Knee Surgery, Sports Traumatology, Arthroscopy
https://doi.org/10.1007/s00167-018-5182-1

KNEE

Cells, soluble factors and matrix harmonically play the concert of allograft integration

Laura de Girolamo[1] · Enrico Ragni[1] · Magali Cucchiarini[2] · Christian J. A. van Bergen[3] · Ernst B. Hunziker[4] · Susanna Chubinskaya[5]

Received: 6 August 2018 / Accepted: 20 September 2018

Abstract
Implantation of allograft tissues has massively grown over the last years, especially in the fields related to sports medicine. Beside the fact that often no autograft option exists, autograft related disadvantages as donor-site morbidity and prolonged operative time are drastically reduced with allograft tissues. Despite the well documented clinical success for bone allograft procedures, advances in tissue engineering raised the interest in meniscus, osteochondral and ligament/tendon allografts. Notably, their overall success rates are constantly higher than 80%, making them a valuable treatment option in orthopaedics, especially in knee surgery. Complications reported for allografting procedures are a small risk of disease transmission, immunologic rejection, and decreased biologic incorporation together with nonunion at the graft-host juncture and, rarely, massive allograft resorption. Although allografting is a successful procedure, improved techniques and biological knowledge to limit these pitfalls and maximize graft incorporation are needed. A basic understanding of the biologic processes that affect the donor-host interactions and eventual incorporation and remodelling of various allograft tissues is a fundamental prerequisite for their successful clinical use. Further, the importance of the interaction of immunologic factors with the biologic processes involved in allograft incorporation has yet to be fully dissected. Finally, new tissue engineering techniques and use of adjunctive growth factors, cell based and focused gene therapies may improve the quality and uniformity of clinical outcomes. The aim of this review is to shed light on the biology of meniscus, osteochondral and ligament/tendon allograft incorporation and how collection and storage techniques may affect graft stability and embodiment.
Level of evidence V.

Keywords Allograft · Meniscus · Tendon · Cartilage · Integration · Cytokines · Inflammation · Irradiation · Deep-freezing · Scaffold

✉ Enrico Ragni
enrico.ragni@grupposandonato.it

Laura de Girolamo
laura.degirolamo@grupposandonato.it

Magali Cucchiarini
mmcucchiarini@hotmail.com

Christian J. A. van Bergen
cvanbergen@amphia.nl

Ernst B. Hunziker
ernst.hunziker@dkf.unibe.ch

Susanna Chubinskaya
susanna_chubinskaya@rush.edu

[1] IRCCS Istituto Ortopedico Galeazzi, Laboratorio di Biotecnologie applicate all'Ortopedia, Milano, Italy

[2] Center of Experimental Orthopaedics, Saarland University Medical Center, Homburg/Saar, Germany

[3] Department of Orthopedic Surgery, Amphia Hospital, Breda, The Netherlands

[4] Departments of Osteoporosis and Orthopaedic Surgery, Inselspital (University Hospital), Bern, Switzerland

[5] Department of Pediatrics, Rush University Medical Center, Chicago, IL, USA

Published online: 05 October 2018

Introduction

Allograft tissues play a vital role in orthopaedic procedures, especially in knee surgery, where for many procedures, allograft reconstruction may be offered to the patient as an alternative to autograft tissue. In fact, allografts offer the advantages of decreased operative times and increased potential for additional surgeries and eliminate the clinical shortcomings associated with autograft harvesting such as limited availability of donor tissue and donor site morbidity [19].

Beside the most studied and characterized bone allografts, recent advances in tissue engineering have increased the interest in meniscus allografts, osteochondral allografts and ligament allografts. Meniscal tears are the most common knee injuries with an annual reported incidence of 60–70 per 100,000 persons [6, 38] and over 1 million surgeries performed annually in the USA [92]. Notably, meniscal allograft transplantation has a 95% success rate at a mean of approximately five years [63]. Further, a systematic review of clinical outcomes after osteochondral allograft transplantation in the knee reported a short-term complication rate of 2.4%, with an 82% overall success rate [16]. Altogether, these data show that allografts are a valuable treatment option in orthopaedics, especially in knee surgery. Finally, regarding ligaments, the incidence of the rate of rupture of the anterior cruciate ligament (ACL) is 200,000 cases/year in the USA [21]. Revision rates after ACL reconstruction showed for both allografts and autografts a very high and similar success rate (93% and 91%, respectively) 24 months after surgery [7].

Despite these similar outcomes, very little is known about the basic science of integration, remodelling and healing of allografts, crucial factors necessary to suggest clinical indications or contraindications. Ideally, a graft used for surgical reconstruction should be able to recreate the anatomical and biomechanical properties of the native tissues by guaranteeing safe fixation together with a rapid biological integration, quick recovery time and no donor site morbidity. It is, therefore, crucial to take into consideration that not all allograft tissues are alike, and different tissues behave uniquely in the biological niches of the human body.

The aim of the review was to analyse the existing biological knowledge for meniscus allografts, osteochondral allografts and ligament allografts to compare and identify shared or different biological processes and biomechanics. Notably, this work confirms that current procedures, although specific for each graft type, maintain in a similar fashion effective and safe biological activity of meniscal, osteochondral and tendon implants, and place these valuable tissues appropriately in the range of surgical choices to provide the greatest benefit to patients.

Meniscal allograft

The chances of meniscus healing are high when the tear is in the outer third of the meniscus, because the supply of blood is better at (red–red zone) or near (red-white) the outer edge. On the contrary, massive tears in the avascular zone of the meniscus (white–white) usually do not heal and lead to pain, swelling and locking of the knee. In the cases where a torn meniscus has been removed leaving minimal tissue remaining resulting in persisting symptoms, then meniscus transplantation is recommended and, although graft survival time has been reported to be limited between ten and 16 years, ameliorated patient-reported outcome measures confirm a crucial importance for this procedure in improving life quality [90].

