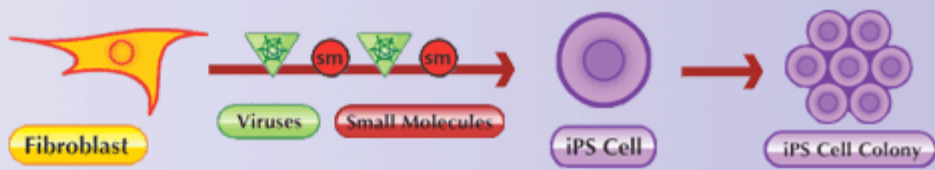


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A satellite cell surprise

Megan Scudellari¹

Muscle stem cells have unexpected age-dependent genetic requirements

It is not uncommon for the scientific community to infer adult stem cell biology from developmental studies. But a new *Nature* paper cautions against that practice, demonstrating for the first time that genes critical to muscle stem cell development in the mouse embryo are not required for maintenance, self-renewal or differentiation of the same stem cells in the adult mouse¹.

"The big expectation in most stem cell fields is that adult stem cells recapitulate embryonic pathways," says Christoph Lepper, predoctoral fellow at the Carnegie Institution in Baltimore, Maryland and first author on the study. "But there is something different about these adult stem cells compared to their progenitor state."

In 2004, Lepper joined [Chen-Ming Fan's](#) laboratory at Carnegie, a research group with a focus on musculoskeletal development, especially



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prenatal myogenesis — the early formation of muscle. But Lepper arrived with a strong interest in adult regeneration, and Fan suggested they combine their interests in an investigation of the molecular requirements for muscle stem cells to regenerate muscle after an injury.

They decided to study *Pax7*, a paired-box transcription factor implicated in both events. In 2000, [Michael Rudnicki](#) and colleagues at McMaster University in Ontario, Canada, found that *Pax7* is critical for the specification of muscle stem cells, called satellite cells, during development — *Pax7* germline mutants fail to produce satellite cells, severely compromising muscle regeneration. They also found that *Pax7* is expressed in adult satellite cells². "If *Pax7* is important to make these satellite cells and is expressed by these cells, then it's probably critical for satellite cell function in adults," Lepper thought. The only way to know for sure was to make a conditional knockout, using recently developed inducible Cre/loxP lineage-tracing strategies to knock out a *Pax7* allele in adult mice. "Our expectation was if we inactivate *Pax7*, the adult mice should be markedly deficient in muscle regeneration," he recalls.

But the first round of injury in the conditional knockouts did not go as planned — muscle regeneration proceeded normally. "I was very worried," says Lepper, who feared the mice he developed were only partial knockdowns. He ran to Fan and confessed the problem. But after a year of generating the conditional knockout mice, using homologous recombineering to make targeting constructs and inserting them into the animals' genomes, the two weren't ready to give up. They performed extensive western blots, RT-PCR and immunofluorescence analyses of the mice, all of which showed no *Pax7* transcripts or any lingering *Pax7* protein. In other words, the conditional *Pax7* knockout seemed to be working, but muscles in the adult mice were just fine.

Puzzled, the team tested their knockdown assay in one-week-old mice, in an effort to recapitulate Rudnicki's germline mutant phenotype. It worked: *Pax7* inactivation in young mice caused a severe defect in muscle regeneration. "That was the most exciting day in the lab," says Lepper. Inactivating *Pax7* caused different phenotypes in adult and developing mice. "It really told us our assay was working, and there really was something different about adult satellite cells."

A second round of injury and regeneration in adult knockdowns showed that the *Pax7* -deficient satellite cells were able to self-renew and generate new muscle. To be sure that a *Pax7* homolog, *Pax3*, wasn't compensating for the loss of *Pax7*, the researchers knocked it down as well, and myogenesis proceeded normally.

After five years of ups and downs, the researchers are sure: *Pax7* is required for myogenesis during development, but not after. They even narrowed the timeline, finding that *Pax7* is required before postnatal day 21; after that, satellite cells function independently of the gene. "It was entirely unexpected," the authors write in their conclusion.

The results challenge conventional wisdom that knowledge gained from developmental studies can be applied to adult stem cell biology. "We know a lot about embryogenesis but are lacking in studies for adult

stem cells," says Lepper. "We believe more studies like this will now come out."

With *Pax7* and *Pax3* out of the running, Lepper and Fan now plan to investigate the genetic program that is operating in adult satellite cells and see how it compares to that of their embryonic progenitors.

References

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Author affiliations

1. [Megan Scudellari](#) is a freelance writer based in Durham, North Carolina.

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