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Tissue Engineering: a Potential Therapy for Anterior Cruciate Ligament Reconstruction

Rebecca Miller

Writer's Comment: After my horse tore a ligament and had to retire from competition, I became interested in soft tissue injuries and their capacity for healing, or lack there-of. Since then, I have been lucky enough to perform research in Dr. Keith Baar's laboratory, which has exposed me to the field of tissue engineering. So when Dr. Amy Clarke gave us the seemingly daunting task of writing a literature review on a health topic of our choice, I immediately knew my subject. ACL ruptures and their subsequent surgeries are common; however, the emerging science of bioengineered replacement ligaments remains largely unnoticed. Through my work in the lab, I have become acutely aware of many of the major pitfalls of the current surgical reconstruction options for ACL tears. As an aspiring orthopedic surgeon, I recognize the importance of finding a surgical option that will provide the patient with the best outcome. For this reason, I was compelled to write a review comparing the current surgical options with the potential use of engineered ligaments. I hope this review excites people about the research that is out there: Ligaments are being grown in the lab, and it's happening right here on our campus.

Instructor's Comment: My abiding image of Rebecca is this: on the day of oral presentations, as she taught a mini-seminar on the topic of her literature review, she pulled a small glass vial seemingly out of thin air. In it was a bioengineered anterior cruciate ligament, its size disguising the enormity of the achievement it represents. Rebecca works in the lab that created this prototype of what could become a standard of ACL reconstruction. As a future orthopedic surgeon, she might even use a version of this manufactured ligament to help those hobbled by ACL tears regain full function. It was certainly one of the best visual aids I'd ever seen a student use to underpin a presentation. But it is so like Rebecca that this little marvel of science took a backseat to her calm, absolutely clear discussion of the problems of ACL reconstruction and the role of bioengineering in addressing them. Her splendid literature review reflects her deep understanding of these problems

and, more than that, her ability to collate and condense the relevant research so elegantly.

– Amy Clarke, University Writing Program

Abstract

Anterior cruciate ligament (ACL) ruptures are common among active individuals. The avascular structure of ligaments prevents natural healing; therefore, reconstructive surgery is often performed. Current surgical options include use of either an autograft composed of the patient's hamstring tendons or bone-patellar tendon-bone complex (BPTB), or an allograft composed of a cadaver BPTB. Despite improvements in surgical techniques, many patients experience debilitating side effects, prompting the search for a superior graft. This paper evaluates the autograft and allograft methods, discussing the main drawbacks of each, and then presents two models of engineered ligaments that show potential as ACL replacements. Recent studies suggest that engineered ligaments have the capacity to overcome many of the major pitfalls of the autograft and allograft, encouraging further exploration of tissue engineering as an alternate therapy.

Keywords: ACL reconstruction; autograft; allograft; tissue engineering

Introduction

Injuries to the anterior cruciate ligament (ACL) are common in orthopedics, with roughly 200,000 cases presenting annually in the United States alone [1]. The ACL functions to limit anterior motion of the tibia with respect to the femur and is one of the most commonly injured ligaments in sports [2,3]. Due to the limited vasculature of ligamentous tissues, the ACL has little ability to heal on its own. Therefore, approximately 85% of all reported ACL ruptures undergo reconstructive surgery to restore functionality of the knee [1]. Additionally, roughly 1 in 5 athletes will require a second surgery due to re-rupture [3].

Current surgery options use either tissue taken directly from the patient (autograft) or tissue from a human cadaver (allograft) to replace and reconstruct the ruptured ACL. Whether one method is more effective remains a point of contention among surgeons. The autograft provides adequate strength, but nearly 50% of patients will experience some degree of donor site morbidity [4]. The allograft allows for quicker healing and eliminates the risk of donor site morbidity; however, it also has a significantly higher chance of re-rupture in active individuals [5]. Tissue engineering is emerging as a potential alternate therapy in response to these problems. The two leading models include a silk scaffold seeded with mesenchymal stem cells (MSCs) and a 3-D bone-ligament-bone construct (BLB). Successes in animal trials and promising similarities between the engineered grafts and native ACL tissue provide sufficient evidence to encourage tissue engineering as an alternate therapy. Engineered grafts show potential for reducing many of the debilitating risks associated with the current surgical options; therefore, further research is imperative.