For the transplant to succeed, the new meniscus must perform the same biological and mechanical functions of the original meniscus to stabilize and support the knee. Presence of viable donor cells is believed to readily sustain the graft extracellular matrix, therefore, leading to superior mechanical and structural features [94]. In this situation, to maintain the maximal viability and metabolic activity of the meniscal cells, procurement should take place as soon as possible and no longer than 12 h after death [79]. In case of storage over an extended period of time, deep-freezing techniques in the presence of cryoprotectants have been proposed [91], with percentage of cell survival up to 54% [34].

Briefly, after implantation, both donor cells and their DNA are either no longer detectable or are detectable in much smaller amounts than host cells and DNA. In goats, Jackson and colleagues observed that donor cells present in the grafts did not survive after 4 weeks [48]. In a rabbit model, medial menisci at 12 and 26 weeks after transplantation showed active collagen remodelling of the allografts coincident with revascularization and cellular repopulation [96]. The repopulation was explained by an increase in the expression of type I and III procollagen mRNAs at 12 weeks, especially near the region of the synovial capsule. Intriguingly, at 26 weeks, type I procollagen mRNA expression became prominent with only a small amount of type III procollagen, indicating the adaptation of the repopulating cells from the host to the allograft [96]. Such results corroborate the finding that, in dogs, reimplanted menisci were repopulated with cells originated from the adjacent synovium which were able to migrate over the surface of the meniscus to invade the deeper layers of the tissue [4]. Consistently, in humans, Debeer showed that, after 12 months, the DNA of the meniscal allograft was 95% identical to that of the recipient, demonstrating that the graft is almost entirely repopulated by host cells that seem to be derived from the synovial membrane [23]. Further, in humans at a mean of 16 months post-transplantation, meniscal and synovial membrane

biopsy showed the presence of viable cells with positive markers for synovial and fibroblast-type cells that appear to remodel actively the matrix since polarized light microscopy demonstrated evidence of active remodelling [76].

Another factor affecting tissue integration is the recipient's immune response against the donor cells, a major issue in graft transplantation [29]. Although considered an immunoprivileged tissue due to a low cell number within a dense environment of extracellular matrix, fresh meniscal allografts have been demonstrated to express class I and II histocompatibility antigens, which confer the potential for host immune response [52]. Moreover, the cancellous bone plugs often associated with meniscal allografts can trigger a robust host immune response similar to other forms of bone graft [59]. In rats, even if the immune response is not clearly detectable, as also observed in the sera of grafted mice [65, 66], histologic evidence of rejection was noted indicating important contribution of immune system in the transplant survival [95]. A popular method to reduce graft immunogenicity, and useful for long storage period, is deep-freezing, since donor cells can be destroyed together with denaturation of histocompatibility antigens [10]. The disadvantage of this technique is that the freezing process may damage the collagen net of the meniscus in terms of both the size and degree of disarray of the collagen fibril, possibly reducing the biomechanical properties [33]. Lyophilisation is another method to preserve the tissue although it also produces changes in the size of allografts, which may cause severe problems with graft sizing during transplantation [10]. Finally, gamma irradiation, often used to minimize the risk of disease transmission, may also compromise the material properties of the graft [10]. Due to all these issues, to date, fresh-frozen grafts are among the most widely used in clinical practice by virtue of their ease of preparation, non-immunogenicity and the possibility of applying secondary sterilization techniques. Supporting this choice, a recent meta-analysis on 2853 allografts clearly showed no significant difference in allograft survival at final follow-up between frozen and lyophilized/irradiated grafts [22].

Osteochondral allograft

Articular cartilage lesions, either focal defects or more diffused as in the early phase of osteoarthritis (OA), are generally difficult to reconstruct, mainly due to a lack of vascularisation that could provide regenerative progenitor cells to sites of damage. Nevertheless, despite the observation that chondral defects do not heal spontaneously, they may be induced by the use of appropriate carrier materials and signalling substances, to be repopulated by cells for repair that migrate from the synovial membrane to the lesion site [43, 45]. Osteochondral defects may become filled with a blood clot originating from the subchondral bone marrow that allows for the mobilization and osteochondro-differentiation of marrow progenitor cells, namely mesenchymal stem cells—MSCs [82]. However, the repair tissue in both types of lesions appears to be of fibrocartilaginous nature, predominantly containing type-I collagen versus smaller proportions of type-II collagen and cartilage-specific proteoglycans. The tissue does not have the re-establishment of an arcade-like organization of the fibrillar extracellular matrix (ECM) architecture nor a zonal stratification of the chondrocytes, and of poor biomechanical tissue quality relative to the original, hyaline cartilage, progressing to cartilage degeneration over time and ultimately to irreversible OA [12, 14, 42, 43, 67, 82].

Despite the availability of a number of surgical options including marrow-stimulating techniques, cell/tissue implantation such as autologous chondrocyte implantation, administration of MSCs either alone or in combination with scaffold, osteochondral transplantation or mosaicplasty, periosteal/perichondral grafts, and replacement surgery, none can reliably reproduce the natural integrity of the native cartilage adjacent to the lesions [24]. Osteochondral allograft transplantation remains to be a viable option for osteochondral repair, especially for large osteochondral and chondral defects, producing excellent long lasting results [56]. Bugbee defined a fundamental paradigm of osteochondral allograft transplantation: "viable chondrocytes of the graft survive storage and subsequent transplantation while maintaining their metabolic activity and sustaining their surrounding matrix to provide an intact structural and functional unit to replace diseased articular tissue" [13]. Therefore, the presence of viable chondrocytes is crucial to maintain tissue composition, structure, and function of the implanted graft and to maximize chances of long-term survival of the allograft, storage conditions must be manipulated to limit.

