Archives of Orthopaedic and Trauma Surgery (2019) 139:305–316
https://doi.org/10.1007/s00402-018-3057-z

ORTHOPAEDIC SURGERY

Articular cartilage regeneration and tissue engineering models: a systematic review

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Received: 21 July 2018 / Published online: 31 October 2018

Abstract

Introduction Cartilage regeneration and restoration is a major topic in orthopedic research as cartilaginous degeneration and damage is associated with osteoarthritis and joint destruction. This systematic review aims to summarize current research strategies in cartilage regeneration research.

Materials and methods A Pubmed search for models investigating single-site cartilage defects as well as chondrogenesis was conducted and articles were evaluated for content by title and abstract. Finally, only manuscripts were included, which report new models or approaches of cartilage regeneration.

Results The search resulted in 2217 studies, 200 of which were eligible for inclusion in this review. The identified manuscripts consisted of a large spectrum of research approaches spanning from cell culture to tissue engineering and transplantation as well as sophisticated computational modeling.

Conclusions In the past three decades, knowledge about articular cartilage and its defects has multiplied in clinical and experimental settings and the respective body of research literature has grown significantly. However, current strategies for articular cartilage repair have not yet succeeded to replicate the structure and function of innate articular cartilage, which makes it even more important to understand the current strategies and their impact. Therefore, the purpose of this review was to globally summarize experimental strategies investigating cartilage regeneration in vitro as well as in vivo. This will allow for better referencing when designing new models or strategies and potentially improve research translation from bench to bedside.

Keywords Articular cartilage · Cartilage regeneration · Tissue engineering · Chondrogenesis · Hyaline cartilage

Introduction

Articular, hyaluronic cartilage with its special biomechanical characteristics is crucial for the almost frictionless movement of articulating joints. Yet, its wear and degenerative processes that are estimated to occur in about 9% of the US population as early as 30 years of age will result in osteoarthritis (OA) in the long-term [1]. In fact, articular defects larger than 4–16 mm^2 rarely heal even with continuous passive motion [2–5]. Other than the cartilage defect size, factors such as species, age, sex, and anatomic location play an important role in defect healing as well [6, 7]. Cartilaginous lesions, however, do not heal restitutio-ad-integrum but rather form fibrous tissue with mechanical properties inferior to the original tissue [8].

As cartilage has very limited regeneration capacities, treatment of OA yields tremendous economical burdens and is not always satisfactory—especially for young patients—research in cartilage regeneration and cartilage tissue engineering has become one of the most important fields of research in orthopedics and related science [9–11].

Multiple strategies such as (stem-)cell-based therapies, cell-free tissue engineering, biophysical stimulation, cartilage transplantation and mathematical models were developed in the pursue of cartilage regeneration (Fig. 1). Some of these strategies have resulted in techniques, which have already advanced into clinical application (e.g., autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte transplantation (MACI), mesenchymal stem cell stimulation/ microfracturing (MF), osteochondral

