Profile of Se-Jin Lee

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In the late 1990s, Se-Jin Lee was exploring the effects of regulatory genes in mice when he found a gene with a remarkable phenotype (1). "These mice have a doubling of muscle mass throughout the body," says Lee. He had been identifying and characterizing new members of the TGF-β family of signaling proteins that he called growth/differentiation factors (GDFs) and had knocked out various GDFs in mice, including GDF8. "When we knocked it out, it turned out to have this hypermuscular phenotype," says Lee.

Lee renamed GDF8 "myostatin," and over the next two decades his laboratory went on to elucidate how it works. Lee has even sent myostatin-knockout mice to the International Space Station to see how microgravity would affect them (2). Lee's work has shown that myostatin blocks muscle growth and its absence dramatically increases skeletal muscle mass. By targeting TGF-β signaling in muscles, Lee has generated mice that had four times more muscle mass than normal (3). In addition, he reported the identification of naturally occurring myostatin mutations in double-muscled breeds of cattle, as well as in a heavily muscled child (4, 5).

Dysregulation of myostatin can lead to a variety of problems. For example, overexpressing myostatin in mice induces a muscle-wasting condition known as cachexia, which often results from cancer, AIDS, sepsis, and heart disease (6). Blocking myostatin in mice can mitigate muscle loss and improve muscle function in muscle-degenerative conditions, such as muscular dystrophy, as well as during aging. Lee has worked on harnessing myostatin inhibition to develop new treatments for patients with muscle-degenerative and muscle-wasting conditions.

Now a professor of genetics and genome sciences at the University of Connecticut Health Center and Jackson Laboratory, Lee was elected to the National Academy of Sciences in 2012. In his Inaugural Article (7), Lee describes his latest research on TGF-β signaling in muscles.

Se-Jin Lee. Image credit: Charles Camarda (photographer).

Interest in Regulatory Proteins

Lee's first real foray into science occurred when he had to declare an undergraduate major at Harvard University. "I was interested in chemistry and interested in medicine, and so I thought biochemistry would be a good major to pursue, despite not really even understanding what biochemistry was, to be honest," says Lee. It proved to be a good launchpad, as his burgeoning interest in the chemical and biological sciences spurred him to pursue an MD/PhD at The Johns Hopkins University.

Lee joined the laboratory of Daniel Nathans, who had recently won the Nobel Prize in Physiology or Medicine and was starting to work on the regulation of cellular genes. "It was just an absolutely tremendous learning experience interacting with Dan and watching how he approached science. The experience was completely transformative," says Lee. "He always said to work on something that you found interesting and important regardless of what anyone else thought," he says.

After his MD/PhD, Lee joined the Carnegie Institution of Washington in Washington, DC (now the Carnegie Institution for Science) as a staff associate. "I was used to being very independent and so I wanted

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to try this position where you would have a period of time to work completely independently," he says.

This was when Lee first decided to focus on the TGF-β superfamily of signaling molecules. At the time, 11 members of this family were known, and all had intriguing properties. "I thought that the family had to be bigger than that, and so I just went out and searched for new members of the family," says Lee.

This was before the human genome project, so Lee had his work cut out trying to identify other potential family members. "I spent a lot of time just making guesses and fishing for these proteins," says Lee. He named the first one he found growth differentiation factor 1, or GDF1. "I was optimistic enough to think that I was going to find a bunch more," says Lee.

Therapeutic Potential of Myostatin

After two and a half years at the Carnegie Institution, Lee joined The Johns Hopkins University as a faculty member and continued the search for GDFs. He soon found a dozen more, including the landmark discovery of GDF8, or myostatin.

Over the next several years, Lee would try to uncover not only myostatin signaling but also its potential therapeutic applications. "We were excited from the very beginning for the possible applications that it might have for improving human health," says Lee. "I tried to keep our focus on really understanding at a very detailed molecular level how myostatin works, how it's regulated, and how it signals so that we can figure out the best ways to manipulate the system for applications," he says.

Lee says several companies, including pharmaceutical firms such as Pfizer, Novartis, and Eli Lilly, have taken myostatin inhibitors into clinical trials. He says there have been phase 2 or 3 trials for a wide range of conditions, including muscular dystrophy, cancer, diabetes, lung disease, and kidney disease.