Currently, the preferred protocol for storage is graft harvesting within 24 h of donor demise and preservation at 4 °C to improve cartilage stiffness, cellularity and matrix content, and decrease surface degeneration [70]. Fresh allografts have consistent chondrocyte viability despite a limited shelf life. Several studies showed that chondrocyte viability is higher than 90% up to 8 days following harvest, although between 28 and 45 days this value drops down to less than 66% [56, 98]. As an alternative, frozen grafts have a prolonged storage time despite reduced chondrocytes viability. To avoid this, cryoprotectants, such as glycerol, DMSO (dimethyl sulfoxide) or ethylene glycol, are often used in the freezing process although being far to give results comparable to fresh grafts [31]. DMSO appeared to be the most effective facilitating recovery of approximately 15% of the chondrocyte viability [49]. However, these chemicals have the disadvantage of being not evenly distributed across the depth of the graft resulting in unequal freezing patterns [49,

68]. Finally, a physiological temperature of 37 °C has also been proposed for storage [31, 69]. In this conditions, a two/three-fold increase over fresh techniques has been scored, with > 70% chondrocyte viability for at least 8 weeks after harvest [31]. Importantly, graft quality measurements were not different from controls stored at 4 °C [31]. Another study supported these findings showing > 80% chondrocyte viability at 37 °C compared to 45% for grafts preserved at 4 °C at 4 weeks [69]. To date, independently from the storage approach, the average time from procurement to implantation of an osteochondral allograft is 24 days and ranges from 15 to 43 days [69] and in a goat model, chondrocyte viability, histology, equilibrium aggregate modulus, proteoglycan content, or hypotonic swelling of the implanted fresh osteochondral allograft did not differ significantly based on pre-implantation storage time between 1 and 42 days [75].

Beyond storage, various factors and mechanisms have been described to impact/limit repair tissue integration in cartilage lesions in vitro, including alterations in the chondrocyte phenotype and cell death processes and the presence of factors that inhibit adhesion/integration or promote tissue inflammation. Processes of cell apoptosis and necrosis that may impair tissue integration have been demonstrated in articular chondrocytes in a region of cell death with empty lacunae and loss of metachromasia in the ECM at the interface between and within the repair tissue and adjacent host cartilage during spontaneous, graft-associated, or scaffold-guided repair [44, 72, 82, 87]. Such processes may potentially hinder further the intrinsic limited capacity of the cells to migrate to interface areas [80] while leading to the production of inflammatory cytokines (interleukin 1—IL-1, tumour necrosis factor alpha—TNF-α, nitric oxide—NO) and of matrix degrading enzymes (matrix metalloproteinases—MMPs) that affect tissue repair [26, 58]. Alterations of the chondrocyte phenotype with an abnormal production, turnover, crosslinking, deposition, and orientation of ECM components are also critical cellular features associated with impaired cartilage repair and integration, subsequently leading to the formation of a tissue of lesser biomechanical quality [2, 25, 43]. Finally, there is also strong evidence that a number of ECM and joint compounds have the capacity to impede tissue adhesion in cartilage repair mechanisms such as proteoglycans (aggrecan, decorin, biglycan) and lubricin/proteoglycan 4 [8, 74, 77].

Another crucial risk affecting integration and being potentially fatal is given by infection, although exceedingly rare. Clostridium contamination risk rises with the delay occurring between donor death and tissue acquisition [50]. In US, the American Association of Tissue Banks (AATB) released safety guidelines concerning donor screening, serologic, viral, and bacterial testing together with procurement and storage requirements [64]. To improve the safety of allograft use, both banks and surgeons are bound to keep tracking information and report any allograft-related infection [39].

Though excellent results have been reported, integration of implanted osteochondral allograft with surrounding host osseous and cartilage tissue remains an issue also in vivo. For example, Pallante-Kichura et al. [71] described a wide spread of bone cysts and altered bone structures in the joints that received osteochondral allografts in adult Boer goats. This, though, can be species-specific as there is not much literature on cyst formation after osteochondral allograft transplantation in other species or humans.

To address host tissue integration, a few technical improvements and supplemental treatment options have been tested in vitro and in animal models in vivo, but not much has been translated in to clinical settings. One technical improvement is the graft insertion technique. Numerous studies have shown [13, 35, 51] that the impact used to insert the graft generates impulses sufficient to cause cell death and apoptosis followed by matrix degradation and eventual graft failure. Another possible improvement is the use of bone marrow aspirate concentrate (BMC) and platelet rich plasma (PRP) to repopulate the osseous portion of an osteochondral allograft with cells and deliver osteogenic proteins [85]. PRP and BMC, with their array of bioactive factors, are supposed to improve cartilage regeneration, bringing stem cells and growth factors to the site of injury. Stoker`s group showed, in dogs, that BMC and (with a lower efficacy) PRP provide a superior osseous integration, potentially due to the ability of viable cells to repopulate both the surface and deep areas of the graft osseous portions. These cells exhibit a robust and sustained capability to produce osteoinductive proteins such as osteoprotegerin, to increase bone mineral density and bone volume, as well as to produce bone morphogenetic protein 2, known to stimulate osteogenesis. An ability of viable cells, both chondrocytes and progenitor cells, to repopulate cartilage surface was also observed using Agili-C scaffold (CartiHeal, Israel). In an equine model of micro fracture, BMC was able to consistently improve collagen orientation and collagen type II content, including the formation of a hyaline-like repair tissue [30]. Therefore, allografts augmented with BMC or PRP in the osseous portion of the graft might be a promising new option to minimize treatment failures, to improve graft survivorship and integration, and thus patient outcomes.

Tendon allograft

The use of allogenic tendon tissues is more common in the United States than in other parts of the world and offers several possible advantages compared to autografts, e.g., a reduced operative time, avoidance of donor site morbidity, and possibly faster postoperative recovery [15, 27].