Drawbacks of current therapies

Autograft

Donor site morbidity is the hallmark problem of the autograft, with greater than 50% of patients experiencing some form of pain or malfunction at the donor site [4]. The BPTB is generally preferred over hamstring tendons due to the intact interfaces with bone and decreased graft laxity [6,7]. However, problems at the donor site are inherent, such as osteoarthritis of the patellofemoral joint [4]. In a study performed by Seon et al., 43% of patients receiving BPTB autografts had developed degenerative osteoarthritis within 11 years. Additionally, 80% of patients were unable to perform at the same competitive level prior to injury [8]. Debilitating pain at the donor site is another serious problem. Breitfuss et al. performed a retrospective study with a two-year follow-up timeframe [4]. 61% of patients complained of pain at the donor site upon examination, while another 46% experienced functional pain when kneeling. Shortening of the patellar tendon is an additional risk, as over 70% of the previous cases experienced some degree of tendon shortening, ultimately leading to changes in mechanics [4]. Finally, patellar fracture is a potentially serious, albeit rare, complication [9]. While the BPTB provides adequate strength, donor site morbidity has the potential to cause devastating side effects.

Allograft

The allograft eliminates the risk of donor site morbidity, but does not come without negative side effects. An inherent risk in using any allograft is the potential for disease transmission. While uncommon, there have been incidences of viral transmission, including Hepatitis

C and HIV, bacterial infections, and in rare cases, septic arthritis [10]. BPTB allografts are γ-irradiated to decrease the potential for disease transmission and reduce the incidence of bacterial infection. However, when the long-term success of γ-irradiated allografts was compared with fresh-frozen allografts, the irradiated grafts showed a significant increase in laxity and an 8.8% failure rate [5,7]. The high failure rate suggests that γ-irradiation damages the allograft, rendering it less effective as an ACL replacement. This leaves only fresh-frozen allografts as a reasonable replacement option from a mechanics standpoint, but the risks of disease transmission and subsequent infection cannot be overlooked.

Tissue engineering

Tissue engineering involves the use of isolated host cells and sometimes the addition of scaffolds to regenerate a functional ligament. The drawbacks of the current ACL reconstruction options necessitate the development of an alternative therapy, and tissue engineering shows promising results.

Silk scaffold seeded with mesenchymal stem cells

Investigators are experimenting with the use of scaffolds as the basis of engineered ligaments, as scaffolds have the potential to provide adequate strength while the tissue regenerates. Silk is gaining attention as a scaffold material due to its biocompatibility, high tensile strength, and slow rate of degradation to accommodate tissue growth [2]. Previous use of silk scaffolds in small animal models has yielded encouraging results, but a large animal model can more adequately evaluate the stresses a human ACL undergoes [11,12]. Fan et al. have designed a regenerated ACL model using a braided silk scaffold seeded with porcine mesenchymal stem cells (MSCs). The basis for using silk as the scaffold lies in its superior tensile strength; it is capable of load bearing at the moment of implantation [2]. The MSC-seeded scaffold will ideally perform mechanically while the cells proliferate and differentiate, replacing the silk scaffold with their own collagenous matrix. This graft was implanted in a porcine model whereby the native ACL was excised and the experimental graft was inserted. After evaluation at 6 months postoperatively, the results were promising. The cells successfully proliferated and were distributed throughout the scaffold with minimal cell death, verifying silk's biocompatibility. Upon external observation, the experimental graft

resembled native ACL, as fibrous tissue had completely covered the scaffold and silk was no longer discernable. However, the maximal load only reached 52% of native ACL. Means of further strengthening the graft must be investigated before it can act as an ACL replacement. Despite this lowered maximal tensile load, the graft provides sufficient load bearing capabilities for daily activities. The ACL is loaded at only 20% of its maximum capacity under normal conditions, suggesting that this graft has satisfactory tensile properties to support a strong, stable knee joint during the initial recovery period [2].

Three-dimensional bone-ligament-bone constructs

Another method of tissue engineering excludes scaffolds, using only cells to form a 3-D bone-ligament-bone construct (BLB). Scaffold-less ligament models both in vitro and in small animal models prove physiologically similar to native ACLs, and their development is being pursued in larger animal models [13,14]. Ma et al. have designed one such construct using bone mesenchymal stem cells (BMSCs) isolated from sheep. BMSCs were cultured and differentiated until monolayers of bone and ligament-like cells formed [15]. Bone monolayers were placed on either end of a ligament monolayer, forming a 60-80 mm long BLB. Multiple BLBs were placed next to each other and fused until they reached about 3mm in diameter. The BLBs were implanted in sheep after the native ACLs were removed, and the grafts were analyzed after 2, 3, 4, and 6 months of implantation. The collagen fibers were longitudinally oriented, and the bone had a collagen-rich matrix. The graft grew to the size of a native ACL within 4 months of implantation. Tissue remodeling seen after 6 months in vivo suggests that mechanical stimulation improves regeneration [15]. Additionally, there was abundant vasculature and innervation. Tensile testing showed that the BLB maintained similar viscoelastic properties to that of a native ACL, and the maximum load of the graft could exceed the expected in vivo loads [15]. Ultimately, BLB constructs prove to be physiologically similar to native ACLs and present a valid replacement option for ACL reconstruction in the future.

