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Meniscal repair: The current state and recent advances in augmentation

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Abstract

Meniscal injuries represent one of the most common orthopedic injuries. The most frequent treatment is partial resection of the meniscus, or meniscectomy, which can affect joint mechanics and health. For this reason, the field has shifted gradually towards suture repair, with the intent of preservation of the tissue. “Save the Meniscus” is now a prolific theme in the field; however, meniscal repair can be challenging and ineffective in many scenarios. The objectives of this review are to present the current state of surgical management of meniscal injuries and to explore current approaches being developed to enhance meniscal repair. Through a systematic literature review, we identified meniscal tear classifications and prevalence, approaches being used to improve meniscal repair, and biological- and material-based systems being developed to promote meniscal

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AUTHOR CONTRIBUTIONS

Sonia Bansal, Edward R. Floyd, Suzanne A. Maher, and Jay M. Patel contributed to the introduction. Edward R. Floyd, Jorge Chahla, Robert F. LaPrade, and Jay M. Patel contributed to the clinical section. Sonia Bansal performed the systematic review. Michael Kowalski and Jay M. Patel contributed to the biologics section. Elizabeth Aikman, Philip Elrod, Kyley Burkey, and Jennifer L. Robinson contributed to the materials section. All authors contributed to the conclusions section, edited the manuscript, and approved the final version.

CONFLICT OF INTERESTS

Sonia Bansal is a consultant for AGelity Biomechanics Corp. Jorge Chahla received consulting fees from Smith & Nephew, Arthrex, Ossur, Linvatec Corp, and DePuy Synthes Products, and hospitality payments from Medical Devices Business Services Inc, Stryker Corp, and Medwest Associates. Robert F. LaPrade is a consultant for Arthrex, Ossur, Linvatec Corp, and Smith & Nephew, received royalties from Arthrex, Ossur, and Smith & Nephew, received research grants from Ossur and Smith & Nephew, and is on the editorial board of the AJSM, JEO, KSSTA. Suzanne A. Maher is a founder of AGelity Biomechanics Corp. Jay M. Patel is a consultant for NovoPedics Inc.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

healing. We found that biologic augmentation typically aims to improve cellular incorporation to the wound site, vascularization in the inner zones, matrix deposition, and inflammatory relief. Furthermore, materials can be used, both with and without contained biologics, to further support matrix deposition and tear integration, and novel tissue adhesives may provide the mechanical integrity that the meniscus requires. Altogether, evaluation of these approaches in relevant in vitro and in vivo models provides new insights into the mechanisms needed to salvage meniscal tissue, and along with regulatory considerations, may justify translation to the clinic. With the need to restore long-term function to injured menisci, biologists, engineers, and clinicians are developing novel approaches to enhance the future of robust and consistent meniscal reparative techniques.

Keywords

biologics; materials; meniscectomy; meniscus; repair

1 | INTRODUCTION

The menisci are fibrocartilaginous, crescent-shaped wedges located between the femoral condyle and tibial plateau of the knee joint that enable load transmission, stability, and lubrication.[1–4] The ability to withstand and distribute joint forces is attributed to its complex composition and organization. The menisci are comprised primarily of water, collagen, and proteoglycans (PGs),[5] with the majority of the dry weight being circumferentially oriented type I collagen fibers.[2,5] These fibers allow the meniscus to convert axial compressive stresses to circumferential hoop stresses,[6,7] preventing meniscal extrusion and rupture. The menisci also contain radial fibers, which interdigitate amongst the circumferential fibers to prevent their longitudinal splitting.[7–9] The inner third of the menisci, where compressive load predominates, is enriched with type II collagen and PG, exhibiting a more cartilage-like composition.[10] The low amount of vascularization and resident cells (meniscal fibrochondrocytes [MFCs]) in these inner areas,[11–13] especially with aging, decrease the endogenous healing capacity of the menisci following injury.[14]

Despite an elegantly complex structure and composition, meniscus injury is common, with an annual incidence of 66 tears per 100,000 persons.[15,16] To provide symptomatic relief from the mechanical irritation (catching, locking) of a torn meniscus, damaged tissue is removed in a procedure called meniscectomy, approximately 850,000 procedures of which are carried out in the United States annually. However, both partial and total meniscectomy result in increased cartilage contact stresses and these mechanical changes are known to accelerate joint degeneration and lead to osteoarthritis. Despite clinical concerns, meniscectomy is indicated as the treatment of choice for many meniscal tear conditions (e.g., complex, degenerative, avascular), and performed at a rate 5–25 times higher than meniscus repair.[17–19] While both meniscectomy and repair have similar short-term (<2 years) patient-reported outcomes, repairing the menisci better restores joint biomechanics and presumably confers a better long-term prognosis. While the ratio of meniscus repairs to meniscectomy remains low (~10%–15%), the prevalence of repairs has improved globally in the past decade.[17,19–22] As a sign of increasing awareness of the importance of meniscal preservation, the phrase “Save the Meniscus” has become a popular moniker: with 10

manuscripts in the past 10 years[23–32] featuring the phrase in their title, numerous conference proceedings, and a prolific social media handle (#savethemeniscus). Therefore, meniscus repair is clearly gaining in philosophical popularity, but given current limitations, it is not always physically possible or effective.

A multitude of factors influence this potential of meniscal repair. The geometry and location of the tear are highly influential in healing potential, yet the relative rates of types of tears are not readily available or consistent. Furthermore, augmentation of these repair environments has garnered much attention recently, both clinically and preclinically, to enhance and accelerate wound healing. A thorough review of model systems and outcome measures when evaluating these approaches is also lacking.

The goal of this review is to capture the current landscape of meniscus repair and augmentation strategies. We establish: (i) an examination of pertinent literature on meniscal tear classification and incidence rates, (ii) a systematic review on contemporary literature to highlight general trends, approaches, injury types, and models in meniscal repair, (iii) clinical techniques and advances to repair torn menisci, (iv) biologic- and biomaterial-based approaches being explored to augment the reparative process, and (v) model systems, considerations, and challenges for new augmentation procedures before clinical realization.

2 | MENISCAL TEAR CLASSIFICATION AND OBSERVED INCIDENCE

2.1 | Tear classification

Treatment type (meniscectomy vs. repair), method of repair, and healing potential are dependent on a variety of tear characteristics including type, orientation, location, size, and severity.[16,33] A number of classifications related to the shape and orientation of the tear exist: radial, longitudinal, horizontal, flap, bucket handle, complex/oblique, degenerative, and root tears (Figure 1). These tear types, and their prognoses, are discussed further in the Supporting Information. The location of the tear is often classified by circumferential axis position (anterior, body, posterior) and radial axis position (inner, middle, outer). The circumferential classification can have an impact on arthroscopic access, choice of suture repair technique, and stresses faced (greatest in posterior region). The radial classification is also crucial, as the microvasculature of the meniscus is concentrated around the periphery (red-red) and dissipates sharply toward the inner portion (white-white).[11] When not treated, smaller and more localized tears may progress to more substantial injuries; for example, radial tears can extend along the circumferential axis, progressing to oblique or parrot beak tears.

