are organized in developing muscle tissue and whether they influence where myoblasts fuse had hardly been investigated.

Muscle cells organize themselves like an active material

The team, led by Prof. Benoît Ladoux, head of the *Tissue Mechanobiology* division at MPZPM, describes the organization of myoblasts using concepts from physics. This is because myoblasts do not arrange themselves randomly as they grow together. Instead, they self-organize into domains with distinct cellular orientations. Together, these domains form patterns. So-called active nematics serve as model systems that help scientists understand this self-organizing process. In physics, active nematic systems include, for example, liquid crystals, in which molecules align parallel to one another forming an ordered pattern. The myoblasts form comet- and cloverleaf-shaped patterns. At specific points – known as topological defects – the uniform alignment of the cells breaks down. These defects have been shown to be associated with areas of high mechanical stress. It is at these locations that myoblasts preferentially fuse.

Cell and Matrix Alignment in Culture: Color-coded orientation maps of cultured muscle cells, actin filaments, and extra-cellular matrix (fibronectin). The colors correspond to local orientations according to the angular color wheel (right). The matching color maps demonstrate how cellular self-organization closely aligns with the internal actin machinery and remodeled extra-cellular matrix (fibronectin).



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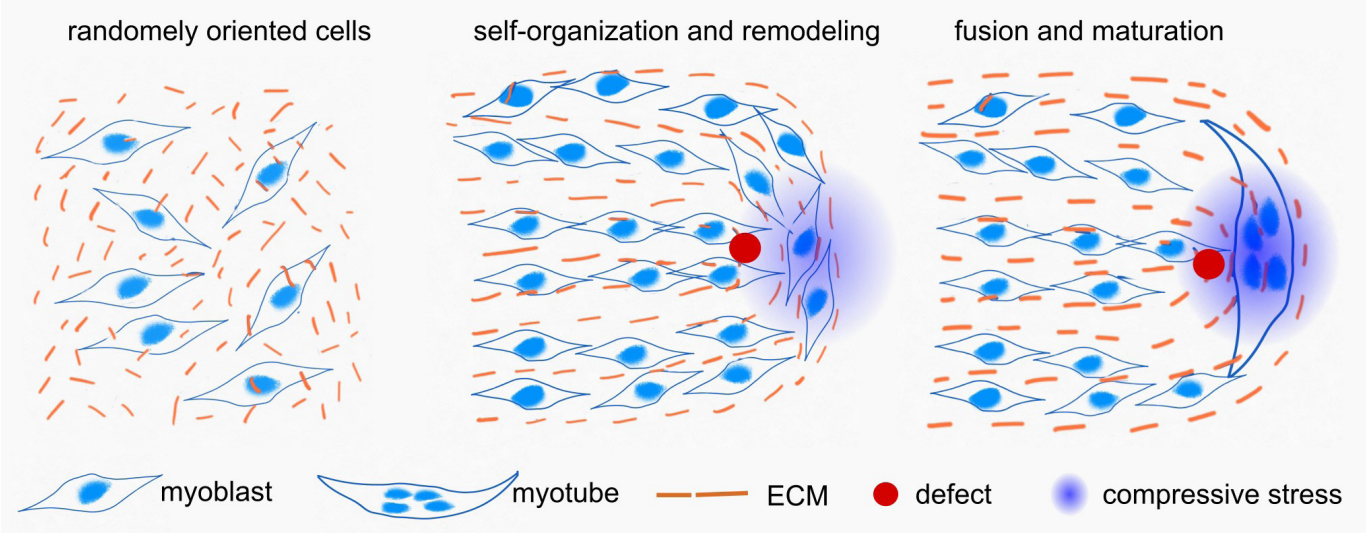

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During muscle formation, mono-nucleated cells (myoblasts, blue) and their surrounding matrix (orange, ECM) are initially disordered (left). As they self-organize and align (middle), their cooperative movement remodels the matrix and form topological defects (red dot). In these areas, mechanical compressive stress (blue glow) intensifies creating a high-stress hotspot that serves as a fusion hub — directing the myoblasts to fuse into mature, multi-nucleated muscle fibers (myotubes) at the defect site (right).

"Using an in-vitro chicken myoblast model alongside advanced force-mapping and live-cell imaging techniques, we were able to demonstrate that myoblasts do not fuse uniformly throughout the tissue, but rather specifically cluster in areas characterized by hotspots of mechanical stress," explains Dr. Sushil Dubey, author of the study and postdoctoral researcher at MPZPM.

The environment "remembers" the cellular organization

The mechanism is not limited to the myoblasts themselves but also encompasses the surrounding intercellular space and the extracellular matrix (ECM). As they align, the myoblasts help shape this matrix. The ECM is a network of proteins that supports the cells and transmits forces. Its organization closely follows the pattern of cell alignment. The researchers were able to show that myoblasts arrange the matrix along their own alignment. The ECM therefore mirrors the organization of the cell layer.

This coupling stabilizes topological defects and reinforces the associated mechanical stress patterns. After the original cell population was removed and fresh myoblasts were placed onto the remaining extracellular matrix, the matrix retained and reproduced aspects of the original mechanical stress pattern. This provides a physical mechanism through which the ECM retains a memory of the original cellular organization and influences the behavior of newly introduced cells.

A feedback loop shapes muscle growth

The study reveals that mechanical forces are not simply a consequence of muscle-cell activity. Instead, they participate in a feedback loop. When myoblasts fuse, they form elongated myotubes. As they develop, they become increasingly aligned, which changes the nematic organization of the tissue. This increases mechanical stresses. At the same time, the cells remodel the ECM, which helps to stabilize the stress patterns. These mechanically organized regions determine where myoblasts will later fuse.

"Muscle formation is not only controlled by biochemical signals. The mechanical environment created by the cells and their surrounding matrix can also influence where fusion occurs," says Ladoux.

From Individual Cells to Organized Muscle

The findings provide a physical framework for understanding how local cellular interactions during muscle formation can lead to large-scale organization. The study suggests that while molecular mechanisms enable muscle cells to fuse, the mechanically organized environment helps determine where fusion is most likely to occur.

This self-reinforcing interaction between cellular activity, the

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extracellular matrix, and mechanical stress could be relevant not only to skeletal muscle development but also to processes in which tissues self-organize during growth and regeneration. This work highlights an important idea in developmental biology: that mechanical forces are not simply a consequence of tissue development but can contribute to its organization.

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