Satellite and stem cells in muscle growth and repair

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The FASEB summer research conference on Skeletal Muscle Satellite and Stem Cells, organized by Thomas Rando, Giulio Cossu and Jeffrey Chamberlain, was held in Indian Wells, California, in July. An international array of researchers gathered to share numerous new insights into the cellular and molecular regulation of stem cells and satellite cells in skeletal muscle biology. The conference is unique in that it brings together investigators from diverse backgrounds, who work on the growth and repair of skeletal muscle in humans and model systems, in health and disease.

Introduction

It is now over 45 years since the first description of the canonical satellite cell in adult skeletal muscle (Mauro, 1961). Satellite cells reside in a niche that lies beneath the basal lamina but outside of the associated muscle fibers (Fig. 1A) (Bischoff, 1990). Satellite cells have long been believed to represent a committed muscle progenitor that is responsible for the postnatal growth and regenerative capacity of skeletal muscle (Seale et al., 2000). Typically mitotically quiescent, satellite cells are activated in response to stress that is induced by weight bearing or by trauma, such as injury (Charge and Rudnicki, 2004). The descendants of activated satellite cells, called myogenic precursor cells or skeletal myoblasts, undergo multiple rounds of division prior to terminal differentiation and fusion to form multinucleated myofibers.

During the course of the last decade, numerous researchers have provided evidence to support the hypothesis that a subpopulation of satellite cells exists that possess stem cell-like properties (Collins et al., 2005). In fact, it has been demonstrated recently that satellite cells represent a heterogeneous, hierarchical population that is composed of a small number of satellite stem cells and a larger number of committed myogenic progenitors (Kuang et al., 2007). Moreover, our understanding of non-conventional myogenic stem cells (side population cells, mesoangioblasts, and muscle-derived stem cells) has been clarified by the appreciation that they might be derived from a pericyte-like cell in muscle tissue (Peault et al., 2007). These and other advances in our understanding of skeletal muscle satellite and stem cell biology were discussed at the recent FASEB conference, which we review below.

Developmental origin of satellite cells

From studies performed in chick and mouse, it has been recently suggested that during early embryogenesis, a cell population that expresses the paired-box transcription factors Pax3 and Pax7, but not any of the known skeletal-muscle-specific markers, arises from the medial part of the somitic dermomyotome. These cells are maintained as a proliferating population throughout development

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and then adopt a satellite cell position that is characteristic of progenitor cells in postnatal muscle (Fig. 1B) (Buckingham and Relaix, 2007). Simon Hughes (King's College, London, UK) discussed the advantages of the zebrafish model for the study of embryonic myogenesis. Zebrafish embryos are optically clear, which allows for easy lineage-tracking in live embryos. By using confocal imaging and informatics systems, researchers can follow the cellular trajectories of one to hundreds of cells in live zebrafish embryos, with the ultimate goal of understanding the exact pathways of cellular movements during embryonic development (Forouhar et al., 2006). Furthermore, 'external cells' that express Pax3 and Pax7 were recently identified at the surface of the somite. The analysis of these cells, which form a dermomyotome-like tissue and give rise to muscle fiber and myoblasts, should bring new insights into muscle morphogenesis and development in the near future (Devoto et al., 2006).

These satellite cell precursors depend on Pax3 and Pax7 expression during embryogenesis for their commitment into the satellite cell lineage and their survival, but little is known about the importance of the myogenic regulatory factors (MRFs), such as MyoD (Myod1, myogenic differentiation 1), Myf5 (myogenic factor 5), Mrf4 (also known as Myf6, myogenic factor 6) and myogenin, in this lineage. David Goldhamer (University of Connecticut, Storrs, CT) reported preliminary results obtained with the Cre/*loxP* lineage-tracing system in mice. They crossed the reporter strain R26R-EYFP [which constitutively expresses the yellow fluorescent protein (YFP) reporter in all cells that undergo recombination at *loxP* sites] with a new MyoD-Cre knock-in mouse in which Cre recombinase is expressed under the same regulatory control as MyoD. Goldhamer's findings lead him to conclude that most, if not all, satellite cells express MyoD in their developmental history. By contrast, by crossing a Myf5-Cre line with the R26R-YFP line, Kuang et al. have found that, after birth, 90% of satellite cells express Myf5 and that Myf5-negative cells are the repopulating stem cells within the satellite cell lineage (Kuang et al., 2007). The differences between the findings of these two studies might be explained by the use of different markers to identify satellite cells. Future studies will settle this issue.