2.2 | Observed incidence

While studies reporting the incidence of meniscal tears exist, tears can be asymptomatic until they progress to a larger size. Identification of a meniscus tear using standard magnetic resonance imaging may not be conclusive, without the addition of advanced imaging[34] and/or arthroscopic visualization. This situation may explain the variability in the reporting incidence of meniscus tears. Nonetheless, in adults, several studies have reported that the medial meniscus is injured more frequently than the lateral meniscus at a 2:1 ratio (Figure

2A) but in pediatric cases the inverse is true.[35–37] It is also clear that these ratios often vary with acute versus traumatic injuries and concomitant injuries, as the biomechanics related to traumatic events will overstress one meniscus or region over others.[44] In both adult and juvenile patients, tears are predominantly located in the posterior region (67.0%–90.6%) but can also span multiple regions (20.3%–40.2%) (Figure 2B). Specifically, shown in adults, the medial meniscus is more likely to exhibit posterior tears (93.1%–97.7%) than the lateral meniscus (34.5%–80.7%).[38–40] Along the radial axis, more than half of tears span multiple zones (red-red, red-white, white-white). The medial meniscus experiences more tears in the red-red tears zone (32.8% vs. 8.6%) but less in the red-white (66.8% vs. 81.9%) and white-white (45.4% vs. 88.8%) zones than the lateral meniscus (Figure 2C; note: some tears involve multiple zones, explaining a total % >100%).[40] Based on our review of the clinical data, longitudinal (18.2%–37.6%) and bucket handle (13.1%–24.0%) appear to be most common (Figure 2D). The medial meniscus has also been reported to be more susceptible to longitudinal tears, while the lateral meniscus is more susceptible to radial tears.[38,40,43] Based on these relative observation rates (Figure 2), and the outcomes of healing (Supporting Information), certain tear scenarios are still problematic and may require augmentation to improve repair quality. Inner margin tears are clearly an issue due to the inherently deficient repair capacity of the avascular tissue. Radial tears are quite common in the avascular zone and disrupt the circumferential fiber network, an additional consideration which must be addressed to improve definitive treatment. Root tears are also common; they negate axial to hoop stress conversion and long-term outcomes are either inconsistent or not yet available. Regardless, repair of all types of tears is not always successful, and improved healing may improve outcomes. Thus, we wish to systematically review and subsequently highlight the recent scientific advances that may benefit the current state of meniscal repair.

3 | SYSTEMATIC REVIEW

3.1 | Systematic review methods

To highlight experimental meniscal tear/repair papers and focus on full-length peer-reviewed publications in the preclinical space, a systematic review was performed. Literature was identified and screened by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[45] PubMed was searched on May 1, 2020, for full-length peer-reviewed journal articles on meniscus repair that were published between December 31, 1979, and May 1, 2020 (Supporting Information—PRISMA Flow Diagram). The following search criteria were agreed on before executing the search: “meniscus repair” OR “meniscal repair” NOT “arthroscopy” NOT “arthroscopic” NOT “acl” NOT “temporomandibular.” Initial results yielded a total of 423 articles across Pubmed. Titles and abstracts were then screened to exclude repeats. Full-text articles were assessed and those studies whose focus was not a basic science perspective to test meniscus repair were excluded. Based on the application of these inclusion/exclusion criteria, a total of 107 full-length peer-reviewed manuscripts were identified. Each article was coded for advancement type (“Technique,” “Biological,” “Material,” or “Hybrid,” combined biological/material intervention), intervention details, experimental model (cells, explant, small animal, or large animal), and animal species (“bovine,” or cow, “canine,” or dog, “caprine” or goat, “lapine,” or rabbit, “murine,” or mouse, “ovine,” or sheep. “porcine,” or pig, “rattus,” or rat, or

"human"). The type of induced injury was also noted to determine the prevalent models utilized. A complete list of these studies is provided in the Supporting Information.

3.2 | Systematic review general findings

Thirty-five technique-focused studies (32.7%), 34 biologic interventions (31.8%), 22 material interventions (20.5%), and 16 hybrid (biological + material) interventions (15.0%) were identified (Figure 3A). Longitudinal tears were most prevalent tear type studied, appearing in 45 of 86 publications (52.3%) followed by radial (10.5%) and bucket handle (8.1%) tears (Figure 3B). Other experimental designs included circular lesions created within the body of the meniscus (12.8%) and an annulus model encompassing a cored-out disc of meniscus (9.3%).

The remaining studies used migration assays, subcutaneous implantation, cell injection, or lap-jointed tissue, among other methods. The majority of studies were in explant models (57.9%), with tissue primarily from bovine (26.1%), human (14.0%), and porcine (11.2%) sources. Large animal models (27.1%) were more prevalent than small animal models (10.2%). Cell-based studies were least prevalent (4.7%) (Figure 3C). The remainder of this review focuses on these three categories of repair (technique, biological, material), and highlights methods for improvement in repair in these categories.

4 | CLINICAL TEAR MANAGEMENT AND ADVANCES IN TECHNIQUE

4.1 | Current management

Due to the spatially variant vasculature of the meniscus, treatment type often depends on the location of the tear along the radial axis.[46] The outer third of the meniscus receives perfusion from the peripheral capsular plexus, while the inner two-thirds is diffusion dependent. Thus, red-red and red-white tears are most frequently repaired, whereas white-white tears are usually excised to alleviate mechanical discomfort.[47] Mounting evidence challenges this practice. Rubman et al. reported white zone repairs failed in only 36% of cases, enough evidence to encourage white-zone repair for young, athletic patients.[48] Similarly, Cinque et al. reported that while white-white repairs were inferior to red-red and red-white repairs, they still improved disability, pain, and functional scores relative to preoperative levels.[49] These results indicate that repair should be attempted in all three zones when possible.[49,50]

Suture repair techniques include "inside-out," "all-inside," and "outside-in" techniques (Figure 4). Inside-out suture repair is the current gold standard, avoiding the introduction of structures which could alter meniscal shape or damage articular cartilage.[61] It also allows for compact suture spacing (~3 mm apart), smaller puncture holes, and secure longitudinal or horizontal mattress suturing perpendicular to the tear. However, the inside-out method requires an open surgical incision and a skilled assistant to protect the soft tissues when passing sutures.[61] Alternatively, an all-inside device can simplify the procedure and decrease operative time, perhaps the reason that many providers prefer all-inside devices. Though reported to be relatively equivalent in outcomes to the inside-out technique,[62,63] the all-inside approach has higher risks of new tear or tear propagation, chondral damage, and local irritation necessitating meniscal removal.[64,65] Finally, the outside-in technique can be

advantageous in specific scenarios (e.g., anterior horn tears[55]) or for most types of tears due to its cost effectiveness.[55,66]

4.2 | Systematic review of technique improvement studies

Recent improvements in these three traditional repair approaches, as well as new techniques in the clinical space, were identified through our systematic review. Within "Technique" studies, articles were coded further into sub-categories ("novel suture pattern," "suture comparison," "device comparison"). The majority (23 of 35, 65.7%) tested commercial medical devices, including arrows, anchors, and all-inside devices marketed by medical device companies. Suture patterns were biomechanically evaluated in 9 of 35 studies (25.7%) and novel patterns were detailed in only 3 (8.6%) (Figure 5A). These surgical advances include cross-stitch, rebar, and transtibial techniques, which have been used to address radial or root tears.[67–69] All but one technique study used explant models, which were primarily bovine or human cadaveric in origin (Figure 5B), and no technique-oriented studies utilized small animal models. "Technique" studies primarily utilized longitudinal tears (27 of 35, 77.1%), over bucket handle (14.3%) and radial tears (8.6%) (Figure 5C). These novel repair devices and techniques may help to improve instantaneous structural integrity, thereby aiding in the restoration of the load-distributing capabilities of the meniscus. However, additional factors may also be needed to enhance the long-term bridging of the two ends of the tear, during and following suture resorption.

