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Cartilage Tissue Engineering; Lessons Learned From Periosteum

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Abstract

Cartilage, due to its unique physiology (lack of vasculature), can be potentially repaired using tissue engineered in the laboratory, by combining cells and with a supporting scaffold. This requires a marriage between material science, cell biology, and translational medicine, a concept well established as Tissue Engineering.

Over the years the *in vivo* and *in vitro* chondrogenic potential of periosteum has been recognised by many researchers and as such periosteum is explored both to repair cartilage defects directly by transplanting periosteum into the cartilage defect or by using periosteum as a cell source for cartilage engineering purposes. The initial example hereof is the first generation of Autologous Chondrocyte Transplantation. Graft hypertrophy and ossification remain the primary drawbacks of cartilage repair strategies using engineered cartilage. These drawbacks may (partially) be due to the endochondral ossification process that can take over when cartilage is repaired. In this process chondrogenesis of progenitor cells is followed by hypertrophy of these cells and subsequent ossification. Periosteal progenitor cells go through this process in order to heal bone fractures. This review provides an overview of the role of periosteum in cartilage repair and cartilage tissue engineering and illustrates how periosteum can be used as a model to study the endochondral process. Such studies may provide clues to further optimize cartilage tissue engineering by identifying important factors which are capable of maintaining cells in their chondrogenic phenotype. Finally, the use of periosteum to engineer cartilage *in vivo* at an extra-articular site is described.

Keywords: Cartilage; Tissue engineering; Endochondral ossification; Periosteum

Introduction

The research area which combines cells with carrier materials to reproduce tissues in the laboratory is called Tissue Engineering (TE). Within the field of TE, scientists of different disciplines such as cell biology, biomaterials, biomechanics, engineering and translational medicine are collaborating and have already made fruitful scientific achievements. Since cartilage consists of a single cell type namely the chondrocyte and has a very poor healing capacity, it was identified earlier on as an ideal candidate for tissue engineering. However, the macromolecular arcade-like collagen architecture of cartilage, which is capable of withstanding an enormous amount of intensive and repetitive forces during life, is challenging to engineer.

Both cartilage and bone are formed during a process called endochondral ossification. Although in the early embryonic phase these tissues start from the same mesenchymal cell condensates, the difference in self-repair capacity is striking [1]. Compared to bone, cartilage has a very poor regenerative capacity. The difference in repair capacity may be partially explained by the presence or absence of periosteum and the lack of inherent vasculature in cartilage. Periosteum is absent in articular cartilage but covers the surface of most bones. It has been demonstrated that the periosteum is critically involved in repair of bone fractures and plays an important paracrine role during skeletogenesis. Especially the cambium layer of the periosteum, which is a source of mesenchymal progenitor cells, has been shown to be capable of forming cartilage and bone *in vitro*, *ex vivo* and *in vivo* [2].

The aforementioned properties of periosteum have been explored to repair articular cartilage. However, due the lack of control over quality and amount of tissue, viability of progenitor cells and unwanted graft ossification, periosteum had become a less popular tissue for cartilage repair. Hypertrophy and ossification of the repair tissue remain undesirable processes hampering good functional cartilage repair. In this context maintaining the appropriate chondrocytic phenotype that can produce type II collagen and other relevant cartilage macromolecules is important in ensuring favourable longterm outcomes in cartilage repair. In this review the historic role of periosteum in the early examples of cartilage repair, using principles of tissue engineering is discussed, and the potential role of periosteum in engineering ectopic cartilage for autologous transplantation is reviewed. The lessons learned from studying periosteal chondrogenesis may unravel factors that may prevent undesirable hypertrophy and calcification of repaired cartilage.