It is a common hypothesis that satellite cells are the cells of origin of rhabdomyosarcomas (an aggressive childhood and adult cancer). Charles Keller (University of Texas, San Antonio, TX) used conditional genetics to temporally and spatially restrict the activation of oncogenes or the inactivation of tumor suppressors to subsets of embryonic and postnatal muscle cell precursors in mice. He presented new and exciting experiments in which his team compared the cancerous outcomes of oncogenic recombinations driven within the different expression domains of myogenic genes. Keller's work increasingly links dysregulation of satellite cell development with rhabdomyosarcomas. We believe that such analyses of muscle-related cancers will open new avenues of research in satellite cell biology.

Signaling pathways in satellite cell activation and differentiation

Embryonic and adult myogenesis are closely related; once satellite cells are activated by a stress to the fiber, they enter the cell cycle and recapitulate the molecular pathways that occur during the development of the skeletal muscle, such as the Wnt, Notch and myostatin pathways, which are crucial regulators of embryonic myogenesis (Shi and Garry, 2006). All of these pathways are
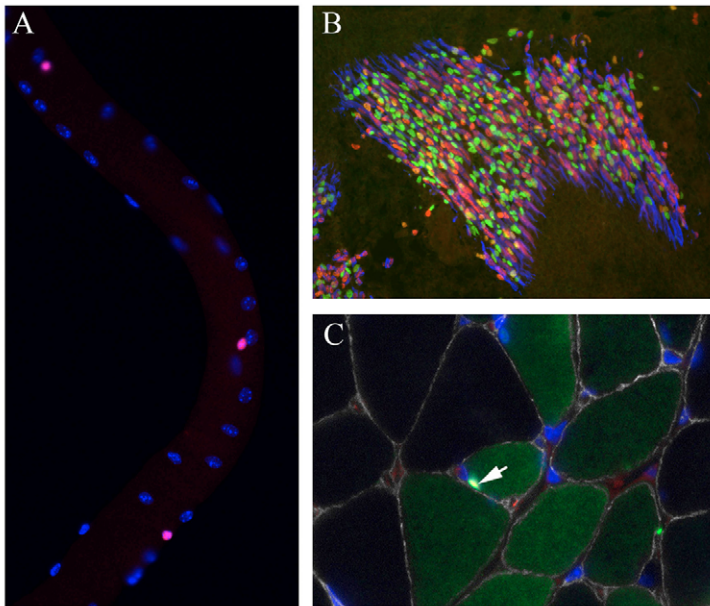
Fig. 1. Different states of the skeletal muscle satellite cell.
(**A**) Pax7-positive satellite cells (red) at the surface of a single fiber isolated from the extensor digitorum longus (EDL) muscle of an adult mouse. Nuclei are stained with DAPI (blue). (**B**) During embryonic development, a Pax7-positive population of myogenic progenitors contributes to myogenesis and gives rise to satellite cells. Cryosection through a masseter muscle from an E14 mouse embryo. Differentiated muscle fibers are stained with an antibody against myosin heavy chain (cytoplasm, blue) and an antibody against myogenin (nuclei, red). Pax7-positive cells (nuclei, green) are located between the newly formed fibers. (**C**) Transverse cryosection of a transplanted mouse tibialis muscle, showing that transplanted YFP-positive satellite cells can fuse with host muscle fibers and contribute to the host stem cell niche. Grafted cells are labeled with an anti-GFP antibody (green) and anti-Pax7 antibody (red). Muscle fiber basal laminas are labeled with a laminin antibody (white) and nuclei with DAPI (blue). Arrow shows a grafted YFP-positive Pax7-positive cell in a satellite cell position. Images in A and B are courtesy of Fabien Le Grand; image in C is courtesy of S. Kuang.

required for the self-renewal or differentiation of stem cell progeny in various systems and are believed to be regulators of satellite cell biology, as discussed in more detail in the following section.