5 | BIOLOGICS IN MENISCAL REPAIR

The use of biologics in orthopedics ("orthobiologics"), has garnered increased interest, especially in meniscal tear management. Biologics are intended to aid in defect closure by introducing additional cells and/or bioactive factors to the interface. These augmentations may be especially beneficial in avascular tears, which have limited endogenous healing capacity. Biologics used in recent clinical studies include fibrin clots, platelet-rich plasma (PRP), and mesenchymal stem cells (MSCs). A more thorough explanation of these factors can be found in the Supporting Information. As biologics for meniscal repair gain clinical traction, laboratory studies are focused on quantifying and characterizing the factors contained within biologic augmentations, the impact these factors have on the formation of meniscal tissue, and the mechanisms driving these processes. Furthermore, while not yet used clinically, growth factors and other bioactive cues can be implemented to improve various steps of meniscal repair. We identified four biologic-based functions (Figure 6) needed to enhance the various stages of meniscal repair: cell recruitment (26.0%), vascularization (10.0%), matrix deposition (52.0%), and inflammation control (8.0%).

5.1 | Cell recruitment

Due to the relatively avascular and acellular nature of the meniscus, the first step of repair augmentation involves the recruitment of cells with healing potential. In addition to the commonly used bone-marrow and adipose-derived MSCs, synovial stem cells,[70,71] blood vessel-derived[72] stem cells, and even chondrocytes,[73] have been delivered locally in preclinical models of meniscal suture repair. Nakagawa et al.[70] isolated and expanded synovial stem cells and injected them into longitudinal defects repaired with suture.

Importantly, cells were localized to the defect site after only 10 min and led to enhanced cellular proliferation and wound closure. Cells may be applied directly to the site of injury during the meniscal repair procedure, whether open or arthroscopic, via injection. Growth factors and scaffold-based cell delivery (see Section 6) can also be utilized at the site of injury to improve exogenous cell localization.[74] Alternatively, cells from the meniscus itself can be harnessed to promote healing.[75] Meniscal progenitor cells and even MFCs have the capacity to produce robust matrix to heal meniscus tears[76,77]; however, their migration to the defect site through the dense extracellular matrix (ECM) presents a challenge. Techniques to improve the migration of meniscus progenitors and fibrochondrocytes include softening the ECM via localized collagenase release,[78] improving cell motility via growth factor[78,79] or serum[80] delivery, and easing cellular migration through nuclear softening.[81] Thus, whether exogenously added or endogenously recruited, supplementary cells at the injury site may be pivotal in the healing of meniscal lesions. Once recruited, these cells can then be guided towards a specified behavior, including vascularization, matrix deposition, or inflammatory relief. Certainly, the optimal type of cell for meniscal regeneration at the repair site is up for debate, and more head-to-head studies comparing cell types for meniscal repair may be required.

5.2 | Vascularization

The variance in healing between the outer and inner meniscus is almost always attributed to differences in regional vascularity. Clinicians have improved blood flow to the inner meniscus via radial perforations,[82,83] but only found a slight, insignificant improvement in patient outcomes. Bioabsorbable conduits have also been suggested to enhance vascular tissue ingrowth.[84] Anatomically, the outer vascularized third of the meniscus contains blood-vessel derived stem cells (CD34+, CD146+), which when isolated and mobilized enhanced avascular tear repair in a rat model.[72] King et al.[85] increased neovascularization more than fivefold via treatment with angiogenin, a proangiogenic factor, in a rabbit defect model. Similarly, endothelial growth factors can promote vascularization of the inner meniscus[86] and may promote cellular proliferation, granular tissue formation, and bridging of the defect.[86,87] Thus, the formation of new blood vessels, or angiogenesis, and their impact on the healing of avascular injury sites need investigation. Collectively, both cell recruitment and vascularization may need to be directed to better encourage ECM deposition/organization.

5.3 | Matrix deposition

The afore-mentioned techniques routinely lead to increased granulation tissue.[86] Any new tissue that bridges the opposing ends of the tear must withstand considerable stresses, and thus robust and appropriate matrix deposition is required. Perhaps the factor most utilized in meniscus regeneration is transforming growth factor β3 (TGF-β3). When added to cultures of stem cells or meniscus fibrochondrocytes, it increased both collagen and PG production and integration strength between two edges of a meniscus tear.[74,88] Similarly, connective tissue growth factor[74,87] and insulin-like growth factor[89,90] led to mechanically superior repair integrity. The biggest challenge for growth factor use is localized and sustained delivery, which can be achieved with scaffold delivery (see Section 6). Finally, an exciting biologic direction is gene therapy with endogenous or exogenous cells.[89,91] For example, a vector to overexpress TGF-β3 in MFCs resulted in increased cell proliferation and matrix

synthesis without delivery of the growth factor itself.[91] Thus, application of genetic vectors or genetically modified cells to meniscus tears may expedite ECM incorporation, though further preclinical and clinical exploration is required.[92]

5.4 | Inflammation control

The synovial environment of the knee joint presents a harsher setting than is typically mimicked in vitro. Inflammation is a natural response to trauma and injury and if not harnessed to augment the repair, will likely inhibit the regenerative process. While inflammatory cytokines that are upregulated in osteoarthritic conditions[93] can promote granular tissue formation, this tissue is mechanically inferior and vulnerable to retear. In vitro, interleukin-1 (IL-1) significantly decreased repair strength, cell migration, and tissue formation,[94,95] but inhibition of IL-1 via a receptor antagonist enhanced integrative repair. Furthermore, other proinflammatory cytokines, such as tumor necrosis factor α and matrix metalloprotease, can be inhibited to improve meniscal healing.[95–97] These findings suggest inflammation leads to a catabolic state in the meniscus, and inflammation control may be needed to maximize repair success, especially in joints with concomitant injury or a more degenerative and/or inflammatory state. Regardless, the spatiotemporal introduction and distribution of these biologic methods are often difficult to control and may need to be combined with material approaches.

6 | MATERIALS IN MENISCAL REPAIR

Historically, meniscus scaffolds have been directed at recreating the native anatomy and its mechanical properties following meniscectomy. As the focus has shifted toward repairing the injured tissue, bioactive materials that integrate with native tissue and include cell-instructive cues to promote physiological healing are paramount. Fibrin glue and collagen wraps are clinically available “materials” to augment meniscal repair, yet there are still no biomaterial-based FDA-approved products for this indication. Below, we highlight material strategies to target specific functions needed to augment repair: biologic delivery to promote cell migration and function, restoration of mechanical properties, and wound closure via tissue adhesives (Figure 7). Additional information is provided in Supporting Information.

