The Role and Activation of Myosatellite Cells in Muscle Regeneration

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Introduction:

Myosatellite cells were first seen under an electron microscope in frog and rat muscles. Later on, other vertebrates were studied to investigate the activity of satellite cells in a variety of organisms. Muscle regeneration is dependent on satellite cell activation and re-entrance into the cell cycle. Satellite cells are considered to be stem cells because of their ability to self-renew and differentiate. Pax3 and Pax7 are transcription factors that regulate satellite cell proliferation.

Future studies investigating the myogenic qualities of satellite cells to incorporate into other healing methods.

Myosatellite Cells:

Myosatellite cells were first discovered in 1961 by Alexander Mauro and Bernard Katz. These cells were observed in frogs, rats, and other vertebrates. It was later concluded that myogenic cells were necessary for myofiber growth and repair throughout one's life [7]. Further studies with satellite cells indicate that myogenic cells are responsible for growth and repair postnatally in skeletal muscles. Myogenic stem cells are located between the myofiber plasmalemma and basal lamina in postnatal life. Myofibers are multinucleated muscle fibers that are formed during embryogenesis when myoblasts transition into immature myofibers.The nuclei of myofibers cannot produce additional nuclei through multiple proliferative states [1].

In the human body, around 35 - 45% of its total mass consists of striated skeletal muscle, making it the most abundant tissue in the body. Skeletal muscles are unique from other cell types. Interiorly, they contain myofibrils that have actin and myosin filaments acting together to produce a muscle contraction [4]. In the juvenile phase of satellite cell growth, the enlargement of muscles promotes the proliferation of satellite cells and the addition of nuclei to the growing

myofibers. Satellite cells are unique in that they are typically dormant until activation through signals from the surrounding environment. Signals are usually invoked from a muscle injury, where the muscle needs to be repaired through the proliferation of satellite cells [1]. Pax3 and Pax7 are transcription factors and markers for myosatellite cell activity. Pax7 is expressed in all satellite cells in adult muscle, while Pax3 is expressed in specific areas of the body in lower levels [4]. Satellite cells are dormant until activation and are responsible for the growth and regeneration of muscle postnatally [9].

Satellite Cell Activation in Muscle Regeneration:

In resting muscles, satellite cells are dormant and only activated in times of trauma [8]. Minor injuries usually amount to minimal proliferation, while severe trauma to the muscle can encourage more satellite cells to gather and proliferate before differentiation. This response mechanism is necessary on a daily basis, since small muscle injuries can happen through one's regular routine. Muscle maintenance is essential throughout one's life. Signals from the muscle niche control satellite cell activation from their dormant state. An inflammatory response usually follows these signals to the affected area [1]. Once activated, satellite cells transition into proliferating myogenic cells with the ability to differentiate into different muscle types. They can fuse with pre-existing myofibers or form new myofibers [8]. The behavior of satellite cells is a highly regulated process with multiple checks and balances [1]. There is a combination of growth factors, niche variables, transcriptional regulator expression, and differentiation factors that influence the activation of satellite cells [8]. A balance between satellite cell dormancy, entry into the cell cycle, proliferation, and ultimate differentiation is required for muscle repair [1]. The complete loss of satellite cells would result in the entire loss of muscle regeneration [3].

Following an injury, satellite cells enter the cell cycle and rapidly proliferate [1]. Because of their high plasticity, skeletal muscles can be restored and function within a few weeks following an injury to the myofibers [4]. They produce myoblasts that connect and fuse to develop new muscle fibers. After the satellite cells repair the damaged area, new dormant cells are produced during muscle homeostasis [6]. Despite their dormant nature, satellite cells are always ready to enter the cell cycle upon activation. After an injury, the damaged tissue sends signals to activatethe satellite cells to migrate to the injured area. Once they arrive at the area of injury, they re-enter the cell cycle and begin to proliferate, turning into myoblasts. Myoblasts leave the cell cycle after the proliferation phase and enter the differentiation phase. Myoblasts transition into mature myocytes which fuse with each other to form myotubes or aid in repairing other damaged myofibers [4]. Because of their ability to self-renew and differentiate, they are considered tissue-specific stem cells and play an integral role in muscle health and regeneration [1].

Role of Pax3 and Pax 7:

Pax3 and Pax7 are transcription factors that are expressed by myosatellite cells [1]. In the diaphragm, over 80% of satellite cells express both Pax3 and Pax7. Tissue specification and organogenesis are dependent upon regulation from pax genes. Muscle fibers are interspersed with pax-positive cells before the cells assume their position under the basal lamina in muscle fibers [9].

In hindlimb muscles, there is no satellite cell expression of Pax3. Their expression as a molecular marker aided in the first observations of satellite cells through light microscopy [1]. Pax3 is not associated with specific embryonic origins or metabolism types, even though satellite

cells are generally correlated with muscles in certain regions of the body [2]. During embryogenesis, satellite cells express both Pax7 and Pax3 in limb and trunk muscles. Pax3 is not expressed during the development of head muscles. Satellite cells regularly express Pax7, but Pax3 is only found in certain muscle groups, such as the diaphragm. During adult muscle myogenesis, Pax3 expression is repressed by microRNA which halts the progression of differentiation [1]. Pax3 may be a factor remaining from embryogenesis when both Pax3 and Pax7 are expressed by myoblasts [4]. Myf5 is a myogenic determination gene that is activated by Pax3 to form skeletal muscles [9].