Wnt signaling

After injury, transcripts of the Wnt morphogens, their Frizzled receptors, and the Wnt antagonists Sfrp (secreted frizzled-related proteins), are detected in the regenerating skeletal muscle tissue (Polesskaya et al., 2003), but a specific role for the Wnt pathway in satellite cell regulation has still not been described. Thomas Rando's team (Stanford University School of Medicine, Stanford, CA) have been involved in deciphering the mechanisms that lead to impaired muscle regeneration with age. He presented new work that demonstrates that the loss of myogenic phenotype during aging in mice is linked with elevated Wnt signaling. By using the Pax7-Cre-ER lineage-tracing system, they found that cells that constitutively express *lacZ* after Cre/*loxP* recombination that once were Pax7-positive satellite cells can lose Pax7 expression and differentiate into fibroblasts in old muscle. By contrast, inhibition of Wnt signaling by either Sfrp3 or dickkopf 1 (potent inhibitors of Wnt canonical signaling), rescues muscle regeneration in aged mice (Brack et al., 2007).

Peter Zammit (King's College, London, UK) retrovirally infected satellite cells with constitutively activated forms of β-catenin and showed that repression of differentiation and maintenance of Pax7 expression occur in infected satellite cells, suggesting that forced canonical Wnt signaling is pro-self-renewal. On the non-canonical side of the story, Charlotte Peterson (University of Kentucky, Lexington, KY) presented new insights from their studies of *Wnt10b*-null mice (Vertino et al., 2005). The mutant myoblasts derived from these mice show increased myogenic differentiation owing to a compensatory increase in Wnt7b, which Peterson links to the activation of a non-canonical Wnt pathway that potentially involves Creb proteins. These results appear to be the starting point of a new and very complex story.

Notch signaling

Notch signaling is potentially a major pathway that regulates the activation and expansion of the satellite cell lineage during embryogenesis (Vasyutina et al., 2007) and in the adult (Conboy and

Rando, 2002). The decline of Notch signaling with age is thought to be another cause of the decreased regenerative potential of aged satellite cells (Conboy et al., 2005). Reshma Taneja (Mount Sinai School of Medicine, New York, NY) presented recently published work that demonstrates that the bHLH transcription factor Stra13 (stimulated by retinoic acid 13) antagonizes Notch1 signaling in mouse satellite cells and regulates the balance between proliferation and differentiation during regeneration (Sun et al., 2007). Addolorata Pisconti from Brad Olwin's lab (University of Colorado, Boulder, CO) described syndecan 3 (Sdc3) as a new regulator of Notch signaling. The loss of Sdc3 in mice induces premature progenitor cell commitment and differentiation. Further description of the role of Sdc3 in the Notch pathway will be of great interest.

Myostatin

Myostatin belongs to the Tgfβ (transforming growth factor β) family of secreted molecules and potentially antagonizes muscle regeneration by limiting satellite cell proliferation and differentiation. Victoria Siriett and Ravi Kambadur (AgResearch, University of Waikato, Hamilton, New Zealand) described the use of a myostatin antagonist, Mstn-ant1, for the rescue in vitro and in vivo of the myostatin inhibitory effect on myogenesis in mice. Mstn-ant1 delivery was suggested to increase the number of activated satellite cells and to enhance their migratory potential, as well as regulating Pax7 expression (Siriett et al., 2007). Thus, antagonism of myostatin appears to represent a potential therapeutic strategy for aged-induced sarcopenia (the degenerative loss of skeletal muscle mass and strength in senescence).

Interactions between satellite cells and their microenvironment

The cell migration and chemosensing of myogenic precursors are required for efficient muscle regeneration, and numerous groups are currently investigating how satellite cell activation and differentiation are modulated by their direct microenvironment, either by cell-surface contact or by other cell-secreted molecules (Chazaud et al., 2003).

An important effector of myogenic differentiation is the cell-surface protein Cdo (Cdo1, cysteine dioxygenase 1). Robert Krauss (Mount Sinai School of Medicine, New York, NY) summarized

some of his lab's accomplishments in characterizing Cdo functions, expression profiles and partners. He presented exciting new data on Cdo activation and proposed that Cdo works via Bnip2 and Cdc42 to initiate a signaling cascade that activates the p38 MAP kinase bound to the scaffold protein JLP (JNK-associated leucine-zipper protein, Spag9) (Takaesu et al., 2006).