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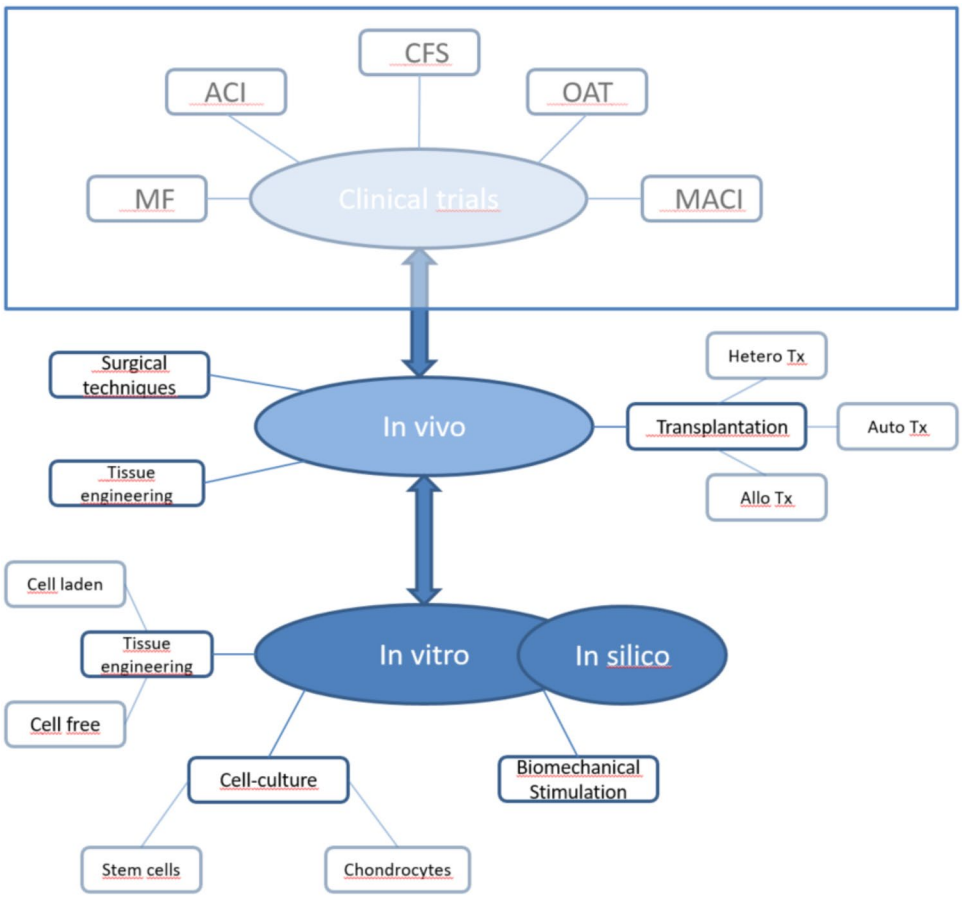

Fig. 1 Overview of cartilage research. Current research on cartilage regeneration spans the in vitro/in silico level, the animal model-based in vivo level as well as the clinically applied level. Principally, strategies (such as *MF* microfracturing, *ACI* autologous chondrocyte implantation, *CFS* cell-free tissue-engineered scaffolds, *OATs* osteochondral autologous transplants, *MACI* matrix-induced chondrocyte implantation) that are used in daily clinical routine or clinical trials have previously been tested on the other levels. At the in vivo level, research is addressing the question of diverse types of transplantation, tissue engineering and surgical techniques. In vitro and in silico research investigates the regenerative potential of cell-free and cell-laden biomimetic scaffolds, the influence of biomechanical stimuli, the usage of different cell lines and the predictive capability of computational tissue models

autologous transplantation (OAT)). So far, all of these techniques have limitations and mostly result in fibrous cartilage-like tissue rather than perfectly regenerated cartilage. Thus, predictive models that are as close to clinical reality as possible are urgently necessary for future translational research.

The purpose of this review was to globally summarize experimental strategies investigating cartilage regeneration in vitro as well as in vivo. This will allow for better referencing when designing new models or strategies and potentially improve research translation from bench to bedside.

Strategies, techniques, approaches

A PubMed search for models investigating single-site cartilage defects as well as chondrogenesis was conducted using the Boolean search string: ((“articular cartilage” AND (repair OR regeneration OR “tissue engineering” OR transplantation)) OR chondrogenesis) AND model. Based on this search, 2217 articles were found on January 23rd 2018. Articles were evaluated for content by title and abstract. Articles including new models or approaches of cartilage regeneration were included. This was based on the study titles, abstracts and—in cases of doubt—reading of the manuscript.

Multiple mechanisms and etiologies of cartilage defects have to be addressed when treating the defect. Therefore, different in vivo models such as a model of chronic articular cartilage and meniscal injury [12], instant cartilage defect models [13, 14], trochlear defect models [15, 16], multiple defect models [17, 18], papain cartilage injury models [19] were developed. Furthermore, there are chondrogenesis models [20–22], in vivo but ex situ models [23, 24], or ex vivo and in vitro cartilage repair models for the prediction of cartilages repair capacity [25–27] and cartilage transplantation models [28]. In addition there are set-ups that allow studying the spontaneous [29, 30] or enzyme-based [31] repair of cartilage defects of limited sizes.

Principally, these models are used for studies that can be categorized into (stem-)cell-based approaches, (cell-free or laden) tissue engineering, (bio)physical stimulation, and mathematical modeling.