The deletion of Pax7 would result in satellite cells and myoblasts undergoing a halt in the cell cycle. There would no longer be a regulation in the myogenesis process. The continuous deletion of Pax7 would stop the growth and re-establishment of satellite cells expressing Pax7 [7]. This reduction in the number of satellite cells would result in a deficit in muscle regeneration, where the phenotype is similar to that of skeletal muscles genetically altered with the lack of satellite cells. Pax7 activates genes necessary for proliferation and differentiation through binding with specific DNA motifs [8]. The combination of a decrease in Pax7 and an initiation of myogenin target differentiating myoblasts and promote withdrawal from the cell cycle [1].

Effect of Exercise on Muscle Regeneration:

Muscle regeneration is a critical part of the healing process before, during, and after exercise. Myosatellite cells rebuild muscles damaged during workouts and aid in their regeneration. Necrosis of injured muscle fibers lead to degradation and increased permeability of the myofibers. IL-6 is a cytokine that is expressed by a variety of cell types and is usually produced in response to a signal from the immune system. Constant elevated levels of IL-6 contribute to decrease in muscle size in times of disease and aging. Exercise also causes elevated levels of IL-6 in muscle. Expression of the IL-6 receptor, IL-6Rα, is found on the myofiber sarcolemma and

responds to exercise. IL-6 promotes proliferation in satellite cells and results in the enlargement

of muscles [2]. Different exercises, such as endurance and strength training, can induce muscle hypertrophy to increase mass and overall strength. Resistance training in old age reduces the frequency of apoptosis in muscle cells and protects them from it in times where they would be more vulnerable [5].

Conclusion:

Myosatellite cells can remain dormant until activation through an inflammatory response of an injured area. Their ability to enter the cell cycle, proliferate, and differentiate make them unique cells in the body. Muscle regeneration and growth is dependent upon satellite cells for their unique capabilities.

Studies continue to investigate the capacity of myosatellite cells in muscle regeneration. Researchers are studying other cells with myogenic capabilities for whole body therapies. Further studies into the mechanisms involved could provide a more comprehensive picture as to whether increased numbers of satellite cells result from general muscle use and activity or as an effect of exercise. Satellite cell functions in adult life, especially in myofiber hypertrophy, could be studied further to determine if its role in myofiber growth extends past early postnatal life.

Reflection:

I feel that my contribution to the introduction and the “Satellite Cell Activation and Muscle Regeneration” section added valuable details to the preexisting information. There was little information surrounding the process of how satellite cells interact with each other and other molecular elements to rebuild muscle tissues. There was a small section on the effect of exercise and the function of satellite cells, but they did not fully capture the relationship between the role of satellite cells in muscle regeneration. My section focused on the interactions and processes that

satellite cells undergo to repair damaged muscles. Prior to my contribution, there were no images depicting any process of muscle regeneration. Attached to my section on satellite cell activation in muscle regeneration, I added an image depicting a schematic of a satellite cell transitioning into myofiber. In comparison to the earlier article, there was less information overall about the details of the process satellite cells undergo during muscle regeneration. The addition of my section highlights the muscle regeneration process on a molecular level and bridges the gap in understanding between some of the sections from the previous versions.

There was a heightened sense of pressure and importance in knowing that individuals besides my class would be viewing my work. Knowing that the information I would be putting on a public platform would be viewed and trusted by people motivated me to ensure that my work was the best quality it could be. I felt that there was a sense of purpose with this assignment in comparison to others. Other people could be relying on the information I provided in my contribution. I read over the information from my article and scanned for information I thought would contribute to a richer understanding of the topic. I saw basic information about the structure of satellite cells and their role in muscle regeneration, but there was not a detailed description of the molecular process of satellite cell activation. I felt that the original article laid out the basics about satellite cells well, but did not go into depth or build upon that foundation. Wikipedia can be used as a source to gain a basic understanding of a topic. It also serves as a reservoir of credible sources that contain more in-depth information about the topic if the reader wants to learn more. I feel that people should have a general idea about how their body works and the mechanisms behind it. Wikipedia could serve as a source for people to simply learn more about themselves biologically. There is a lot of fear of the unknown but exposure and knowledge about different topics can help make them less scary. People should be informed about their

bodies so the next trip to the doctor's office will not be as nerve-racking. I feel that knowledge is important for breaking down stigmas, alleviating fears, and being able to understand others better.

Through the Wikipedia article evaluation process, I learned that there are many checks and balances established to ensure that quality information is put on the website. I did not realize how much peer review and editing went into one article. When I critiqued my selected articles, I pretended that I was a reader with no background knowledge on the topic. I judged the articles based on my comprehension of the topic after reading it. If there were still some areas that I had questions on, I noted that in my feedback. After reading the feedback from my peers, I looked back at my own article and put myself in the same position as I did while reading theirs. For the most part, I agreed with their suggestions and made the appropriate edits.

For my peers, I usually recommended additional information about certain details or subtopics in their article. I felt that these additional details would enhance the overall understanding of the topic. For my own article, my peers recommended that I adjust my sentence structure to aid in the flow. Some of my sentences were too short and choppy while others were long and wordy. It was also recommended that I add images to highlight the key points of my article.

Although I did not receive feedback from other Wikipedia editors, I would have taken that information and critically analyzed my work with their suggestions. I would try to incorporate their new perspective and view my work with a new mindset. I would have made the appropriate changes to enhance clarity, understanding, and flow.

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