Possible disadvantages include a risk of disease transmission, immune rejection, delay in the remodelling and integration processes, and increased costs [15]. Several graft sources are available, including patellar, semitendinosus and Achilles tendons [27]. In theory, allograft tendons can be used for the treatment of many tendinous or ligamentous lesions. However, the literature of allograft tendon use is almost solely dedicated to anterior cruciate ligament (ACL) surgery, with some exceptions such as rotator cuff surgery [15, 46, 86].

Compared with autograft ACL reconstruction, allograft incorporation proceeds with a similar but slower progression [27, 47], with three biological stages: first, an early and acute inflammatory process with ischemic necrosis and no detectable revascularization; then, cell recruitment and chronic inflammation with revascularization, proliferation and collagen remodelling; and finally, a ligamentization phase.

After release of the tourniquet, the knee is readily filled with blood, generating an acute inflammatory response. Within the forming fibrin clot, platelets aggregate and degranulate [36, 84]. Released transforming growth factor-β1 (TGF-β1) attracts neutrophils and monocytes at about 24–48 h after operation [57], inducing them to generate chemokines and additional components of the pro-inflammatory cytokine cascade, including TNF-α, interleukin-1 (IL-1) and platelet-derived growth factor (PDGF). After these early events, until the fourth post-operative week, necrosis increases mainly in the centre of the allograft [78]. Graft necrosis leads to a release of growth factors, which stimulate cell migration and proliferation as well as extracellular matrix synthesis and revascularization [99]. Mesenchymal cells, originating from the host synovial fluid or bone marrow, influx into the intra-articular portion of the allograft which act as a type I collagen scaffold [53, 54]. Donor cell survival is limited in time since donor DNA is replaced entirely by host DNA within 4 weeks [48].

Revascularization starts on the fourth post-operative week [78], progressing predominately from the infrapatellar fat pad distally and from the posterior synovial tissues proximally [89]. Angiogenesis is promoted by monocytes that provide nutrients and oxygen, a process enhanced by hypoxia and high local concentrations of fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF) and nitric oxide. Between 4 and 12 weeks, a strong proliferation phase is accompanied by changes in the extra-cellular matrix. Host fibroblasts and synovial cells repopulate the transplanted tendon after donor fibroblast necrosis during the early phase, and remodel the provisional matrix responding to IL-1, PDGF, and TGF-β [18, 55, 62]. IL-1 produced by macrophages, fibroblasts, and neutrophils induces matrix metallo-proteinases (MMP-1, -3 and -13) to initiate the degradation of collagen fibrils at neutral pH [55, 88]. In a second step, MMP-2, MMP-3, and MMP-14 mediate both collagen degradation and remodelling [83]. MMPs also process cytokines, matrix and adhesion molecules to generate biologically active fragments as regulatory molecules [17]. Further, PDGF and TGF-β, released by degranulation of platelets alpha granules, contribute to increased fibroblast proliferation and production of collagens I, III, and V, proteoglycans, fibronectin and other extracellular matrix components to generate a connective tissue scar [28]. Of note, increased collagen III synthesis (with lower mechanical strength than type I collagen), together with the loss of the original large-diameter collagen fibrils in favour of smaller-diameter fibrils may explain the reduced mechanical strength of the graft versus the intact tendon [47, 78].

From 12 weeks onwards, tendon allograft continuously remodels towards the morphology and mechanical strength of the intact/original tendon or ligament and reaches its maximum properties at around 1 year. Collagen fibres regain their organization, although the heterogeneous composition of collagen fibres of varying diameter of the intact ACL is only partially restored [1]. Cellularity slowly returns to values of the intact tendon between 3 and 6 months with vessels becoming evenly distributed throughout the entire graft at 12 months [78, 89], although the central portion of the graft remains essentially acellular [61].

Fresh tendon allografts have been shown to stimulate an immunologic reaction after implantation in the host, with lymphocyte invasion, hyperaemia, and rejection [5], probably because of the expression of major histocompatibility markers on the surface of viable allograft tendon cells [27]. Fresh allograft tendons have been, therefore, basically abandoned. Freezing the graft alters the major histocompatibility complex and leads to cell death, without altering the structural and mechanical properties [27]. Thus, deep-frozen nonviable grafts are more suitable than fresh tendons because host rejection is a rarity [60]. This also because no histological differences (architecture, fibre orientation, matrix, cell infiltration, fibroblast proliferation, edema and vascularization) between the fresh and frozen samples have been noted [11]. However, a more occult response in frozen grafts might cause the delayed incorporation and ultimately graft failure [3]. Mineralization and trypsinization of freeze-dried allograft tendon has been shown to alter the interface from tendon to bone into mineralized tendon to bone, which may facilitate tendon-to-bone junction healing following tendon or ligament reconstruction [73].

In the preparation process, allograft tendons are usually sterilized and irradiated to inactivate bacterial and viral pathogens. The effect on graft incorporation is not fully understood but there are indications that high doses of gamma irradiation (> 2.5 Mrad) have adverse effects on the biological and mechanical properties of the allograft with respect to autograft (30% average decrease in load to failure) [20, 32, 81, 97], prompting the use of multiple stranded tendons to increase

the mean peak load to failure [93]. However, irradiation of allograft semitendinosus did not alter tendon-to-bone integration in a rabbit ACL model [9]. In addition, the irradiation method and dose also affect tendon properties [41]. For example, fractionation of irradiation doses has led to improved viscoelastic and structural properties of patellar tendons [40] and flexor digitorum superficialis tendons [97]. Similarly, low dose (1.5–1.8 Mrad) gamma irradiation does not significantly affect the failure load of either single stranded or double stranded tibialis tendon grafts [37].

