Satellite Cells– The Unsung Soldiers of the Skeletal Muscle

Ajoy Aloysius*
National Centre for Biological Sciences-TIFR, Bengaluru
Email: ajoybiotech2010@gmail.com

The need to lay low before the combat

In 2005, newspapers reported that a farmer from Mirzapur district (400km from Lucknow) wrote a letter to the President of India seeking permission to euthanize his four sons suffering from the disease Duchene muscular dystrophy. The poor father could not manage the four bedridden children who needed assistance for all their day- to- day activities. This is just one among the several stories about this genetic disorder in which patients and their families go through so much agony. This disease is caused by mutations in the dystrophin gene and leads to the production of a defective muscle protein, which is necessary for muscle strength and contractility. This results in the weakness of all skeletal muscles in the body. According to NIH, one in every 3500 males are affected by this and the number of females affected is relatively less. All the males having this disease are born healthy, but around the age of five muscle weakness begins to show when they get involved in rigorous physical activities. In adolescence, the patients are completely confined to wheelchairs and need assistance for practically everything. Parallel development of breathing problem and other medical complications lead to the demise of patients in their late teens or early 20s. The patients' parents and kin are subject to a lot of emotional trauma as they see the suffering first hand and feel helpless. To know how this genetic problem creates muscle wastage and subsequently leads to death, we should know how normal skeletal muscle is maintained in healthy people.

One of the most worked parts of our bodies whose contributions often go unnoticed in good healthis our skeletal muscle. They are indispensable for any movement in our bodies, ranging

---

* Mr. Ajoy Aloysius, Ph.D. Scholar from National Centre for Biological Sciences-TIFR, Bengaluru, is pursuing his research on "Muscle Stem Cells." His popular science story entitled "Satellite Cells - the Unsung Soldiers of the Skeletal Muscle" has been selected for AWSAR Award.

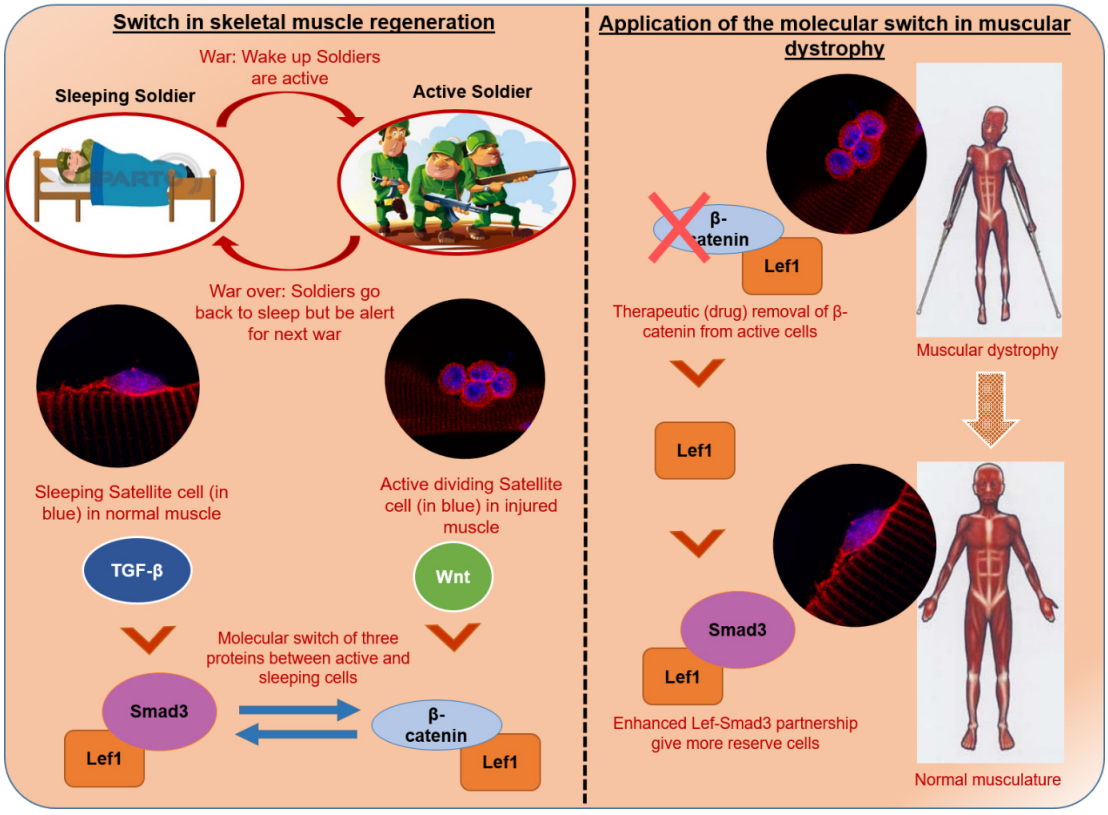
from the slightest twitch in the face when we smile or frown, to the extensive, sustained movement required for running a marathon. Skeletal muscles constitute 40% of our body mass, and face constant wear and tear due to continuous movement and injury. However, most of the time, we do not even feel the potential break down because our bodies have self-healing mechanisms that repair muscle tissue – a process called **muscle regeneration**. The heroes of this process are the Satellite cells- the muscle stem cells housed in little niches along the length of muscle fibres. To use an analogy, let's imagine thesesatellite cells as the soldiers protecting the country. They will be less active when there is no war but are always alert anticipating anemergency. Similarly, the Muscle Satellite Cells (MuSC) stay in a sleep-like quiescent stage as if silently waiting to be called in the event of an injury. Whenever there is an emergency situation, these soldiers are active in the field doing their duty. Likewise, apart from major traumatic injuries by accidents, even minor stretch injuries when we exercise our muscles by lifting weights in the gym are sufficient to send a wake-up call to the satellite cells. When called, they are activated and undergo cell division to replace the lost muscle in the injured tissue.