6.1 | Biologic delivery

As highlighted previously, localized delivery of proteins, nucleic acids, and cells is advantageous in augmenting meniscus regeneration. For success at the time scale needed for repair, sustained retention and release to maintain therapeutic concentrations may be required. Scaffold fabrication techniques alone can control the release of single or multiple factors. For example, biopolymer-based hydrogel scaffolds releasing TGF-β3 increased fibrochondrogenic differentiation and tissue integration.[98,99] Additional introduction of stromal cell-derived factor α (SDF-1)[78] enhanced cell migration, similarly noticed with platelet-derived growth factor[79] and PRP.[100] Further, various material carriers (e.g., microspheres, nanocapsules) can improve factor release.[101] For example, TGF-β3 release from poly (lactic-co-glycolic acid) microspheres promoted extended differentiation and ECM production.[74] These material strategies to incorporate and release biologics increased matrix production, collagen fiber alignment, and mechanical properties, producing a more

physiological repair. Finally, these material and scaffolds can be incorporated with cells (e.g., MSCs), allowing for retention of cells at the defect site, increasing their likelihood to deposit meniscus-specific ECM and heal tears.[102–104]

6.2 | Materials to promote cell adhesion and function

Material-augmented repair provides a biomimetic structure with requisite chemo-mechanical cues to promote cell migration, proliferation, and functional ECM production for wound closure of meniscus tears. Decellularized meniscus extracellular matrix (dECM) is an exciting material in the field, as the major ECM components of the native meniscus tissue (collagen I, collagen II, and glycosaminoglycans) are retained and provide a substrate for cell migration and proliferation.[105–108] The maintenance of meniscus-specific biochemical cues promote cell growth and behavior, in particular the upregulation of fibrochondrogenic markers (ACAN, COL1A2, COL2A1, and COL10A1).[108,109] Furthermore, its porosity allows nutrients and oxygen to diffuse into the scaffold and promote cell growth.[106] Perhaps the only tradeoffs with dECM for meniscal repair are the relatively inadequate mechanical properties compared to native tissue and the potential variability in sourcing and composition.

Material fabrication properties and functionalization with bioactive agents can promote cell adhesion and function. Biocompatible materials can allow cell attachment and stimulate collagen deposition, increasing integration strength.[110,111] Baek et al. fabricated core-shell electrospun fibers; a collagen shell to promote cell attachment and new matrix synthesis, and a core of poly(lactic acid) for mechanical strength. Histological and mechanical assessment illustrated increased integration with native meniscus tissue. Further, scaffold mechanics, and specifically the fibers used, can enhance cellular invasion and collagen deposition, illustrating the importance of scaffold microenvironment on cell sensation, deformation, and migration.[112] Finally, routinely used polymers (e.g., polycaprolactone, poly(vinyl alcohol)) can be functionalized with unique biomolecules[113,114] or peptides[115,116] for cellular recruitment and adhesion, often the first step in augmenting meniscus repair.

6.3 | Matching native mechanical properties

One of the most critical components of meniscal repair is recapitulating the circumferential and radial alignment of collagen fibers, permitting physiological stress distribution across the tissue and across the articular cartilage, which it protects.[117] Electrospinning is a unique scaffold fabrication method that produces nanofibers that mimic the native collagen fibril diameter and arrangement, and can be tuned to create circumferential and radial fiber alignment to match native tissue.[118–120] Moreover, new collagen production from seeded MSCs followed the electrospun fiber direction, enhancing mechanical properties in the circumferential direction. Polyester and collagen solutions can also be electrospun and organized to achieve mechanical properties similar to the native meniscus.[111,118] Electrospun scaffolds have improved the degree of meniscal repair in both in vitro and in vivo models,[78,121,122] yet the integration of the scaffold with tissue to produce a continue, mechanically function interface remains challenging.

6.4 | Tissue adhesives

For many of the materials options discussed previously, arthroscopic implementation may be complicated with current surgical tools. In response, a relatively new arena in augmenting meniscal repair is the development and use of "bioadhesives."[123] Two potential materials for tissue adhesion and integration are fibrin glue and synthetic polymers. Fibrin glues are used clinically, utilize crosslinking pathways of fibrin clots for tissue adhesion,[124,125] and can increase cell migration and integration of ECM components, but it is mechanically inferior in sealing defect edges. Alternatively, synthetic polymers can maintain cell viability (e.g., isocyanate-terminated polymers), while significantly enhancing shear adhesive strength relative to fibrin glue.[126,127] While prefabricated scaffolds require an incision to be inserted into place,[106,110] material adhesives can be introduced arthroscopically and crosslinked in vivo,[74] and thus may be especially useful for tear locations that are not readily accessible for suture repair.

7 | MODEL SYSTEMS FOR AUGMENTED MENISCUS REPAIR

To evaluate biologic- and material-based augmentation approaches preclinically, appropriately integrated preclinical test platforms and evaluation criteria are required.[128] We revisited our systematic review within the "Biological," "Hybrid," and "Materials" studies, and articles were further analyzed (Figure 8A). Regarding model systems, all three categories had a similar percentage of cell/scaffold (5.8%–9.1%) and large animal (31.8%–44.1%) studies. Interestingly, biologic and material interventions utilized explant models (41.2% and 50.0%, respectively) much more often than hybrid interventions (18.8%), which instead used small animal models (37.5%) more than biologic or material studies (8.8% and 9.1%, respectively). This may speak to the need for hybrid models to prove both biological efficacy and effective delivery, which are more clinically relevant in animal models compared to explants. Moreover, the individual components of these hybrid approaches may have already been investigated in in vitro and explant models, and thus the combination can undergo translation more quickly.

Regarding injury model, biological and material studies utilized clinically relevant tears (50.0% and 54.5%, respectively) at more than twice the rate of hybrid interventions (18.8%), likely due to the relative "youth" of hybrid techniques, which may require proof-of-concept experimentation. All three types of studies used the "annulus" model (8.8%–13.64%), yet circular punch defects were utilized only in biological and hybrid studies (26.5% and 18.8%, respectively), and not in materials-based solutions. The difficulties of creating circular scaffolds and the lack of clinical relevance may inform the lack of circular models in materials interventions. Meanwhile, subcutaneous evaluation is common in material and hybrid studies (9.1% and 37.5%, respectively) but not present in biological studies, likely because material safety and biocompatibility are essential to novel biomaterials. Lastly, two injury models were only seen in one type of study. Biological studies uniquely used migration assays (5.9%) given their emphasis on enhancing migration, and materials studies uniquely employed "lap-jointed" tissue models (13.6%) to assess integration strength (Figure 8B).

For preliminary testing of these approaches, an annulus model is frequently employed; evaluation of the repair interface should involve both mechanical (push-out testing[96,129]) and biological (histology and subsequent scoring,[130] matrix characterization) outcomes. However, since each tear pattern compromises different meniscal fiber networks, these annular models may need to account for the circumferential versus radial axis. As translation moves to small and large animals, functional, mechanical, and biological outputs remain important.[131,132] Since the majority of in vivo repair studies have involved vertical longitudinal tear models, which already have relatively successful clinical outcomes, preclinical models that introduce radial and root defects may better address more problematic tear types.