Conclusions

Proposed data confirm that allografts can be effective in response to patients' clinical, biological and functional demands. Limitations in current knowledge on the host-graft interaction stem from the following: 1) notion that "often allograft works"; 2) reported cases on allograft failure usually address technical, graft or patient related issues, and not the integration aspects; 3) retrieved biopsies of failed allograft are small in size and normally do not contain host/graft interplay regions; 4) patients with well-performing grafts typically do not undergo imaging assessment of graft-host integration; 5) large animal studies are expensive, especially if require long-term follow-up, and finally, 6) limited funding opportunities exist to research the mechanisms of graft integration. Many biological issues such as chemical composition, incorporation, remodelling and immune responses are still to be further assessed. It clearly emerges that cell types, growth factors and cytokines are involved in a coordinated manner during the early inflammatory and further remodelling phases. A better understanding of the complex biological events occurring at the host-implant interface will at last lead to improved biologically-driven design strategies for allogeneic implants.

Author contributions LdG, ER, MC, CJAvB, EBH and SC have been involved in drafting the manuscript and revising it critically. All authors read and approved the final manuscript.

Funding No funding has been received for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Abe S, Kurosaka M, Iguchi T, Yoshiya S, Hirohata K (1993) Light and electron microscopic study of remodeling and maturation process in autogenous graft for anterior cruciate ligament reconstruction. Arthroscopy 9:394–405
2. Ahsan T, Sah RL (1999) Biomechanics of integrative cartilage repair. Osteoarthr Cartil 7(1):29–40 **(review)**
3. Arnoczky SP (2006) The biology of allograft incorporation. J Knee Surg 19(3):207–214
4. Arnoczky SP, DiCarlo EF, O'Brien SJ, Warren RF (1992) Cellular repopulation of deep-frozen meniscal autografts: an experimental study in the dog. Arthroscopy 8(4):428–436
5. Arnoczky SP, Warren RF, Ashlock MA (1986) Replacement of the anterior cruciate ligament using a patellar tendon allograft. An experimental study. J Bone Jt Surg Am 68(3):376–385
6. Baker BE, Peckham AC, Pupparo F, Sanborn JC (1985) Review of meniscal injury and associated sports. Am J Sports Med 13(1):1–4
7. Barber FA, Cowden CH 3rd, Sanders EJ (2014) Revision rates after anterior cruciate ligament reconstruction using bone-patellar tendon-bone allograft or autograft in a population 25 years old and younger. Arthroscopy 30(4):483–491
8. Bastiaansen-Jenniskens YM, Koevoet W, Feijt C, Bos PK, Verhaar JA, Van Osch GJ, DeGroot J (2009) Proteoglycan production is required in initial stages of new cartilage matrix formation but inhibits integrative cartilage repair. J Tissue Eng Regen Med 3(2):117–123
9. Bhatia S, Bell R, Frank RM, Rodeo SA, Bach BR Jr, Cole BJ, Chubinskaya S, Wang VM, Verma NN (2012) Bony incorporation of soft tissue anterior cruciate ligament grafts in an animal model: autograft versus allograft with low-dose gamma irradiation. Am J Sports Med 40(8):1789–1798
10. Binnet MS, Akan B, Kaya A (2012) Lyophilised medial meniscus transplantations in ACL-deficient knees: a 19-year follow-up. Knee Surg Sports Traumatol Arthrosc 20:109–113
11. Bitar AC, Santos LA, Croci AT, Pereira JA, França Bisneto EN, Giovani AM, Oliveira CR (2010) Histological study of fresh versus frozen semitendinous muscle tendon allografts. Clinics (Sao Paulo) 65(3):297–303
12. Buckwalter JA, Mankin HJ (1998) Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect 47:487–504
13. Bugbee WD, Pallante-Kichura AL, Görtz S, Amiel D, Sah R (2016) Osteochondral allograft transplantation in cartilage repair: graft storage paradigm, translational models, and clinical applications. J Orthop Res 34(1):31–38
14. Caplan AI, Elyaderani M, Mochizuki Y, Wakitani S, Goldberg VM (1997) Principles of cartilage repair and regeneration. Clin Orthop Relat Res 342:254–269
15. Cerulli G, Placella G, Sebastiani E, Tei MM, Speziali A, Manfreda F (2013) ACL reconstruction: choosing the graft. Joints 1(1):18–24
16. Chahal J, Gross AE, Gross C, Mall N, Dwyer T, Chahal A, Whelan DB, Cole BJ (2013) Outcomes of osteochondral allograft transplantation in the knee. Arthroscopy 29(3):575–588
17. Chandler S, Cossins J, Lury J, Wells G (1996) Macrophage metalloelastase degrades matrix and myelin proteins and processes a tumour necrosis factor-alpha fusion protein. Biochem Biophys Res Commun 228:421–429
18. Chang YC, Yang SF, Lai CC, Liu JY, Hsieh YS (2002) Regulations of matrix metalloproteinase production by cytokines, pharmacological agents and periodontal pathogens in human peridontal ligament fibroblasts cultures. J Peridontal Res 37:196–203
19. Chiarello E, Cadossi M, Tedesco G, Capra P, Calamelli C, Shehu A, Giannini S (2013) Autograft, allograft and bone substitutes in reconstructive orthopedic surgery. Aging Clin Exp Res 25(Suppl 1):S101–S103
20. Conrad BP, Rappé M, Horodyski M, Farmer KW, Indelicato PA (2013) The effect of sterilization on mechanical properties of soft tissue allografts. Cell Tissue Bank 14:359–366