Once the emergency situation is over, the surviving soldiers go back to the resting state for rejuvenating themselves, which is essential for the active participation in forthcoming situations. Similar to this, some of these activated satellite cells go back into the dormant state, to replenish the stock of quiescent satellite cells which will be required to repair injuries in the future. While in this sleep-like state, the satellite cells do not multiply in number but keep the machinery ready to multiply whenever the signal comes.

So what happens in the muscular dystrophy condition? Let's go back to the soldier analogy again; imagine a situation where the war never stops and the soldiers don't have a choice but to keep fighting. They don't have time to go back to the resting phase and rejuvenation. The continuous activity tires them which reduces their performance, eventually leading to death and losing the battle. This is exactly the situation in muscular dystrophy, the genetic mutation in dystrophin makes this protein non-functional or completely absent in skeletal muscle. This makes the patient's muscle a never-endingbattlefield with frequent injuries, wear and tear. Our muscle soldiers, the satellite cells are active continuously to repair the injury. Because of the persisting injury, the satellite cells do not go back to the resting or quiescent state for self-renewal. This results in a reduction in their number and quality of performance. In the end, the patient's muscle weakens due to the deprivation of rejuvenated satellite cells, which ends up in muscle wastage. Hence, it is clear that this sleeping state is very critical for the performance of satellite cells. Thus an in-depth understanding of this quiescence state and the self-renewal of these satellite cells is crucial to devise strategies for combating muscular dystrophy.

How these satellite cells maintain the quiescent state is still not well understood. Prof. Jyotsna Dhawan's lab in CCMB, Hyderabad, mainly focuses on studying the mechanisms of quiescence. Interestingly, my researchin this lab found that there is a molecular switch inside the nucleus of the satellite cell that controls the switch between active and quiescent states.

We published the finding recently in ***Science signaling***. This molecular switch consists mainly of three proteins, specifically transcription factors that bind DNA and switches genes on and off.



These transcription factors are tightly regulated by external signalling cues. More specifically, in the activated satellite cells, transcription factor Lef1 partners with β-catenin which is controlled by the activation of the Wntsignalling pathway. This partnership turns on genes required for the active proliferation and terminal differentiation of these satellite cells to form muscle. When these active cells go back to the sleep state, the Wntsignalling pathway has to be turned off, leading to the absence of β-catenin. Hence Lef1 which was previously bound to β-catenin switches its partner to a different molecule Smad3. This is under the control of another signalling pathway called TGF-β. This Lef1-Smad3 transcription factor complex switches on genes required for the quiescence and self-renewal of satellite cells. Thus, the same molecule Lef-1 binds with different partners and controls the fate of satellite cells.

Surprisingly, our study also clearly showed that removal of β-catenin in activated satellite cells leads to the enhancement of Lef1-Smad3 partnership which makes these cells go back to quiescence and thus increasing their self-renewal ability. This is critical to ensure the reserve cells are there if required for future unpredictable bouts of repair study has shown one of the mechanisms which maintain the resting state in these satellite cells. As explained before, a major issue in the case of muscular dystrophies is the absence and/or reduction of these quiescent cells. Our findings have made it clear that switching Lef1-βcatenin to Lef1-Smad3 partnership will enhance the quiescence

and self-renewal of satellite cells. Further studies can be done to identify therapeutic strategies (possibly a drug) to enhance the molecular partnership of Lef1-Smad3 in the active satellite cells in muscular dystrophy patients. This will help return the cells to the quiescent state and can potentially improve muscle regeneration and reduce muscle wastage. Thus, the lifespan and quality of life of the patients can be improved. As of now, there is no cure for muscular dystrophy besides steroid treatment for improving muscle strength to a smaller extent which comes with large side- effects. Stem cell therapies are under clinical trial and will take years before actually being applicable. This research emphasizes that it would be impossible to find solutions to incurable ailments without delving into the details of how our cells function and thoroughly understanding the mechanisms behind them.