(Stem) cell-based approaches

Several groups investigated the chondrogenic potential of mesenchymal stem/stromal cells (MSC) by co-culturing

these cells with chondrocytes [32] on biodegradable scaffolds [33], by silk-fibroin-mediated co-culturing [34], by platelet-rich fibrin [35] or plasma addition [36], or by just implanting MSCs arthroscopically into cartilage defects [37] (Fig. 1). Other researchers primed MSCs into a chondrogenic differentiation before implantation [38], injected them as a cell suspension into the joint [39] or mixed them with hyaluronic acid before injection [40] and found elevated hyaline cartilage parameters such as glycosaminoglycans but no organized hyaline cell matrix. Furthermore, authors mobilized subchondral MSCs in an ovine model and attempted to support cartilage differentiation by adding 10 kDa chitosan to the site of the defect [41]. The authors stated that chitosan was insufficient to improve repair. In addition, MSCs from other localizations such as the suprapatellar fat body were used for experimenting on cartilage regeneration in a severe osteoarthritic mouse model [42]. MSCs for cartilaginous differentiation were also obtained from Wharton jelly (human umbilical cord blood-derived MSCs/ hUCB-MSCs) [43–45], the perivascular matrix [46], the subchondral bone [47] or chondrogenic clonal MSCs (sC-MSCs) [48] were selected and used for cartilage regeneration experiments. However, there is evidence that bone-derived and peripheral MSCs have similar characteristics in terms of biological markers and chondrogenic potential [49]. All these studies therefore underlined the chondrogenic potential of MSCs and demonstrated biochemical—yet not anatomical—similarities to original hyaline cartilage. However, it remains questionable whether allogeneic transplantation of MSCs would contribute to articular cartilage formation or result in pure fibrocartilage-like tissue formation as previously observed in untreated defects [50].

A recent study by Sun et al. used MSCs and stimulated these in an in vivo rabbit model with TGFβ to observe cartilage regeneration [51]. These types of approaches also include IL-6 stimulation [52], TNF-α inhibition [53], IL-1β and BMGF-3 supplementation [54], IGF respective FGF-2 gene transfer [55, 56], G-CSF stimulation [57], rAAV5-IGF-1 transduction as well as SOX-9 stimulation of MSCs [58]. Stimulating certain chondrogenic pathways, these studies showed more vitality in the cartilaginous cell lines compared to controls groups without any humoral/growth factor supplementation.

Other techniques tried to stimulate chondrocyte differentiation via exposing cells to substrates of the original biochemical environment of articular cartilage. Thus, a study by Lin et al. preconditioned MSCs in a methacrylated hyaluronic acid scaffold and dynamic compression before implanting cells into cartilaginous defects and found the chondrogenic potential of preconditioned cells superior to un-preconditioned MSCs [59]. Furthermore, agarose appears to be a supportive material to enhance the chondrogenic potential of MSCs [60], similar to (sodium) alginate [61], hydroxyapatite [62] and hyaluronic acid [63]. In addition, seeding of these cells into 3D scaffolds further enhances their chondrogenic differentiation [64]. Ude et al. identified adipose stem cells (ADSC) and bone marrow stem cells (BMSC) as promising and widely available source for induction of autologous chondrogenesis [65] that may be bedded in poly-lactide-*co*-glycolide scaffolds [66]. Special therapeutic potential for cartilage repair seems to have $CD271^{+}$ marrow stromal cells [67]. Muscle-derived stem cells were evaluated for their cartilage repair potential as well and were found to benefit cartilage repair by having beneficial effects on chondrogenesis and preventing angiogenesis [68, 69].

In an experimental study, induced pluripotent stem cells (iPSCs) were seeded onto polycaprolactone (PCL)/gelatin scaffolds and found to result in better cartilage restoration after implantation in an in vivo model than the scaffolds alone [70, 71]. A study by Toh et al. used human embryonic stem cell-derived cartilage cells (HCCEC) that were encapsulated into hyaluronic hydrogel [72] and found tissue regeneration when implanted into local cartilage defects. As most chondrocytes lose chondrogenic potential after only seven doublings, Williams et al. identified a novel progenitor cartilage cell subpopulation that is capable of maintaining its chondrogenic potential [73].

Using a so-called cell sheet technique, Sato et al. tried to imitate the biological architecture of hyaline cartilage with its different layers [74, 75]. Similarly, 3D cell cultures mimic the zonal organization of articular cartilage and the resulting matrix seems to be of stable biomechanical properties [76].