Periosteum - a historical perspective

The outer surface of bones is covered by a condensed, fibro-collagenous layer called periosteum. This periosteal layer is tightly attached to the underlying bone by collagen fibers. These so-called Sharpey's fibers penetrate deep into the outer cortical tissue. Two morphologically distinguishable layers can be found in periosteum; (i) the outer, thicker fibrous layer, and (ii) the layer adjacent to the bone called the cambium layer (Figure 1). The definition "cambium" refers to the cambium layer of the trunk of a tree [3]. The cambium layer in the periosteum contains mesenchymal progenitor cells with osteo- and chondrogenic potential. Periosteum is highly active during fetal development when it generates osteoblasts for the appositional

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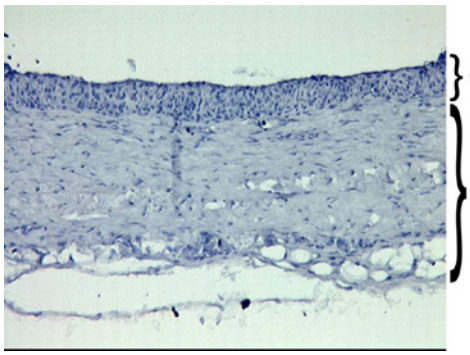

Figure 1: Periosteum stained with thionine. The cambium layer contains a high density of progenitor cells and is attached to the bone. The fibrous layer contains less cells that are predominantly fibroblastic (magnification 200X).

growth of bone. In 1942, Duhamel was the first to publish a report which recognised the osteogenic function of periosteum [4]. Culturing periosteum was first described by Fell [5]. These reports of Duhamel and Fell reported about the osteogenic capacity of periosteum. Now it becomes more and more clear that osteogenesis of periosteum is due to the process of endochondral ossification. The first phase of the endochondral process is chondrogenesis and it was the group of Caplan in the nineties which reported about the chondrogenic capacity of periosteum [6,7]. Caplan's group mostly used (super) confluent isolated chick periosteum cells to examine the osteogenic and chondrogenic capacity of these cells. At this time the group of O'Driscoll reported an *ex vivo* culture model [8]. In this model whole periosteal tissue grafts are isolated and cultured in a bilayer of agarose. Work of the group of O'Driscoll confirmed earlier reports of Press (1924) and Owen (1970) that the osteochondral potential of periosteum decreases with age [9,10]. *In vitro* Transforming Growth Factor (TGF)-β and members of its superfamily such as Bone Morphogenic Proteins (BMP's) are used to trigger chondrogenesis of periosteal cells. *In vivo*, Parathyroid hormone related peptide (PTHrP) is expressed by periosteum [11]. PTHrP acts together with Indian Hedgehog (Ihh) in a negative feedback loop regulating the pace of chondrocyte proliferation and terminal hypertrophic differentiation in the developing growth plate, thus growth of long bones is also influenced by periosteum in a paracrine way [12]. Post-natal and even after closure of the growth plates periosteum remains important for fracture healing. In case of a bone fracture especially cells of the periosteal cambium layer are involved in bone formation via the endochondral ossification process. During this process cartilage tissue is formed. This cartilage undergoes hypertrophy, dies and leaves a template behind for invading cells to deposit bone tissue and providing the necessary vascularisation [13]. The thickness and chondrogenic potential of periosteum decreases with increasing age [14], thereby deteriorating the natural healing capacity of the bone. Periostin is expressed by the periosteum and increased periostin expression is found under mechanical stress (e.g. fracture) [15]. This adhesion molecule is believed to play a role in the recruitment of osteoblast precursors [16] and thus determines, in part, the fracture healing capacity at places where periosteum is covering bone. At locations where periosteum is absent (e.g. within the joint capsule of the femoral neck) fractures heal slowly. This may be explained by decreased availability of mesenchymal precursors, but also by virtue of absence of periostin and other important periosteum-excreted paracrine factors. This concept is strengthened by the fact that removing periosteum surrounding a fracture leads to absence of cartilage in the fracture callus [17] and consequently impairs the fracture healing process.

Hypertrophy and ossification after cartilage repair

One year after Duhamel reported the osteogenic function of periosteum, Hunter was the first to recognise that articular cartilage, once destroyed, does not heal spontaneously [18,19]. Whereas the progenitor cells in bone marrow and periosteum contribute to bone formation during fracture healing, articular cartilage is largely deprived of these progenitors. Although it has been shown that the superficial layer of articular cartilage and the synovial membrane contain mesenchymal progenitor cells [20,21], cartilage has a limited ability for self repair [22]. Cartilage defects may arise due to trauma or cartilage degeneration. