How Human Cells Get Their Marching Orders

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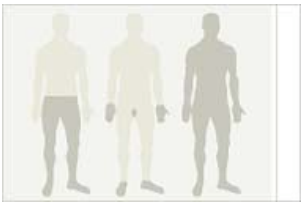
The human body may seem to change little over the years, but beneath this deceptive calm, cells are in constant flux as old ones are discarded and new ones appear. How do the new recruits know where they are meant to go?

Multimedia



Graphic: A G.P.S. Device in Your Skin

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Biologists at Stanford University say they have discovered a coordinate system in human cells that defines their position in the body. This seems to be the first time a cell-based positioning system has been reported for the adult body of any animal, though positioning systems that guide cells in embryogenesis are well known.

The coordinate system, if confirmed, may shed light on processes like wound healing and lend some hope to the prospect of regenerating human tissues from mature cells, as happens in animals like newts and salamanders, rather than from stem cells, the goal of cell therapy.

The Stanford team, led by Howard Chang and John L. Rinn, focused on fibroblasts, a type of cell that is the mainstay of the deep skin and the surfaces that cover the inner organs. Believing that not all fibroblasts are alike, though they may look alike, the team analyzed which genes were turned on or off in fibroblasts sampled from many body sites.

They detected different subsets of genes that were active in fibroblasts from different sites, suggesting that each cell was getting three pieces of information that together would specify a location, the team reports in the current issue of the journal Public Library of Science Genetics.

In this coordinate system, the Stanford researchers propose, one bit of information tells a cell whether it is meant to be part of the body's inner or outer surfaces. A second directs it to the body's top or bottom half. A third specifies whether it is at the near or far point of any body appendage, be it arm, leg or penis. The researchers believe that there are more precise positioning cues that they have not yet picked up.

Dr. Rinn said that by looking at the settings of these three coordinates he could tell where in the body a fibroblast came from — something impossible with any other kind of

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cell.

The fibroblasts, which secrete much of the material in which the skin's cells are embedded, lie in the bottom layer of the skin. Above lie the five layers of the surface skin, composed of constantly shed cells known as keratinocytes.

The bottom layer of the skin is derived from an embryonic tissue different from the surface layer and is known to determine the fate of the surface cells. If surface skin cells from a chicken's wing are transplanted to its leg, they will grow into scales, not feathers. Extending this idea to the new coordinate system, Dr. Rinn suggested that the keratinocytes, which have no positioning system, must take their cues from chemical signals emitted by the fibroblasts beneath.

When the skin is cut, how does the body gauge the size of the wound and the amount of new tissue that must be generated?

Dr. Chang said the positioning system could be of help. If two fibroblasts that should lie some distance apart come in contact with each other after wound closure, that could signal how much new tissue was needed to restore their usual distance.

The Stanford team believes that the genes primarily responsible for the fibroblast coordinate system belong to the so-called hox family of genes, which are known to shape each region of the body during the formation of the embryo.

The hox genes were thought to be switched off after development was completed, but the Stanford findings show that they are still active in adult fibroblasts. A hox gene designated HOXA13 was found to be switched on in all fibroblasts taken from the fingers, toes and foreskin, presumably because it helps shape surrounding tissue into an extremity.

Cliff Tabin, an embryologist at Harvard Medical School, said that the Stanford report was "very interesting and certainly novel," but that he wondered if the fibroblast coordinate system might not be just an inactive leftover from embryonic life. The Stanford team has yet to show that the adult fibroblasts behaved any differently because of their different coordinate settings, he said.

Elaine Fuchs, an expert on skin cells at Rockefeller University, also questioned whether the pattern found by the Stanford researchers was "merely an evolutionary remnant of nature's fun and fancy in creating body surfaces," or whether it signaled a real adult-life activity of the fibroblasts.

Dr. Chang said that this was a good point and that he was addressing the issue in experiments.

Dr. Tabin also said the Stanford finding should encourage biologists who hope to make humans regenerate lost limbs. Newts do not regenerate their limbs from stem cells, but from mature cells, which are made to revert to a stemlike state. This mass of stemlike cells, known as a blastema, then builds a new limb based on the positional information in the mature cells at the wound site.

A wrist blastema builds a new wrist, even if transplanted elsewhere in the newt's body, and a shoulder blastema builds a new shoulder-length limb.

Most vertebrate animals do not regenerate their tissues and, until now, no one knew that adult cells retained this positional information. "I've no idea if we'll get vertebrate regeneration to occur in the foreseeable future, but if we have the presence of positional information in human cells, that is a good thing," Dr. Tabin said.

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