Yet another strategy of pursuing cartilage repair and restoration is the usage of differentiated chondrocytes, e.g., autologous chondrocyte implantations with and without scaffold (ACI) [77–80], microfracturing [81, 82], nanofracturing [83], cartilage minced technique [84] and osteochondral autologous transplantation [85–87] with platelet-rich plasma [88]. Bonasia and colleagues quantified that the healing capacity of allogenic juvenile, autologous adult and combined juvenile-adult cartilage fragments and found the latter to be a promising strategy for one-stage surgery [89]. Another study by Gelse et al. showed that pure autologous cartilage transplants do not heal a cartilage defect and rather remain as inert structures within the defect. They concluded that integrative cartilage repair depends on additional cells that are capable of replication [90]. This is supported by an ovine animal study that found better results for autologous chondrocyte implantation when primary harvesting included a higher dose of chondrocytes [91]. An important study by Nixon et al. questioned whether the defect depth (full-thickness vs. partial thickness) may also influence the repair capacity and found evidence for good healing in partial thickness, avascular defects that were treated by ACI [92, 93].

In addition to the defect depth, the localization of the defect is of importance as forces in biomechanically loaded zones may limit cartilage regenerative processes, especially when using potentially differentiating cells [94]. Thus, tracking of implanted or injected (MSC) cells can provide important information on the in vivo situation [95–97].

Robinson and colleagues demonstrated a successful cartilage reconstruction when transplanting human live epiphysis to rabbits [98] and another study stated that xenotransplantation of pig chondrocytes into partial thickness articular cartilage defects in rabbits did result in cartilage-like tissue formation without any signs of graft vs. host rejections or infiltration by immune cells [99]. In contrast, there is evidence that xenografts are unsuitable for transplantation into human cartilage defects due to severe immunological reactions [100]. An in vitro study by Prado et al. established a model for xenoimplantation of (pig) chondrocytes into human articular cartilage defects [101]. Similar set-ups were also used for studying humoral responses rather than tissue formation [102].

Jackson and collaborators [29] experimented with cartilage allografts and found that the structural features of the graft are essential for its long-term viability. According to this paper, inferior structural features were caused by trauma during transplantation and lymphocyte infiltration. In this study, the tidemark was damaged during harvesting and thus would allow immunological access to the implanted cartilage. It also seems to be crucial under which conditions grafts are stored until transplantation to maintain the tissues' structural features [103]. An additional reason for failed allotransplanted (OAT) grafts might be the induction of caspase-3 cascade leading to apoptosis, while isotransplanted grafts would not show any signs of cell death [104]. The iliac crest cartilage transplantation for articular cartilage restoration is also a promising strategy that seemed to yield satisfying results in an in vivo model [105] or the implantation of adenovirus-transduced chondrocytes that are overexpressing proteins involved in cartilage homeostasis [106].

Tissue engineering

Tissue engineering for cartilage follows two principle strategies: usage of natural tissue with similar characteristics as cartilage and de-novo synthetization of materials mimicking biomechanical, biochemical and structural features of cartilage (Fig. 1). Huwe et al. used such costal cartilage for articular cartilage repair [107] and other experimenters used auricular cartilage [108], periosteum [109] or tendon autografts [110], the latter with diminished success.

The majority of studies conducted in cartilage tissue engineering, however, investigated the properties of synthesized scaffolds of diverse composition. Generally speaking, there are two types of approaches: cell-free and cell-laden scaffolds.

Cell-free scaffolds

Materials typically used for these cell-free scaffolds were bacterial nanocellulose [111], polyethylene glycol in combination with hyaluronic acid [112] or chondroitin sulfate [113], collagen-hydroxyapatite hybrids [114–116], aragonite-hyalorate membranes [117], acrylamide hydrogels [118–120], alginate/chitosan compounds [121, 122], poly(DL-lactide-*co*-glycolide) [123–125]. Other groups experimented with poly(ethylene glycol)-terephthalate-poly(butylene terephthalate) (PEGT/PBT) [126] or -fumarate [127], agarose/polyglycolic acids (PGA) [128–130], porous polycaprolactone (PCL) [131–133], hydroxyapaptite bioceramics with poly-L/D-lactide (PLA) coating [134] porous tantalum [135], decellularized osteochondral extracellular matrix (ECM) [136], or poly(ester-urethane) scaffolds [137]. Some of these materials came into clinical application but are now widely rejected due to disappointing long-term results [36, 138–140]. Another at-the-time very experimental approach was the injection of elastin-like polypeptide gels for intra-articular cartilage defect filling. However, gels degraded rapidly and were biologically unstable [141]. The synthetic gastrin receptor antagonist AG-041R was similarly used for cartilage damage re-filling [142].