8 | LOOKING TO THE FUTURE

Meniscal repair is a developing field. A PubMed search for meniscus/meniscal repair yielded over 3100 manuscripts, with nearly half in the past 5 years. Tear management has shifted away from meniscectomy towards procedures to salvage native tissue. Technique-based innovations like transtibial tunnel repairs[133,134] have improved time-zero repair mechanics, yet some scenarios remain problematic (e.g., avascular and root tears) and bridging of the tear can be elusive. However, laboratory research has developed methods that may improve functional outcomes. Here, we performed a systematic review to highlight new techniques and trends (biologic- and material-based) to suggest the future landscape of meniscal repair. Certainly, while this systematic review may have missed much of the cutting-edge work in augmenting meniscal repair in the clinic, we were able to emphasize much of the preclinical work that can better characterize and evaluate specific elements of repair. In particular, cellular recruitment (exogenous or endogenous) and control upon arrival, and scaffolds and adhesives that help bridge tears, are exciting directions, both alone and in combination.

The discussed augmentation strategies are indeed promising, utilizing technical advances in sports medicine, innovative biological strategies such as gene editing and cell localization, and novel material chemistries and strategies to enhance the healing process. One of the biggest question marks that remains is reestablishing the natural geometry of collagen fibers that were severed during the initial tear. While studies have shown enhanced integration strength with augmentation, these properties are often a fraction of native tissue, leaving the repair site susceptible to retear. Another avenue of future exploration involves precise control of cells at the injury site; the introduction of a tear perturbs the mechanical and biochemical microenvironment, which may need to be accounted for when designing new therapies. Furthermore, many of these approaches do not account for some meniscal deterioration that can occur quite rapidly post-injury. The loss of matrix elements, mainly PGs around the free defect edge, may compromise the mechanical integrity of tissue around the repair site. Thus, techniques that fortify meniscal tissue around the site of injury may be advantageous.

While novel sutures and repair devices have been approved for clinical use, the biologics and materials discussed may require appropriate safety and efficacy testing, complicating the regulatory pathway. Currently, the only meniscus-related products in the market, other than

sutures, are for replacement after partial or full meniscectomy (ActiFit, CMI, Trammpolin, FibroFix, NUSurface), and are comprised of widely characterized biological or synthetic materials. Utilizing predicate materials/factors, and minimal manipulation of biologics, would ease translation. Furthermore, therapies that harness current clinical augmentations (e.g., PRP) would be advantageous, and research to understand the basic science implications of these biologics would be fruitful.

Additional variables including sex, age, pre-existing conditions, and concomitant injuries play a role in meniscal injury and healing. Personalizing the approach represents a future direction in clinical management, even more so as we start to appreciate knee-to-knee variability in joint mechanics.[135] Indeed, we should not lose sight of the fact that any potential solution should restore the ability of the meniscus to distribute load across the articular surfaces of the knee joint. Moreover, the rehabilitation process is also integral; strict timetables for early phases protect the surgical repair, especially as new tissue is deposited to bridge the tear.[136] Earlier weight-bearing has been attempted, but higher re-tear rates are observed with weight-bearing under 6 weeks. Thus, the development of augmentation techniques should observe and potentially accelerate healing during this timeline.

One limitation of the systematic review and the preclinical literature is the emphasis on traumatic tears, and thus the disregard for degenerative tears. Degenerative tears are often observed with other articular pathologies or are within aging joints that complicate the healing process and reduce the possibility of successful repair.[137,138] Typically treated conservatively first with physical therapy and, as a last resort, with partial meniscectomy, [139–141] the long-term prognosis of these injuries is bleak. Additionally, degenerative menisci have likely experienced significant matrix loss and aberrant cellular behavior; thus, to save the meniscus in these case, fortification and stabilization techniques[142,143] may better restore healthy meniscus function when combined with repair. Finally, in more severe cases, while note clinically recommended, degenerative tears may need to be treated with replacement allografts or scaffolds,[144–146] since the remaining meniscal tissue may be too compromised. These approaches could achieve greater success if coupled with inflammatory relief to combat the likely upregulated cytokine concentration that inhibit meniscal regeneration. In general, combination approaches that slow the degeneration of both the meniscus and surrounding joint environment may be clinically beneficial in the management of these more degenerative injuries.[147]

In conclusion, we summarized the current state of meniscal tear management and highlighted basic science approaches that may improve repair. The meniscus remains a heavily researched tissue, as evidenced by increased journal publications and conference presentations. The Orthopaedic Research Society established a Meniscus Section in 2016, highlighting the variety of research in the field and leading to more collaborative efforts between biologists, engineers, and clinicians. We hope that these efforts yield new and exciting meniscal repair techniques to improve management following tears.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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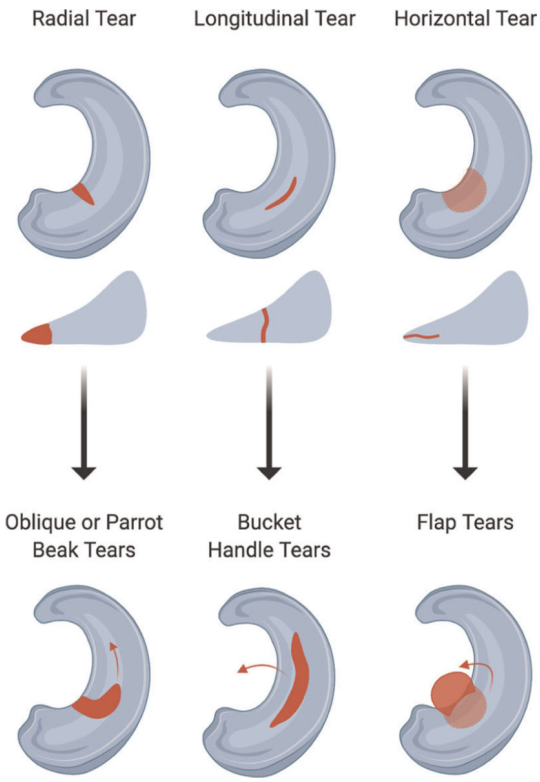


FIGURE 1.

Schematics of prevalent meniscal tears. Schematics of radial, longitudinal, and horizontal tears, in both axial and cross-sectional views. Arrows indicate the progression of these smaller tears to larger and more complex versions