Tissue engineering as a potentially superior therapy

The silk scaffold and BLB models represent two promising engineered ACL replacements, and their success thus far is encouraging. Engineered ligaments address the major pitfalls of both the autograft

and allograft. Donor site morbidity is avoided because grafts can be created in vitro with scaffolds and non-invasive cell sources such as BMSCs. BMSCs are immunosuppressive and promote tissue growth, making them an ideal cell source for regenerating ligaments [15]. These cells can be taken from an autogenic source without the problems of donor site morbidity, or from an allogenic source without the risk of transplant rejection. Allogenic BPTB grafts grew in popularity because they eliminated donor site morbidity; however, the risk of infection remains a cause for concern [7]. Engineered grafts address this problem as well.

Additionally, engineered ligaments create grafts that physiologically represent native ACLs. Engineered grafts can potentially regenerate bone-ligament interfaces. Furthermore, the mechanical properties of hamstring tendons and the patellar tendon differ from adult ACLs, for example in their viscoelasticity and stress-relaxation responses [15]. Engineered ACLs, on the other hand, can be designed as replicates of native ACLs, sharing the same biomechanics. The native ACL is designed to withstand physiological stresses placed on the knee and is vital in pivot movements [10]. The different functional requirements of hamstring tendons, patellar tendons, and ACLs could be responsible for some of the graft failure seen in both current types of surgeries [15]. Replacing a ruptured ACL with a graft that maintains the same biomechanical properties allows the graft to respond to physiological loads at the knee appropriately, reducing the chances of re-rupture. The possibility of creating a physiological and biomechanical replicate of the native ACL makes engineered ligaments a compelling option for ACL replacement.

Conclusion

Tissue engineering shows potential for overcoming the drawbacks associated with the current graft options for ACL reconstruction. The high incidence of donor site morbidity, risk of infection, and high failure rate indicate the need for a superior therapy. The lack of immune response in current animal models suggests the possible use of allogenic sources such as BMSCs, eliminating the risk of donor site morbidity and drastically decreasing the risk of infections and rejection. Additionally, tissue engineering provides the opportunity to create a biomechanical replicate of a native ACL, further reducing the failure rate.

The preliminary successes of these engineered models encourage further research to overcome the challenges of designing a tissue-engineered alternative. The development of tissue of clinically relevant size, the potential of in vitro mechanical stimulation in bioreactors, and the maturation process of the engineered tissue must be explored further. In coming years, engineered ligaments could reduce the negative side effects of the current ACL surgical options, leading to better patient outcomes.

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Solar Agriculture: A Repeat of History

Raul Moya

Writer's Comment: The last essay assignment of my UWP 101 class challenged me to observe, analyze and comment on any location in California of our choosing. The location had to exhibit a conflict between urban and wild, and I saw this as an excellent opportunity to learn more about my hometown. I grew up in the High Desert, a triangular stretch of sparse land tucked between two mountain ranges. For me, the desert has always had a sort of rugged, wild appeal which grew the farther it got from any population centers. Over time, as more and more people came to the High Desert, the cities got bigger, and so did their energy needs. The constant sunshine that characterizes the desert enabled the development of massive solar farms that now encroach upon untouched lands. This contrast between the wild spaces of the desert and the urban expansion of solar farms provided the perfect backdrop to my essay, and so I delved into the various historical, technological and environmental variables that comprise the continual conflict between development and conservation that exists in the High Desert and California as a whole.

Instructor's Comment: The students in section 29 of UWP 101 in Fall 2014 persisted through pretty adverse conditions: the class met for three hours at a stretch, met at night, met only once a week, even skipping one week for Veteran's Day. To make things worse, the instructor (that would be me) set up a writing project in which those same hardy students wrote a series of components of a single long essay that only came into being in the process of writing. And each student had to actually visit and care about the place – the contested ground – that was his or her subject. That "caring about" that makes for good writing is often the hardest thing for students who are working so hard in so many arenas. But it came naturally to Raul. In the very first draft of the descriptive component of his essay, his deep affection for the place he grew up, and his equally deep distress at what is happening there, was evident. But merely expressing his own concerns would not have made this the essay that it is. Raul's ability to give equal care to considering the legitimate concerns driving the very changes he laments creates an essay that