21. Cooper JA, Sahota JS, Gorum WJ 2nd, Carter J, Doty SB, Laurencin CT (2007) Biomimetictissue-engineered anterior cruciate ligament replacement. Proc Natl Acad Sci USA 104:3049–3054
22. De Bruycker M, Verdonk PCM, Verdonk RC (2017) Meniscal allograft transplantation: a meta-analysis. SICOT J 3:33
23. Debeer P, Decorte R, Delvaux S, Bellemans J (2000) DNA analysis of a transplanted cryopreserved meniscal allograft. Arthroscopy 16:71–75
24. DiBartola AC, Everhart JS, Magnussen RA, Carey JL, Brophy RH, Schmitt LC, Flanigan DC (2016) Correlation between histological outcome and surgical cartilage repair technique in the knee: a meta-analysis. Knee 23(3):344–349
25. DiMicco MA, Sah RL (2001) Integrative cartilage repair: adhesive strength is correlated with collagen deposition. J Orthop Res 19(6):1105–1112
26. Djouad F, Rackwitz L, Song Y, Janjanin S, Tuan RS (2009) ERK1/2 activation induced by inflammatory cytokines compromises effective host tissue integration of engineered cartilage. Tissue Eng Part A 15(10):2825–2835
27. Eagan MJ, McAllister DR (2009) Biology of allograft incorporation. Clin Sports Med 28(2):203–214
28. Eppley BL, Woodell JE, Higgins J (2004) Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg 114:1502–1508
29. Farrar CA, Kupiec-Weglinski JW, Sacks SH (2013) The innate immune system and transplantation. Cold Spring Harb Perspect Med 3(10):a015479
30. Fortier LA, Potter HG, Rickey EJ, Schnabel LV, Foo LF, Chong LR, Stokol T, Cheetham J, Nixon AJ (2010) Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J Bone Jt Surg Am 92(10):1927–1937
31. Garrity JT, Stoker AM, Sims HJ, Cook JL (2012) Improved osteochondral allograft preservation using serum-free media at body temperature. Am J Sports Med 40(11):2542–2548
32. Gasimov E, Sabah D, Yilmaz O, Kececi B, Oktem G (2014) Experimental remodellation of extracorporeal irradiated autogenous and allogenic patellar grafts. Eur J Orthop Surg Traumatol 24(8):1539–1547
33. Gelber PE, Gonzalez G, Lloreta JL, Reina F, Caceres E, Monllau JC (2008) Freezing causes changes in the meniscus collagen net: a new ultrastructural meniscus disarray scale. Knee Surg Sports Traumatol Arthrosc 16:353–359
34. Gelber PE, Gonzalez G, Torres R, Garcia Giralt N, Caceres E, Monllau JC (2009) Cryopreservation does not alter the ultrastructure of the meniscus. Knee Surg Sports Traumatol Arthrosc 17:639–644
35. Gitelis SL, Bodker A, Laurent MP, Kirk SS, Filardo G, Meyer MA, Hakimiyan AA, Rappoport L, Wimmer MA, Cole BJ, Chubinskaya S (2018) The effect of surgical insertion and proinflammatory cytokines on osteochondral allograft survival and metabolism. Cartilage 9(3):284–292
36. Goodman RB, Pugin J, Lee JS, Matthay MA (2003) Cytokine-mediated inflammation in acute lung injury. Cytokine Growth Factor Rev 14:523–535
37. Greaves L, Hecker A, Brown C (2008) The effect of donor age and low-dose gamma irradiation on the initial biomechanical properties of human tibialis tendon allografts. Am J Sport Med 36(7):1358–1366
38. Greis PE, Bardana DD, Holmstrom MC, Burks RT (2002) Meniscal injury: I. Basic science and evaluation. J Am Acad Orthop Surg 10(3):168–176
39. Hinsenkamp M, Muylle L, Eastlund T, Fehily D, Noel L, Strong DM (2011) Adverse reactions and events related to musculoskeletal allografts: reviewed by the World Health Organisation Project NOTIFY. Int Orthop 36(3):633–641
40. Hoburg A, Keshlaf S, Schmidt T, Smith M, Gohs U, Perka C, Pruss A, Scheffler S (2011) Fractionation of high-dose electron beam irradiation of BPTB grafts provides significantly improved viscoelastic and structural properties compared to standard gamma irradiation. Knee Surg Sports Traumatol Arthrosc 19(11):1955–1961
41. Hoburg A, Keshlaf S, Schmidt T, Smith M, Gohs U, Perka C, Pruss A, Scheffler S (2015) High-dose electron beam sterilization of soft-tissue grafts maintains significantly improved biomechanical properties compared to standard gamma treatment. Cell Tissue Bank 16(2):219–226
42. Hunziker EB (1999) Articular cartilage repair: are the intrinsic biological constraints undermining this process insuperable? Osteoarthr Cartil 7(1):15–28 **(review)**
43. Hunziker EB (2002) Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthr Cartil 10(6):432–463
44. Hunziker EB, Quinn TM (2003) Surgical removal of articular cartilage leads to loss of chondrocytes from cartilage bordering the wound edge. J Bone Jt Surg Am 85-A(Suppl 2):85–92
45. Hunziker EB, Rosenberg LC (1996) Repair of partial-thickness defects in articular cartilage: cell recruitment from the synovial membrane. J Bone Jt Surg Am 78(5):721–733
46. Indelli PF, Dillingham MF, Fanton GS, Schurman DJ (2004) Anterior cruciate ligament reconstruction using cryopreserved allografts. Clin Orthop Relat Res 420:268–275
47. Jackson DW, Corsetti J, Simon TM (1996) Biologic incorporation of allograft anterior cruciate ligament replacements. Clin Orthop Relat Res 324:126–133
48. Jackson DW, Simon TM, Kurzweil PR, Rosen MA (1992) Survival of cells after intra-articular transplantation of fresh allografts of the patellar and anterior cruciate ligaments. DNA-probe analysis in a goat model. J Bone Jt Surg Am 74(1):112–118
49. Judas F, Rosa S, Teixeira L, Lopes C, Ferreira MA (2007) Chondrocyte viability in fresh and frozen large human osteochondral allografts: effect of cryoprotective agents. Transplant Proc 39(8):2531–2534
50. Kainer MA, Linden JV, Whaley DN, Holmes HT, Jarvis WR, Jernigan DB, Archibald LK (2004) Clostridium infections associated with musculoskeletal-tissue allografts. N Engl J Med 350(25):2564–2571
51. Kang RW, Friel NA, Williams JM, Cole BJ, Wimmer MA (2010) Effect of impaction sequence on osteochondral graft damage: the role of repeated and varying loads. Am J Sports Med 38(1):105–113
52. Khoury MA, Goldberg VM, Stevenson S (1994) Demonstration of HLA and ABH antigens in fresh and frozen human menisci by immunohistochemistry. J Orthop Res 12:751–757
53. Kleiner JB, Amiel D, Harwood FL, Akeson WH (1989) Early histological, metabolic, and vascular assessment of anterior cruciate ligament autografts. J Orthop Res 7:235–242
54. Kleiner JB, Amiel D, Roux RD, Akeson WH (1986) Origin of replacement cells for the anterior cruciate ligament autograft. J Orthop Res 4:466–474
55. Knauper V, Will H, Lopez-Otin C, Smith B, Atkinson SJ, Stanton H, Hembry RM, Murphy G (1996) Cellular mechanisms for human procollagenase-3 (MMP-13) activation: evidence that MT1-MMP (MMP-14) and gelatinase a (MMP-2) are able to generate active enzyme. J Biol Chem 271:17124–17131
56. LaPrade RF, Botker J, Herzog M, Agel J (2009) Refrigerated osteoarticular allografts to treat articular cartilage defects of the femoral condyles. A prospective outcomes study. J Bone Jt Surg Am 91(4):805–811
57. Leask A, Holmes A, Abraham DJ (2002) Connective tissue growth factor: a new and important player in the pathogenesis of fibrosis. Curr Rheumatol Rep 4:136–142

