Stem cell surprise for tissue regeneration (w/ Podcast)

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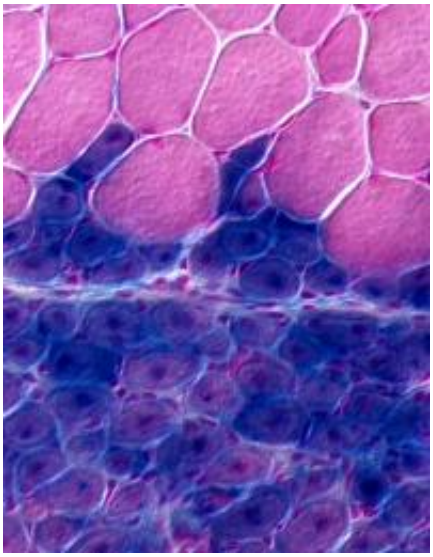

This cross section of hind limb muscle tissue is from a mouse five days after injury. The uninjured cells are at top and stained red. The blue cells below are regenerating muscles cells. They were labeled with a blue stain and formed from muscle stem cells. Credit: Christoph Lepper

Scientists working at the Carnegie Institution's Department of Embryology, with colleagues, have overturned previous research that identified critical genes for making muscle stem cells. It turns out that the genes that make muscle stem cells in the embryo are surprisingly not needed in adult muscle stem cells to regenerate muscles after injury.

The finding challenges the current course of research into muscular

dystrophy, muscle injury, and regenerative medicine, which uses stem cells for healing tissues, and it favours using age-matched stem cells for therapy. The study is published in the June 25 advance on-line edition of *Nature*.

Previous studies have shown that two genes Pax3 and Pax7, are essential for making the embryonic and neonatal muscle stem cells in the mouse. Lead researcher Christoph Lepper, a predoctoral fellow in Carnegie's Chen-Ming Fan's lab and a Johns Hopkins student, for the first time looked at these two genes in promoting stem cells at varying stages of muscle growth in live mice after birth.

As Christoph explained: "The paired-box genes, Pax3 and Pax7 are involved in the development of the skeletal muscles. It is well established that both genes are needed to produce muscle stem cells in the embryo. A previous student, Alice Chen, studied how these genes are turned on in embryonic muscle stem cells (also published in Nature). I thought that if they are so important in the embryo, they must be important for adult muscle stem cells. Using genetic tricks, I was able to suppress both genes in the adult muscle stem cells. I was totally surprised to find that the muscle stem cells are normal without them."

The researchers then looked at whether the same was true upon injury, after which the repair process requires muscle stem cells to make new muscles. For this, they injured the leg muscles between the knee and ankle. They were again surprised that these muscle stem cells, without the two key embryonic muscle stem cell genes, could generate muscles as well as normal muscle stem cells. They even performed a second round of injury and found that the stem cells were still active.

The scientists then wondered when these genes become unnecessary for muscle stem cells to regenerate muscles. It turned out that these embryonic genes are important to muscle stem cell creation up to the

first three weeks after birth. What makes the muscle stem cells different after three weeks? The scientist believe that these two embryonic muscle stem cell genes also tell the stem cells to become quiet as the organism matures. After that time is reached, they "hand over" their jobs to a different set of genes. The researchers suggest that since the adult muscle stem cells are only activated when injury occurs (by trauma or exercise), they use a new set of genes from those used during embryonic development, which proceeds without injury. The scientists are eager to find these adult muscle stem cell genes.

"We are just beginning to learn the basics of stem cell biology, and there are many surprises," remarked Allan Spradling, director of Carnegie's Department of Embryology. "This work illustrates the importance of carrying out basic research using animal models before rushing into the clinic with half-baked therapies."

Source: Carnegie Institution