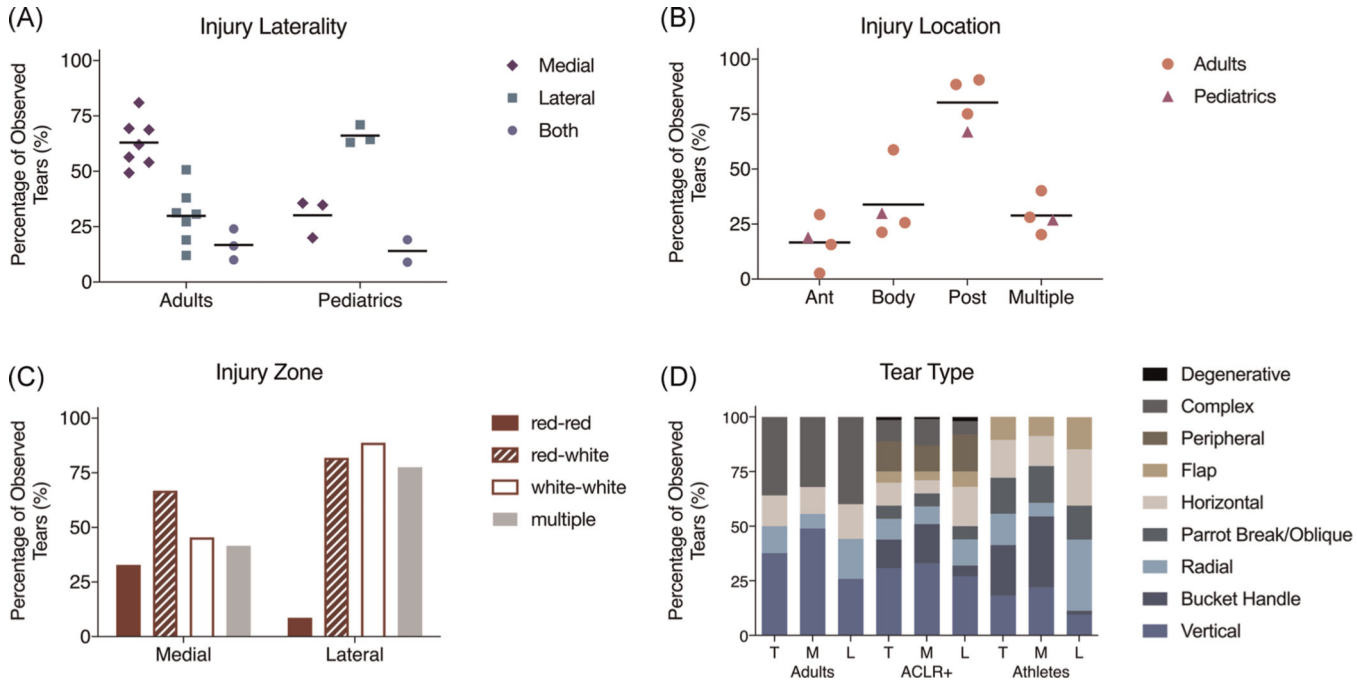


FIGURE 2.

Meniscus tear observed incidence rates (% of observed tears within each study) from the literature. (A) Rates for affected meniscus (medial, lateral, or both) in adult (including adults with ACL reconstruction (+ACLR) and Athletes) and pediatric populations. Data from Jackson et al. (2019), Robinson et al. (2011), El Mansori et al. (2018), Kim et al. (2019), Ridley et al. (2017), Christino et al. (2019), Baker et al. (1985), Terzidis et al. (2006).[35–42] (B) Rates by region (anterior, body, posterior, multiple) in adult (including +ACLR and Athlete) and pediatric populations. Data from Jackson et al. (2019), El Mansori et al. (2018), Kim et al. (2019), Terzidis et al. (2006).[35,38–40] (C) Rates by vascular zone (outer = red-red, intermediate = red-white, inner = white-white, multiple) in the medial and lateral menisci in adult populations. Data from Terzidis et al. (2006).[40] (D) Rates by tear type and affected meniscus (T, M, and L) in general adults, ACLR+ adults, and adults who are athletes. Data from Jiang et al. (2017), El Mansori et al. (2018), Terzidis et al. (2006).[38,40,43] ACL, anterior cruciate ligament; L, lateral; M, medial; T, total incidence

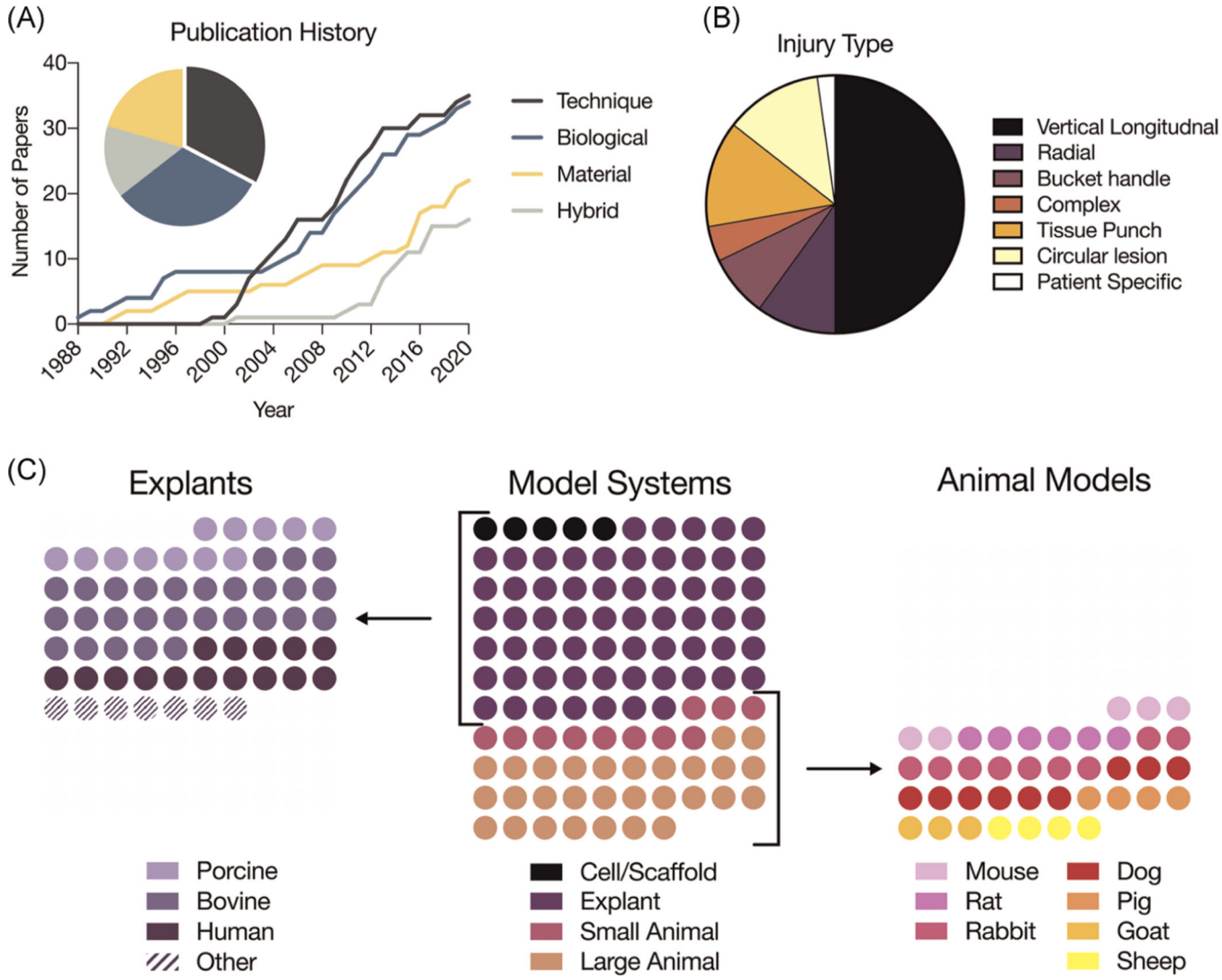
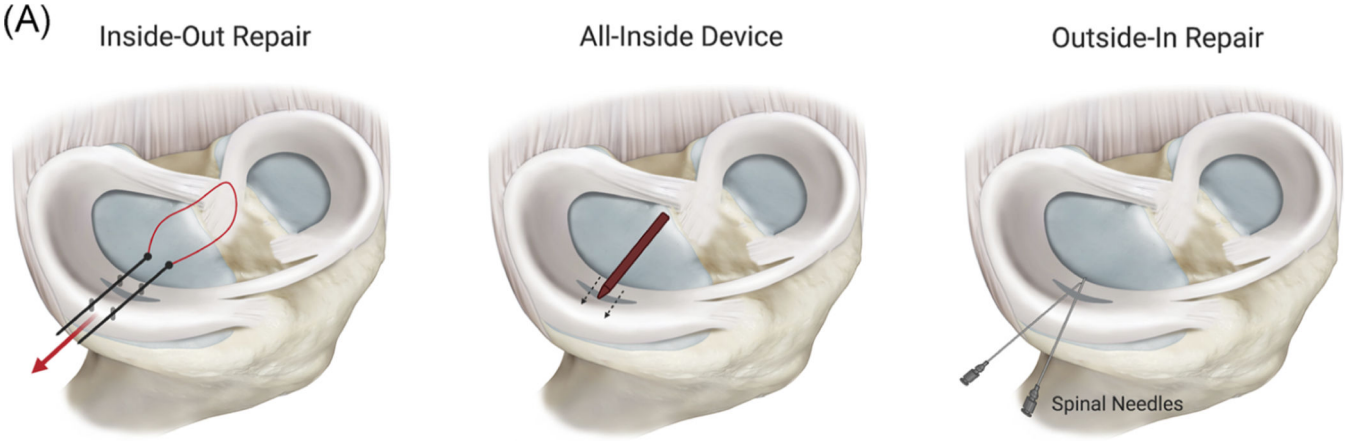