58. Lotz M (2001) Cytokines in cartilage injury and repair. Clin Orthop Relat Res 391:S108–S115 **(review)**
59. Lubowitz JH, Verdonk PCM, Reid JB III, Verdonk R (2007) Meniscus allograft transplantation: a current concepts review. Knee Surg Sports Traumatol Arthrosc 15(5):476–492
60. Mahirogullari M, Ferguson CM, Whitlock PW, Stabile KJ, Poehling GG (2007) Freeze-dried allografts for anterior cruciate ligament reconstruction. Clin Sports Med 26(4):625–637
61. Malinin TI, Levitt RL, Bashore C, Temple HT, Mnaymneh W (2002) A study of retrieved allografts used to replace anterior cruciate ligaments. Arthroscopy 18(2):163–170
62. Marui T, Niyibizi C, Georgescu HI, Cao M, Kavalkovich KW, Levine RE, Woo SL (1997) Effect of growth factors on matrix synthesis by ligament fibroblasts. J Orthop Res 15(1):18–23
63. McCormick F, Harris JD, Frank RM, Hussey KE, Wilson H, Gupta AK, Abrams GD, Bach BR, Cole BJ (2014) Meniscal allograft transplantation reoperation rates, operative findings, and survival analysis: a review of 200 consecutive transplants at minimum two-year follow-up. Orthop J Sports Med 2(1 Suppl):2325967114S00003
64. Mroz TE, Joyce MJ, Steinmetz MP, Lieberman IH, Wang JC (2008) Musculoskeletal allograft risks and recalls in the United States. J Am Acad Orthop Surg 16(10):559–565
65. Ochi M, Ikuta Y, Ishida O, Akiyama M (1993) Cellular and humoral immune responses after fresh meniscal allografts in mice. A preliminary report. Arch Orthop Trauma Surg 112:163–166
66. Ochi M, Ishida O, Daisaku H, Ikuta Y, Akiyama M (1995) Immune response to fresh meniscal allografts in mice. J Surg Res 58:478–484
67. O'Driscoll SW (1998) The healing and regeneration of articular cartilage. J Bone Jt Surg Am 80(12):1795–1812 **(review)**
68. Ohlendorf C, Tomford WW, Mankin HJ (1996) Chondrocyte survival in cryopreserved osteochondral articular cartilage. J Orthop Res 14(3):413–416
69. Pallante AL, Bae WC, Chen AC, Görtz S, Bugbee WD, Sah RL (2009) Chondrocyte viability is higher after prolonged storage at 37 °C than at 4 °C for osteochondral grafts. Am J Sports Med 37(Suppl 1):24S–32
70. Pallante AL, Görtz S, Chen AC, Healey RM, Chase DC, Ball ST, Amiel D, Sah RL, Bugbee WD (2012) Treatment of articular cartilage defects in the goat with frozen versus fresh osteochondral allografts: effects on cartilage stiffness, zonal composition, and structure at six months. J Bone Jt Surg Am 94(21):1984–1995
71. Pallante-Kichura AL, Cory E, Bugbee WD, Sah RL (2013) Bone cysts after osteochondral allograft repair of cartilage defects in goats suggest abnormal interaction between subchondral bone and overlying synovial joint tissues. Bone 57:259–268
72. Peretti GM, Campo-Ruiz V, Gonzalez S, Randolph MA, Wei Xu J, Morse KR, Roses RE, Yaremchuk MJ (2006) Tissue engineered cartilage integration to live and devitalized cartilage: a study by reflectance mode confocal microscopy and standard histology. Connect Tissue Res 47(4):190–199
73. Qu J, van Alphen NA, Thoreson AR, Chen Q, An KN, Amadio PC, Schmid TM, Zhao C (2015) Effects of trypsinization and mineralization on intrasynovial tendon allograft healing to bone. J Orthop Res 33(4):468–474
74. Quinn TM, Hunziker EB (2002) Controlled enzymatic matrix degradation for integrative cartilage repair: effects on viable cell density and proteoglycan deposition. Tissue Eng 8(5):799–806
75. Ranawat AS, Vidal AF, Chen CT, Zelken JA, Turner AS, Williams RJ (2008) Material properties of fresh cold-stored allografts for osteochondral defects at 1 year. Clin Orthop Relat Res 466:1826–1836
76. Rodeo SA, Seneviratne A, Suzuki K, Felker K, Wickiewicz TL, Warren RF (2000) Histological analysis of human meniscal allograft. A preliminary report. J Bone Jt Surg Am 82:1071–1082
77. Schaefer DB, Wendt D, Moretti M, Jakob M, Jay GD, Heberer M, Martin I (2004) Lubricin reduces cartilage–cartilage integration. Biorheology 41(3–4):503–508
78. Scheffler SU, Unterhauser FN, Weiler A (2008) Graft remodeling and ligamentization after cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 16:834–842