Cell-laden scaffolds

When cell-free scaffolds started to be questioned in terms of cartilage restoration capacity, cell-laden scaffolds became important in tissue engineering using scaffold materials that were similar to those mentioned above. Here, again, there are stem cell-based and differentiated chondrocytes-based approaches.

A recent study by Levato and colleagues pursued the strategy of loading bioprintable hydrogel with cartilage-derived progenitor cells [143]. Furthermore, MSCs were seeded onto PLA (alginate) [144–146], PLGA membranes [147, 148] or bioceramic beta-tricalcium phosphate (beta-TCP) [149]. All of these techniques resulted in the formation of cartilage regeneration tissue.

Other authors used PGA-fibrin scaffolds and seeded monolayered, cell-cultured chondrocytes onto it, finding a mechanically stable structure [150]. Similarly, a biphasic construct of articular chondrocytes and porous calcium phosphate [151], agarose [152], collagen I/III [153], atelocollagen/PLLA [154], hyaluron [155], gelatin/chondroitin-6-sulfate/hyaluronan [156], or thermoreversible polymers [157] were evaluated for cartilage restoration capacity. A study using chondrocyte-loaded collagen membranes showed cartilage healing as well [158]. It could also be

shown that microfracturing seems to facilitate the healing capacity of collagen cell-laden scaffolds [159] or chondrocyte fibrin suspensions [160].

Certain physical parameters are important for a successful tissue formation. Thus, a higher degree of stiffness of the scaffold yields beneficial effects on chondrogenesis [161–163]. Proper fixation of implanted scaffolds may also play a crucial role to guarantee stability and thus allow for subsequent tissue adaption [164, 165]. Chen and colleagues build three-dimensional electrospun gelatin/PLA scaffolds containing chondrocytes that build cartilage tissue [166]. An Italian group placed minced cartilage on a hyaluronic acid-fibrin-platelet-rich-plasma (PRP) scaffold for successful one-stage cartilage repair in rabbits [167] and a compatriot group found similar results when using autologous chondrocytes in similar scaffolds [168].

The technique of a fibrin-glue polymer with suspended chondrocytes was not pursued in further studies [169]. Also, metal implants (oxidized zirconium, cobalt-chromium) for the coverage of cartilage defects are not a potential treatment option as articulating cartilage exhibited significant damage after 1 year of follow-up [170].

Yet it remains questionable whether scaffold-associated techniques qualify for high-quality cartilage regeneration in the future [116].

Biophysical stimulation

As articular cartilage is exposed to high mechanical loads, its structure is perfectly adapted to sustain these forces over long periods of time [171]. Hence, tissue-engineered cartilage has to imitate these features to effectively regenerate cartilage defects [172]. However, mechanical loading does not only yield advanced structural requirements on articular cartilage, it also induces chondrogenesis via the PKA/CREB-Sox9 and PP2A pathway [173] if forces do not exceed a certain level [174].

Thus, some authors exerted mechanical stimuli on in vitro tissue-engineered cartilage constructs and observed enhanced tissue integrative properties [175, 176]. Others found that optimal mechanical stress (gradual weight bearing vs. continuous passive motion) would support cartilage differentiation [177, 178] more than joint distraction only [179], although other authors claim joint distraction to be an effective treatment method [180]. Furthermore, the influence of shear stress was explored by applying fluid (cell culture medium) shear stress [181]. Cell vitality was enhanced by substituting hyaluronic acid on cartilage surface by reducing shear-trauma [182]. Yet, success of this procedure for cartilage regeneration may largely depend on the defect location and its direct exposure to mechanical forces [183, 184]. Another study combined synergistically mechanical stimuli with TGFβ supplementation [185]. Pulsed electromagnetic field therapy for the treatment of full thickness cartilage defects in rabbits was shown to have potential for cartilage formation [186]. Ultrasound treatment, however, did not show any effect on cartilage regeneration [187].

