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Learning How Animals Regenerate Body Parts

By NICHOLAS WADE

The best possible kind of regenerative medicine would surely be to entice the body to use nature's own methods to regrow a damaged limb or organ. The genes that made the structure in the first place are still present in every cell of the body but somehow repressed. Could they not be reactivated to make the patient as good as new?

Many animals do regenerate parts of their bodies. Deer regrow their antlers, and some lizards their tails. The zebra fish can also regrow its tail, and researchers at the Salk Institute have now taken a first step toward understanding how.

The minnowlike zebra fish, a common sight in tropical aquariums, is a standard laboratory animal, and although mice are probably more common in labs, they do not regrow their tails. The Salk team assumed that animals would regenerate a limb by using the same set of genes as were deployed during embryonic development, so they looked at a class of master genes that controlled an egg's development into an embryo.

These genes are governed by a special kind of dual-purpose switch, which represses the genes but prepares them for activity. Thus, the master genes spring into action the instant the switch is flipped.

These dual-purpose switches were at first thought to be confined to the egg and embryonic stem cells, where they were discovered three years ago. But the switches are now being noticed in adult cells as well.

The Salk Institute scientists — Scott Stewart, Zhi-Yang Tsun and Juan Carlos Izpisúa Belmonte — have now found that dual-purpose switches control many of the 100 or so genes that are activated in the regenerating cells of a zebra fish's tail. They report their findings in the current Proceedings of the National Academy of Sciences.

The switches consist of chemical modifications to the chromatin, the material that wraps and controls access to the DNA of every cell. Genes are most directly controlled through nearby regions of DNA that are themselves turned on by certain regulatory proteins. But a second layer of control is built into the chromatin, which has to unpack itself if the regulatory proteins are to have access to the underlying DNA.

Zebra fish tails can be cut off with a razor blade (the fish are anesthetized first). Within 12 hours, genes that are usually silenced throughout the fish's adult life are turned on.

The Salk biologists have found that a key event in this activity is the appearance of an enzyme known as a methylase. The methylase homes in on the chromatin and removes chemical attachments from one half of the dual-purpose switches, and the genes are turned on.

The team has shown they can prevent the cut tails from regenerating by giving the fish a drug that inhibits the methylase. Dr. Belmonte said in an interview that he hoped to develop techniques for the opposite process, that of initiating regeneration by turning on the methylase gene.

Do people have the same dual-purpose switches built into their genetic circuitry?

“It would be wonderful,” Dr. Stewart said, “if we have retained the whole apparatus for regeneration but for the trigger.”

One reason for hope is that the genes for embryonic development are very similar in all vertebrates. But in people, a wound prompts the formation of only scar tissue.

An approach to regeneration, followed in stem cell research, is to take an embryonic stem cell and try to nudge it down the right paths of development toward a particular kind of adult tissue. Nature, though, seems to do the opposite, starting with adult cells. In the zebra fish, the adult cells at the site of the wound turn into a blastema, a set of cells that have reverted to a stemlike state, and each type of cell then grows and divides to reform the muscles, nerves or skin of the missing tissue. The rationale of nature’s approach is presumably that the adult cells know things, like their proper position and population size in the body, which embryonic cells do not.

“Both approaches are valid,” Dr. Stewart said. “Human stem cells are much more in vogue and easier to obtain funding for. But we’ve said, ‘Let’s see how nature does it.’ ”