Helen Blau (Stanford University, Stanford, CA) presented exciting new work using engineered scaffolds in artificial niches in vitro to culture stem cells. Blau showed us impressive recordings of time-lapse microscopy of live single cells in hydrogel microwells. It was evident that this approach holds much promise to address experimentally the role of extrinsic tethered and soluble factors that regulate satellite cell fate determination and self-renewal.

Transcription factor control of satellite cell proliferation and differentiation

A handful of specific transcription factors are necessary to drive the molecular regulation of satellite cells. Daniel Garry (University of Minnesota, Minneapolis, MN) discussed the molecular regulation of *Foxk1*, a member of the forkhead/winged-helix family of transcription factors. *Foxk1*-null mice have fewer satellite cells and impaired regeneration. Foxk1 has recently been described as regulated by Sox15 (SRY-box containing gene 15) via Fhl3 (four and a half LIM domains 3); all three transcription factors coordinately regulate the myogenic progenitor cell population and skeletal muscle regeneration (Meeson et al., 2007). Garry presented new results that link the lack of Foxk1 to an induction of p21 in *Foxk1*-null cells and discussed a novel pathway in which the Foxk1 repression of p21 results in satellite cell activation.

Pax7 is a major regulator of satellite cell development and differentiation during embryogenesis and postnatal life. *Pax7*-null mice show marked muscle wasting together with a complete absence of functional satellite cells (Kuang et al., 2006). Michael Rudnicki (Ottawa Health Research Institute, Ottawa, Canada) presented new findings on its multiple functions. Genome-wide analysis of Pax7 DNA-binding sites by chromatin immunoprecipitation (ChIP) combined with high-throughput sequencing identified candidate Pax7 target genes and implicated Pax7 in transcriptional networks that are related to many aspects of myogenesis. Tandem affinity purification and mass spectrometry identified the association of Pax7 with a histone-methyltransferase complex that leads to the transcriptional activation of specific chromatin domains. These results lead to the idea that Pax7 drives the myogenic identity of the satellite cell lineage through epigenetic modifications.

A novel paradigm for the regulation of Pax7's paralog, Pax3, was described by Stéphane Boutet from Thomas Rando's lab (Stanford University School of Medicine, Stanford, CA). He showed that Pax3 is regulated by ubiquitination and proteasomal degradation during satellite cell activation. Intriguingly, it is a monoubiquitylated form of Pax3 that undergoes proteasomal degradation and not a polyubiquitylated form. He showed that specific lysines account for this regulation and demonstrated that a stable mutant form of Pax3 inhibits myogenic differentiation. Thus, Boutet proposed that control of Pax3 degradation is an essential step for the progression of the myogenic program beyond commitment and that monoubiquitylation can also be interpreted as a destruction signal by the proteasome (Boutet et al., 2007).

The first targeted mutations of the *Myf5/Mrf4* locus in the early 90's showed that the loss of these genes in mice leads to defects in primary myotome formation, resulting in severe malformations and in perinatal death (Braun et al., 1992). However, the field had to wait for the further characterization of this locus and for advances in gene targeting before the first viable *Myf5*-null mice became available (Kaul et al., 2000). Both Shahragim Tajbakhsh (Institut Pasteur and CNRS, Paris, France) and Thomas Braun (Max-Planck Institute for Heart and Lung Research, Bad Nauheim, Germany) discussed the phenotype of adult *Myf5*-null mice. Tajbakhsh reported that mutant mice show signs of repeated regeneration and more adipose infiltration in the muscle tissue following a freeze injury (Gayraud-Morel, 2007). Braun spoke about his recently published work that shows that Myf5 supports efficient regeneration by enabling transient myoblast regeneration (Ustanina et al., 2007). They agreed on the fact that compound *Myf5*-null/*mdx* mutants show constant regeneration and an aggravation of the dystrophic phenotype, presumably owing to satellite cells lacking proliferative potential (*mdx* mice lack functional dystrophin and are thus an animal model of human Duchenne muscular dystrophy). It is striking, however, that although Myf5 and MyoD can each compensate for the loss of the other during embryogenesis, they cannot efficiently compensate for each other in an adult context, and it is clear that whereas MyoD regulates satellite cell differentiation, Myf5 function is related to satellite cell proliferation. Why, and how, the balance between these two MRFs is orchestrated during muscle regeneration remains elusive; this question will certainly be assessed in the future.