Mathematical modeling

A novel and more abstract strategy to investigate chondrogenesis as well as regeneration and healing of cartilage are in silico approaches (Fig. 1). Raimondi and colleagues established such an experimental-computational model to investigate which type of cell culture medium and which conditions would benefit cultured cartilage and found perfusion with concomitant pressure cycling to be most beneficial [188]. As the optimal mechanical properties of a scaffold in vivo are not completely clarified yet, Kelly and Prendergast made computational predictions on the most suitable degree of stiffness for the scaffold, encouraging researchers to increase the stiffness to enhance cartilage formation [189]. A finite element model describing the orientation of collagen fibers in articular cartilage, may be useful for planning future loading protocols for tissue engineering [190]. Other groups computed that cyclic compressive loading would add to the vitality of chondrocyte cell cultures [191] and that certain mechanical [189, 192, 193] or oxidative [194] stimuli contribute to osteochondral defect repair as well. Besides pure theoretical approaches, computational simulations for in vitro chondrocyte cell cultures were developed based on cell culture read-outs as well [192]. This approach made predictions more reliable and biology-adjusted and thus allowed for calculation of chondrocyte tissue formation or cartilage growth based on measured data [193, 195–197]. Although some of these studies used data from real experiments, they do not overcome the problem of simulating the in vitro rather than the in vivo situation. From a more etiopathologic perspective, Stender et al. computed a finite element model to describe the changes in the subchondral cortical bone, calcified cartilage, the articular cartilage as well as the subchondral trabecular bone [198]. There is also a model simulating cell migration, proliferation and differentiation after ACI [199]. Although it does not seem suitable for translational purposes as it has not been matched with in situ data, it matches with clinical observations that stem cell seeding alone may not be superior to chondrocyte implantation. As TGFβ is crucial for the transformation of MSCs [200] into chondrocytes a differential equation model was developed to predict the concentration necessary to induce chondrogenesis in MSCs [201]. So far there are no big data models that use a bottom-up approach with data from in vivo or vitro experiments that try to simulate the multiparametric dimensions of a cartilage system similarly as it has already been done in systems biology.

Table 1 Papers of particular interest are summarized in this table and have been highlighted as the following: [a] of special interest, [b] of outstanding interest

	Author/year	Contents
[b]	de Vries-van Melle, M.L./2012 [26]	Osteochondral model for the in vitro investigation of different repair techniques
[a]	Sato, M./2014 [74]	Technique for tissue-engineered chondrocyte layers that form a type of scaffold
[b]	Nixon, A.J./2017 [158]	Testing of clinically established method (MACI) with second look and histological readouts
[b]	Levato, R./2017 [143]	Bioprintable cell-laden hydrogels with chondrocyte line cells
[a]	Theodoropoulos, J.S./2016 [175]	Investigation of biomechanical impaction on cartilaginous regeneration
[a]	O'Reilly, A./2016 [192]	In silico model using experimental data for prediction of biomechanical influence on osteochondral repair
[b]	Shibuya, N./2014 [104]	Allotransplantation of cartilage results in apoptosis and may induce acute rejection
[a]	Juhasz, T./2014 [173]	Molecular pathway responsible for chondrogenesis is activated through biomechanical stimulation
[b]	Meretoja, V.V./2012 [32]	Co-culturing of chondrogenic cells and MSCs results in enhanced chondrogenesis
[a]	Kon, E./2010 [114]	Cell-free scaffold that advanced into clinical application

Conclusion/summary

Current experimental (and thus clinical) strategies for articular cartilage repair have not yet succeeded to replicate the structure and function of innate articular cartilage. In recent years, novel tissue-engineered materials as well as original cell-based approaches have become predominant in this field of research (papers of particular interest are summarized in Table 1). In fact, those approaches aim for de-novo synthesis of articular cartilage. Likewise, in silico modeling will become a crucial instrument for the development of novel strategies and the fast-track prediction of their healing potential. Encouragingly, strategies aiming for (auto-)regeneration or substitution of cartilage—such as allogeneic transplantation with/without immunosuppression—may yield great potential. In the past three decades, knowledge about articular cartilage and its defects has multiplied in the clinical as well as in the experimental setting (Fig. 1; Table 1). There is, however, much work yet left to be done to decipher the molecular mechanisms responsible for guiding regenerative processes and to the find appropriate ways to modulate them for therapeutic strategies.

Author contributions All authors contributed to the conception and design and drafting of the article, critically reviewed the article for important intellectual content, collected and assembled the data from the available literature, and gave final approval of the article.

Funding There is no funding source.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

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