FIGURE 3.

Summary of systematic review findings. (A) Publication history of papers included in the systematic review from 1988 to 2020. Papers categorized across technique, biological, material, and hybrid (combined biological/material) interventions. (B) Graph of prevalent injuries/models (annulus model and circular lesion) utilized in studies. (C) Graph of model systems used in studies in systematic review (middle) and expansions of explant species (left) and large animal model species (right). Each circle presents one study that has utilized that system or model (n = 107)

(A)



(B)

	Radial	Vertical	Horizontal	Ramp	Root	Comment
Inside-Out	Used as hybrid or augment	Gold Standard	Ideal	Gold Standard	Used as hybrid or augment in root repair	Used as hybrid or augment in root repair
All-Inside	Not suitable	Very Common	Acceptable	Used with Posteromedial portal	Not suitable	Higher risk of complication
Outside-In	Acceptable	Acceptable	Acceptable	Risk of neurovascular injury	Not suitable	Useful for Anterior Horn tears
Transtibial Pull-out	Used as hybrid or augment	Not suitable	Not suitable	Not suitable	Gold Standard	Used with Inside-out suturing for radial, root tears

FIGURE 4.

Schematic and recommendations for meniscus repair techniques. (A) (Left) inside-out, (middle), all-inside, and (right) outside-in techniques. (B) Repair techniques (inside-out, all-inside, outside-in) recommended for major tear types discussed (radial, longitudinal, horizontal, ramp [longitudinal tear in the peripheral capsular attachment of the posterior horn], root). Relative use (acceptable, very common, not suitable, etc.), gold standards, and risks are also detailed. Recommendations obtained from the following sources for inside-out (Muckenhirn et al., 2017; Nelson et al., 2013; Kang et al., 2019)[51–53], all-inside (Kang et al., 2019; Negrin et al., 2018)[53,54], outside-in (Menge et al., 2016; Steiner et al., 2018; Dave et al., 2012; Thompson et al., 2014)[55–58], and transtibial techniques (Chahla et al., 2016; LaPrade et al., 2015)[59,60]

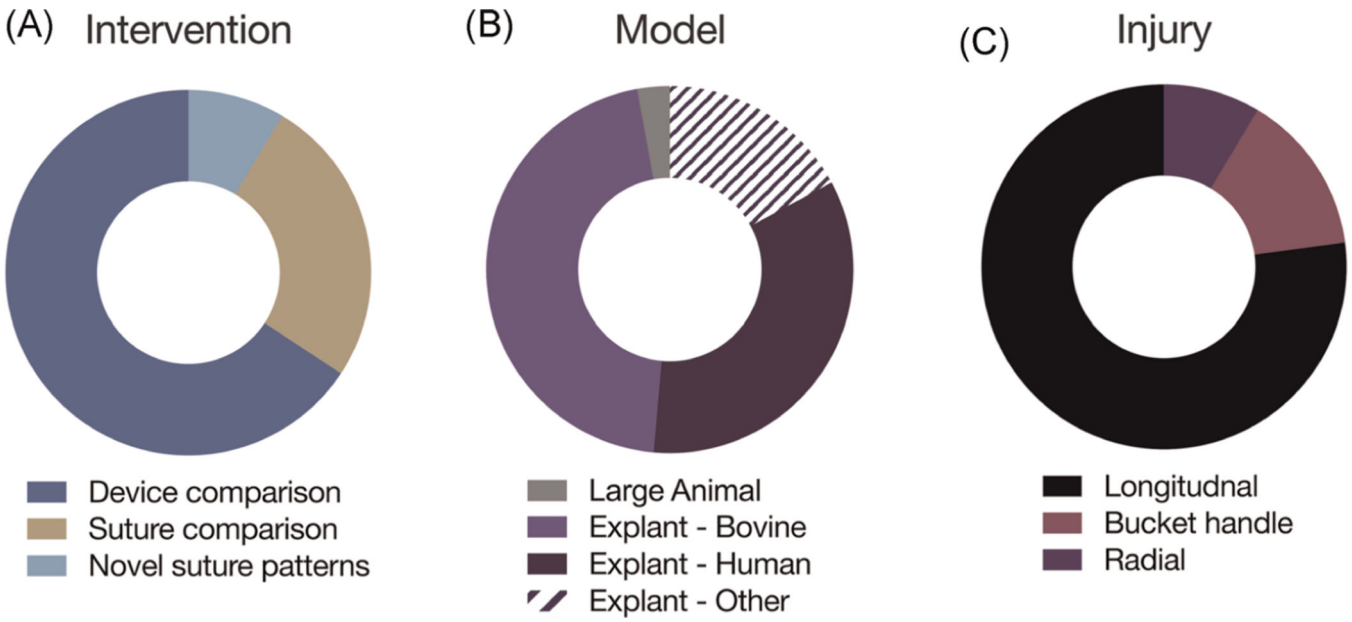


FIGURE 5.