Satellite cell heterogeneity and self-renewal

Satellite cells directly isolated from adult muscle tissues and grafted into host mice contribute both to fiber repair and to the muscle satellite cell compartment (Montarras et al., 2005). Not all satellite cells possess equal potential within the lineage; Pax7-positive/Myf-negative satellite cells represent a stem cell compartment that, following intramuscular transplantation, can extensively contribute to the satellite cell reservoir throughout a host muscle (Fig. 1C) (Kuang et al., 2007).

Numerous researchers are currently trying to find out which satellite cell population harbors the most potent regenerative and self-renewal potential. Another important question derives from the observation that the expansion of satellite cells in culture before their engraftment reduces their regenerative capacity (Montarras et al., 2005). What are the differences between quiescent and activated satellite cells that restrict their stem cell characteristics?

Bradley Olwin (University of Colorado, Boulder, CO) assessed the problem using $BaCl_2$ to induce in vivo muscle regeneration in mice, followed by the transplantation of heterologous GFP-positive muscle fibers, without irradiation or immunosuppression. He described an impressive $\geqslant 50\%$ increase in the mass of the recipient muscle 30-60 days after transplantation, proving that satellite cells' regenerative potential is enhanced by its microenvironment, the muscle fiber. He also detailed serial transplantation experiments, in which chimeric fibers extracted from the first grafted muscle were transplanted into a secondary recipient, and he showed that GFP-positive satellite cells deriving from the first donor were again able to engraft the satellite cell pool in the secondary host. The questions arising from this work include: why does the mass of the grafted muscle increase dramatically after transplantation? And how do donor cells escape immune surveillance by the host? If Olwin and his team succeed in answering these questions, they might represent one of the next major outcomes in our field.

Using a FACS strategy with a selection based on β1-integrin and Cxcr4 immunoreactivity, which marks 80% of satellite cells, Amy Wagers (Harvard Medical School, Boston, MA) grafted GFP-positive satellite cells into recipient *mdx* muscle and showed a robust regeneration and restoration of muscle function. She also presented results demonstrating the self-renewal of satellite cells

after serial transplantations: GFP-positive satellite cells grafted into a host muscle were purified again after the regeneration of the transplanted tissue and were able to give rise to myogenic colonies in vitro. In the same way, the re-injury of previously engrafted muscle increased the number of GFP-positive cells, suggesting that a de novo recruitment of engrafted cells participates in muscle regeneration.

Terrence Partridge (Children's National Medical Center, Washington, DC), whose lab first grafted intact myofibers into an adult muscle and proved that satellite cells self-renew in vivo (Collins et al., 2005), discussed the difference in grafting efficiency between satellite cells isolated from different muscles. He also described differences between satellite cells from young and aged muscle. As grafts of young and old fibers into host young muscle yield similar reconstruction, Partridge stated that there is a population of self-replacing satellite cells within both young and old muscle (Collins et al., 2007). Hence, the concept that muscle satellite stem cells survive with age preferentially in comparison to committed cells was supported by results from Zipora Yablonka-Reuveni's research team (University of Washington, Seattle, WA). In this group's studies, Myf5 expression was determined by tracing Myf5-driven reporter activity using the *Myf5-lacZ* knock-in mouse. Satellite cells that display Myf5 activity account for 80-90% of the Pax7-positive cells in adult mice. This proportion goes down to 50% in 2-year-old animals.

Analysis of satellite cell quiescence

Since the cells that repopulate the muscle satellite niche are the ones that turn off the expression of MyoD and return to a quiescent state (Olguin and Olwin, 2004; Zammit et al., 2004), one way to find new insights into satellite cell self-renewal is to analyze the molecular regulation of stem cell quiescence. With this question in mind, a few groups presented their results of global gene analyses of freshly isolated satellite cells.

Shin'ichi Takeda (National Center of Neurology and Psychiatry, Tokyo, Japan) discussed the results obtained after microarray analysis of satellite cells sorted with the SM/C-2.6 antibody (this antibody binds an unknown antigen that is expressed by most satellite cells) (Fukada et al., 2007). He presented new data that suggest that the calcitonin receptor is a potential new effector of satellite cell quiescence. Calcitonin signaling prevents satellite cells from entering the cell cycle and inhibits the motility of primary myoblasts. Takeda also showed that satellite cells lose calcitonin receptor expression during activation and that a fraction of activated cells can co-express Pax7 and the calcitonin receptor 7 days after cardiotoxin injection, corresponding to a return to quiescence.