79. Schubert T, Cornu O, Delloye C (2010) Organization: type of grafts, conservation, regulation. In: Beaufils P, Verdonk R (eds) The meniscus. Springer, Berlin, pp 315–320
80. Secretan C, Bagnall KM, Jomha NM (2010) Effects of introducing cultured human chondrocytes into a human articular cartilage explant model. Cell Tissue Res 339(2):421–427
81. Seto AU, Culp BM, Gatt CJ Jr, Dunn M (2013) Radioprotection provides functional mechanics but delays healing of irradiated tendon allografts after ACL reconstruction in sheep. Cell Tissue Bank 14:655–665
82. Shapiro F, Koide S, Glimcher MJ (1993) Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. J Bone Jt Surg Am 75(4):532–553
83. Sharma P, Maffulli N (2006) Biology of tendon injury: healing, modeling and remodeling. J Musculoskelet Neuronal Interact 6(2):181–190
84. Singer AJ, Clark RA (1999) Cutaneous wound healing. N Engl J Med 341:738–746
85. Stoker AM, Baumann CA, Stannard JP, Cook JL (2017) Bone marrow aspirate concentrate versus platelet rich plasma to enhance osseous integration potential for osteochondral allografts. J Knee Surg 31(4):314–320
86. Tachiiri H, Morihara T, Iwata Y, Yoshida A, Kajikawa Y, Kida Y, Matsuda K, Fujiwara H, Kurokawa M, Kawata M, Kubo T (2010) Characteristics of donor and host cells in the early remodeling process after transplant of Achilles tendon with and without live cells for the treatment of rotator cuff defect–what is the ideal graft for the treatment of massive rotator cuff defects? J Shoulder Elbow Surg 19(6):891–898
87. Tew SR, Kwan AP, Hann A, Thomson BM, Archer CW (2000) The reactions of articular cartilage to experimental wounding: role of apoptosis. Arthritis Rheum 43(1):215–225
88. Tsuzaki M, Guyton G, Garrett W, Haas NP, Weiler A (2003) IL-1 beta induces COX2, MMP-1, -3 and -13, ADAMTS-4, IL-1 beta and IL-6 in human tendon cells. J Orthop Res 21:256–264
89. Unterhauser FN, Bail HJ, Höher J, Haas NP, Weiler A (2003) Endoligamentous revascularization of an anterior cruciate ligament graft. Clin Orthop Relat Res 414:276–288
90. van der Wal RJ, Thomassen BJ, van Arkel ER (2009) Long-term clinical outcome of open meniscal allograft transplantation. Am J Sports Med 37(11):2134–2139
91. Verdonk PC, Demurie A, Almqvist KF, Veys EM, Verbruggen G, Verdonk R (2005) Transplantation of viable meniscal allograft. J Bone Jt Surg 87(4):715–724
92. Verdonk PC, Verstraete KL, Almqvist KF, De Cuyper K, Veys EM, Verbruggen G, Verdonk R (2006) Meniscal allograft transplantation: long-term clinical results with radiological and magnetic resonance imaging correlations. Knee Surg Sports Traumatol Arthrosc 14(8):694–706
93. Vinagre G, Kennedy NI, Chahla J, Cinque ME, Hussain ZB, Olesen ML, LaPrade RF (2017) Hamstring graft preparation techniques for anterior cruciate ligament reconstruction. Arthrosc Tech 6(6):e2079–e2084
94. von Lewinski G, Wirth CJ (2010) Meniscal reconstruction: allograft. 10.1. Basic science. In: Beaufils P, Verdonk R (eds) The meniscus. Springer, Berlin, pp 303–315
95. Wada Y (1993) Meniscal transplantation using fresh and cryopreserved allografts. An experimental study in the genetically defined rat. J Jpn Orthop Assoc 67:677–683

96. Wada Y, Amiel M, Harwood F, Moriya H, Amiel D (1998) Architectural remodeling in deep frozen meniscal allografts after total meniscectomy. Arthroscopy 14(3):250–257
97. Wei W, Liu Y, Yang X, Tian S, Liu C, Zhang Y, Xu Z, Hu B, Tian Z, Sun K (2013) Fractionation of 50 kGy electron beam irradiation: effects on biomechanics of human flexor digitorum superficialis tendons treated with ascorbate. J Biomech 46:658–661
98. Williams RJ 3rd, Dreese JC, Chen CT (2004) Chondrocyte survival and material properties of hypothermically stored cartilage: an evaluation of tissue used for osteochondral allograft transplantation. Am J Sports Med 32(1):132–139
99. Yoshikawa T, Tohyama H, Katsura T (2006) Effects of local administration of vascular endothelial growth factor on mechanical characteristics of the semitendinosus tendon graft after anterior cruciate ligament reconstruction in sheep. Am J Sports Med 34:1918–1925