Patients with genetic diseases such as muscular dystrophy experience muscle degeneration that can lead to shortened life expectancy. In addition, many diseases, such as cancer, heart failure, and kidney failure are associated with the wasting syndrome cachexia. "Cachexia is reported to be the major cause of actual mortality in patients with cancer," says Lee. Muscle loss also occurs as a result of disuse in those who are bedridden or in wheelchairs, as well as in the elderly. "So anything we could do to improve muscle strength and muscle mass would potentially be very helpful in lots of disease settings," he says.

So far, however, no myostatin inhibitors have received clinical approval. "Even though in mice we can get really dramatic effects, in humans the effects have been less dramatic," says Lee. He thinks the reason may be that factors beyond myostatin are at play. "I think the key will be broadening the specificity of these inhibitors," says Lee.

Over the years, Lee has elucidated many components of the TGF-β signaling pathway in muscle, including receptors that myostatin binds to—ACVR2 and ACVR2B—and the role of a TGF-β family member called activin and the protein follistatin, which binds to both myostatin and activin (3, 8). He also showed that myostatin normally exists in an inactive complex with part of its precursor protein and that myostatin is activated from this latent state by specific proteases (8, 9).

Lee says a few studies have tested agents in mice that affect more components of the pathway than just myostatin. "What's clear is that if you block more than myostatin, you get a larger effect," says Lee. He's hopeful about the therapeutic potential of these inhibitors. "I still remain quite optimistic because I think it's just a matter of harnessing the capability of growing muscle through this pathway while at the same time avoiding other potentially detrimental effects."

Teasing Apart TGF-β Signaling in Muscles

In 2017, Lee left The Johns Hopkins University to take up a joint position at the Jackson Laboratory and the University of Connecticut Medical School. He maintains a huge colony of genetically engineered mice and says he was excited to have access to the expertise and capabilities of Jackson Laboratory's world-renowned mouse facilities. "This was the perfect move for me to take that mouse work to another level."

Over the past several years, Lee has continued to elucidate the role of TGF-β family members and the receptors ACVR2 and ACVR2B in muscle signaling. He previously showed using in vitro studies that myostatin can bind to both ACVR2 and ACVR2B, which are referred to as type II receptors, and also that mice carrying mutations in ACVR2 or ACVR2B have increased muscling (8, 10). "That suggested that these are the receptors that are used for signaling," he says. "In 2012, we showed that you could block signaling, not in the muscle satellite cells but in the muscle fibers themselves and get the muscle to grow, which suggested that myostatin regulates muscle growth by signaling directly to the muscle fibers," says Lee (11).

All of these results culminated in Lee's Inaugural Article (7). "In [it] we showed much more definitively that the muscle fibers are all you need, because we targeted all the different receptor combinations just in the muscle fibers, and we got these pretty massive effects," he says. "So, in fact, myostatin signals directly to the muscle fibers to regulate growth," says Lee.

The study (7) also further explained the role of the receptors. "If you look at just the ACVR2 and ACVR2B receptors, we showed that targeting either one alone has a small effect, but if you target both of them together now you get this much more substantial effect," says Lee. "This of course has implications for finding a target receptor for drug development," he says. Lee also showed that two type I receptors, ALK4 and ALK5, were also involved in signaling in myofibers and that all four possible combinations of type II and type I receptors were important for muscle regulation in vivo.

In addition, Lee found that targeting this pathway in myofibers led to reduced overall body fat and improved glucose metabolism in mice, similar to effects

in mice completely lacking myostatin. "If you want to think about drug development, targeting muscle could, in and of itself, be a good way to go after a metabolic disease like obesity and type 2 diabetes," says Lee.

Lee's work has revealed how complex TGF-β signaling is in muscle. "There's lots of redundancy and cross-talk and then the family itself is huge," he says. "The nice thing is, there's a lot to figure out, so it'll keep us busy," says Lee. "For clinical applications, what it means is that there are lots of different ways to modulate signaling and fine-tune the system."

Lee is looking forward to the challenge of further deciphering this signaling pathway, hands-on. "The entire receptor story is one that I've been tracking personally at the bench for 20 years now," he says. "So it's particularly gratifying for me to get it to this point."

The years have not diminished Lee's passion for laboratory work. "I just love being at the bench, I love seeing the data come out in real time, moment by moment, and thinking about the implications," says Lee. "To me that's the exciting part of doing science."

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