New mechanical insights into wound healing and scar tissue formation

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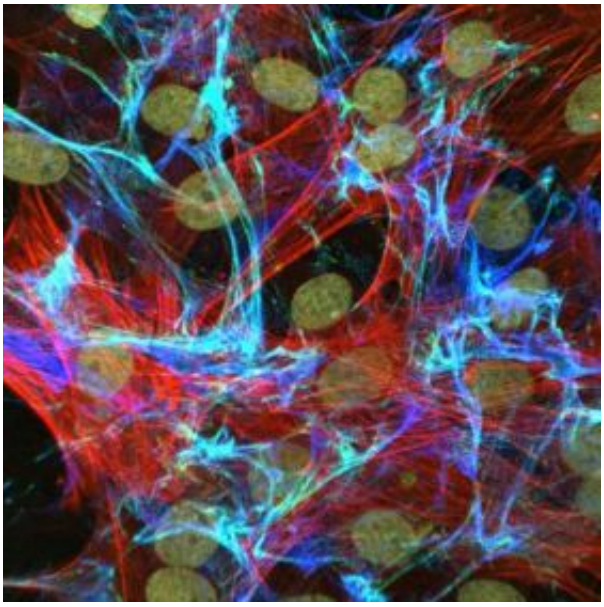

Contractile fibroblasts secrete and organize extracellular matrix fibers (blue) that are loaded with growth factor complexes (green), resulting in a turquoise overlay color. The contractile fibers inside the cells are visualized by detecting a smooth muscle protein (red). The cells' nuclei are visualized in yellow. Credit: EPFL/LCB

New research published today in the *Journal of Cell Biology* illuminates the mechanical factors that play a critical role in the differentiation and function of fibroblasts, connective tissue cells that play a role in wound healing and scar tissue formation.

When we are injured, the body launches a complex rescue operation. Specialized cells called fibroblasts lurking just beneath the surface of the skin jump into action, enter the provisional wound matrix (the clot) and start secreting collagen to close the wound as fast as possible.

This matrix is initially soft and loaded with growth factors. The fibroblasts "crawl" around the matrix, pulling and reorganizing the fibers. The matrix grows stiffer, and at a certain point, the fibroblasts stop migrating and, like Popeye, change into powerful contractile cells, anchoring themselves to the matrix and pulling the edges of the wound together.

The research reported today reveals for the first time that a mechanical mechanism is crucial for this switch from migrating to contractile cells. To make this change, the fibroblasts need to get at their "spinach" -- the growth factor sitting in the matrix which, once liberated, stimulates the production of smooth-muscle proteins. Previously, researchers postulated that the fibroblasts did this by digesting the matrix. But EPFL scientist Boris Hinz, doctoral student Pierre-Jean Wipff and their colleagues have discovered that the cells unlock the growth factor via a purely mechanical process.

With experiments using novel cell culture substrates of varying rigidity, they found that at a certain point, the matrix is sufficiently rigid that cell-exerted force allows the growth factor to pop out, like candy from a wrapper. Once the growth factor is available, the fibroblast expresses the contractile proteins, sticks more firmly to the matrix and starts to contract, pulling the matrix tightly together. In the process it liberates yet more growth factor that in turn stimulates other fibroblasts to become contractile. The mechanical nature of the switch ensures that the contraction only develops when the matrix is "ready."

Although this process will heal a wound quickly, if left unchecked, it can

also lead to a buildup of fibrous tissue. Following trauma to vital organs such as the heart, lung, liver and kidney, overzealous fibroblasts can continue to build fibrous strands, leading to scar tissue buildup that can impair the organ's function.

This condition, called "fibrosis", can be fatal. Fibroblasts are also the culprits in problems caused by implants -- if the implant is too smooth, it never becomes properly incorporated into the connective tissue. But if it is too rough, scar tissue develops around it and it won't function properly. Occasionally, following plastic surgery, unsightly excessive scar tissue can develop in the skin as well. The process can also cause problems in mesenchymal stem cell cultures -- if the culture's substrate is stiff, considerable efforts have to be made to prevent the stem cells from turning prematurely into fibroblasts instead of the desired cell type. Controlling the rigidity of the cell culture is therefore critical.

This new understanding of the mechanical nature of fibroblast activation could be used to reduce or prevent fibrosis from occurring, says Hinz, without inhibiting the growth factor, which serves many other vital functions in the body. There are several possibilities: "You could interfere with the way the cells grab onto the growth factor complex, you could interfere with their attachment points on the matrix, and you could interfere with their contractile forces so that the matrix never gets stiff enough to liberate the growth factor," he suggests.

Citation: Pierre-Jean Wipff, Daniel B. Rifkin, Jean-Jacques Meister and Boris Hinz, "Myofibroblast contraction activates latent TGF-b from the extracellular matrix", Journal of Cell Biology, December 17, 2007.

Source: Ecole Polytechnique Fédérale de Lausanne