The Rudnicki lab's strategy for sorting satellite cells with α7-integrin-positive selection and negative selection of CD31 (Pecam1), Sca1 (Ly6a), CD45 (Ptprc) and CD11b (Itgam), applied to cells extracted from Myf5-Cre*R26R-YFP mice, allows for the efficient isolation of satellite progenitor (Myf5-positive) and stem (Myf5-negative) cells. Fabien Le Grand, from the Rudnicki group, presented results from the comparison of these populations by subtractive suppressive hybridization. This approach showed that both satellite progenitor cells and stem cells express specific genes, and that the hierarchy that exists among these cells is regulated by specific transcription factors and by the Notch signaling pathway.

Didier Montarras (Institut Pasteur and CNRS, Paris, France) reported results from a microarray analysis of Pax3-GFP-positive cells extracted from resting and injured muscle. He identified a large number of transcripts that are differentially expressed between the two conditions. Interestingly, Montarras detected genes related to myogenic differentiation in the quiescent cells and postulated that a fraction of the quiescent cells is always committed to differentiation (Montarras et al., 2005).

Some striking comparisons between the different gene expression analyses performed by these three teams were discussed, and a consensus emerged that genes that function in cell cycle arrest, in Notch signaling, and that encode Krüppel-like factors, are strongly expressed by quiescent cells. This area will clearly be the subject of much further research.

Cellular therapies in muscle disease and atrophy

As previously discussed, freshly prepared satellite cells can participate in skeletal muscle regeneration, but the impossibility of delivering these cells to patients intravascularly limits their efficiency. Exciting advances in both cell-mediated and gene-mediated therapies were discussed at this conference. Giulio Cossu (Hospital San Raffaele, Milan, Italy) presented results obtained with the adult mesoangioblast, a vessel-derived stem cell that can be efficiently transplanted by intra-arterial delivery. The latest advances using these cells resulted in a remarkable clinical amelioration and preservation of motility in the golden retriever dog model of Duchenne muscular dystrophy (Sampaolesi et al., 2006). Cossu also discussed the initiation of the first clinical trials in humans. Mesoangioblasts will be injected into a small muscle of the hand of 14- to 16-year-old boys with Duchenne muscular dystrophy. The major issues for muscle stem cell transplantation in the context of Duchenne muscular dystrophy remain that the patient must follow an immunosuppressive treatment and that the transplanted stem cells do not home to the heart, which is also affected by the lack of dystrophin.

Jeff Chamberlain (University of Washington, Seattle, WA) discussed the use of viral vectors to stably transduce myogenic stem cells with therapeutic genes (Li et al., 2006). Direct intramuscular injection of lentiviral vectors, carrying a mini-dystrophin-eGFP fusion transgene, into neonatal *mdx* mice leads to dystrophin-eGFP expression 2 years after injection and to morphological/physiological improvement. Satellite cells can also be stably transduced and thus contribute to long-term amelioration.

Gillian Butler-Browne (Institute de Myologie-INSERM, Paris, France) reminded us of the major problems associated with cell and/or gene therapy. Her work aims to compare the different cell types that are currently proposed for cell therapy. She presented the generation of immortalized human myogenic cells that have overcome replicative aging, in collaboration with Woodring Wright (Southwestern Medical School, Dallas, TX) (Zhu et al., 2007). She also discussed the impressive reconstruction results obtained in her lab from the transplantation of human-derived AC133 cells into immunodeficient mice (Torrente et al., 2004). The transplanted cells show high myogenicity, can migrate almost the whole distance of the tibialis muscle and can repopulate the satellite cell pool.

Conclusion

Over the last 45 years, our understanding of satellite cell biology has evolved gradually. But with the advent of genetic and molecular tools, an explosion of new information has propelled the field forward during the last decade in new and unexpected ways. Without question, many of the novel results on the biology of satellite and stem cells in muscle growth and repair that were presented at this meeting, point to exciting new avenues of research that will be fruitfully explored in the coming years.

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