Statistics regarding technique-based studies for meniscus repair. (A) Technique advancement by category, (B) model system, and (C) injury type

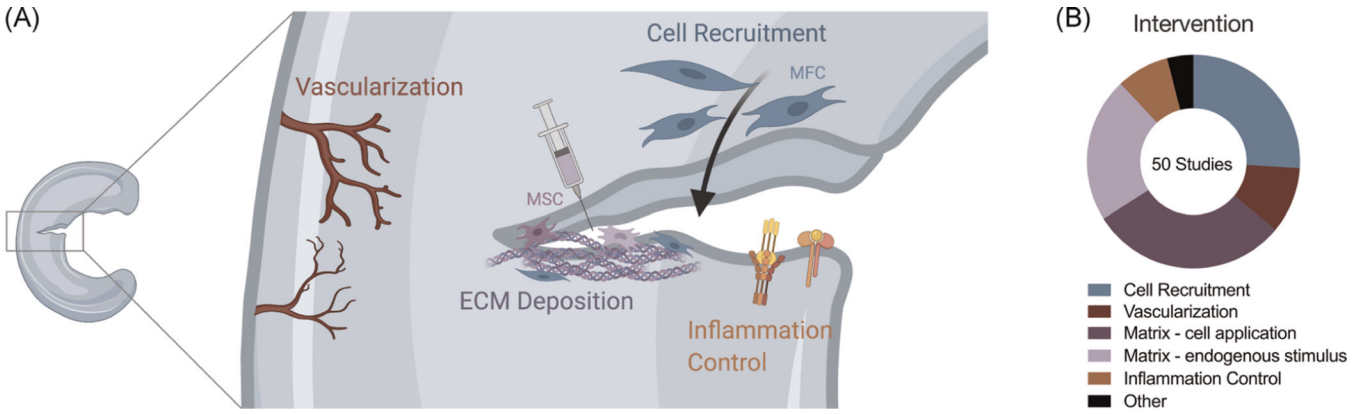


FIGURE 6.

A look at the intended functions of biological intervention. (A) Schematic of four major themes in biological repair. (B) Statistics reflecting the prevalence of each theme

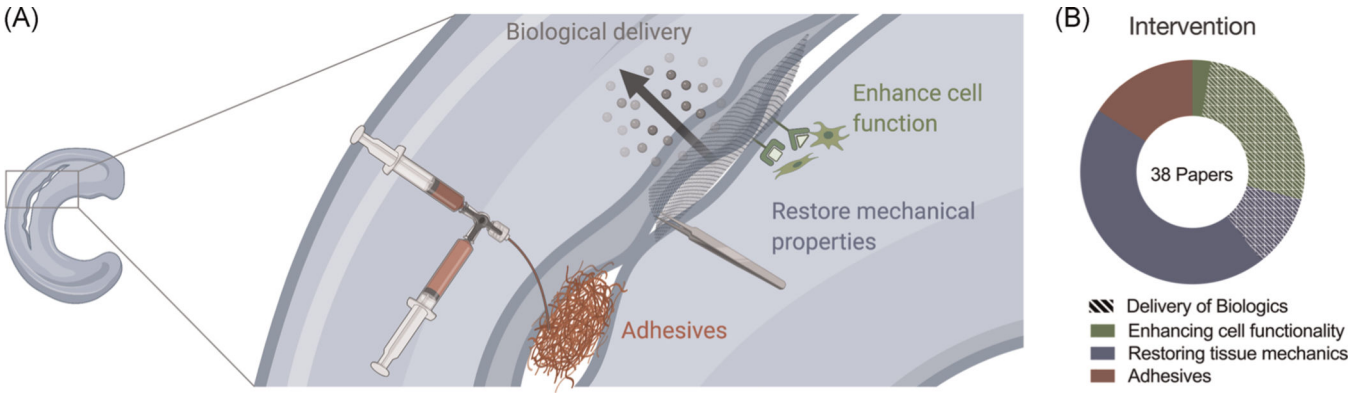


FIGURE 7.

A schematic of the types of material intervention for repair. (A) Schematic of four major themes in materials-based repair. (B) Statistics reflecting the prevalence of each theme

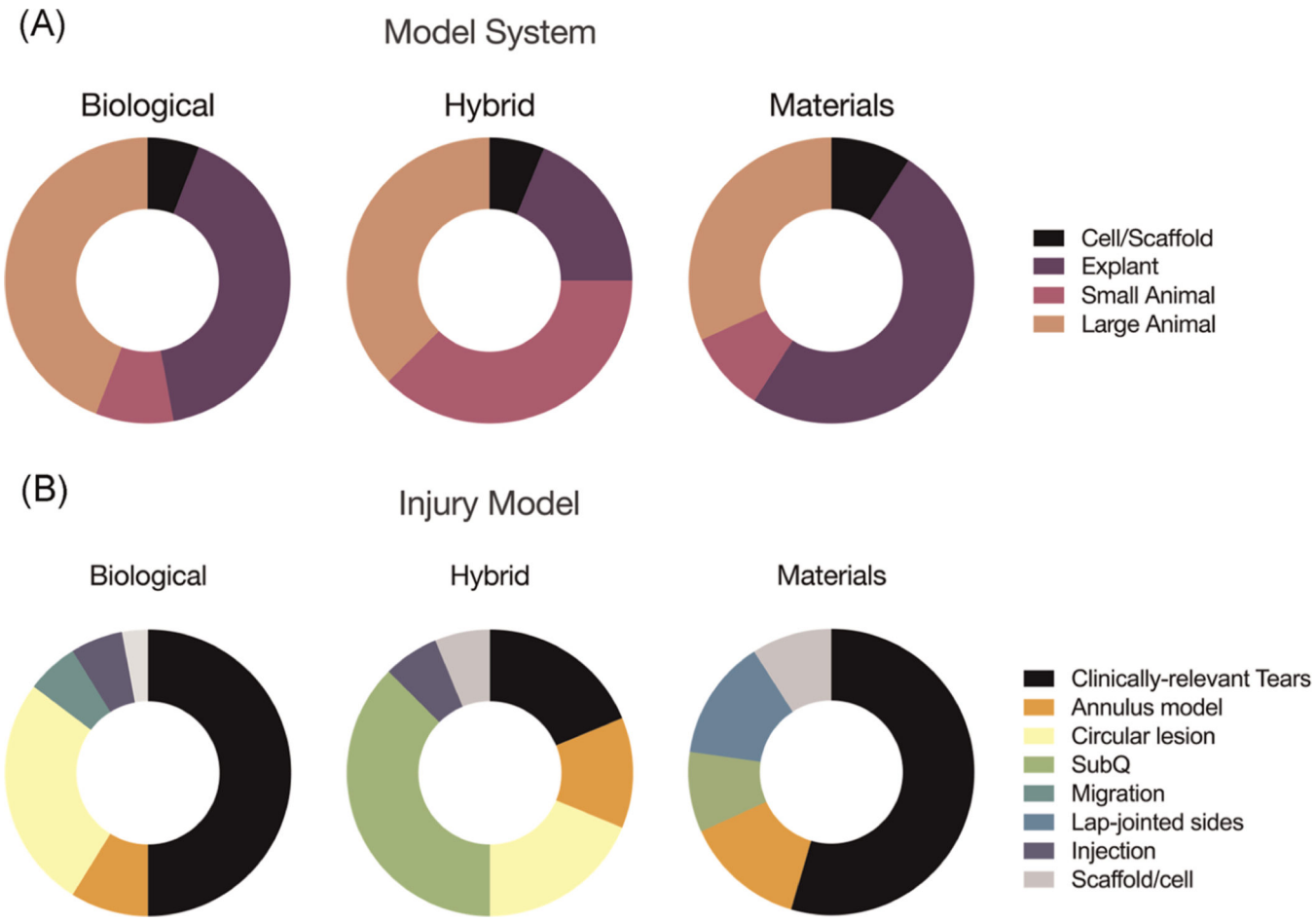


FIGURE 8.

Statistics of biological, hybrid, and material interventions for meniscus repair. (A) Model systems and (B) injury models in each type of intervention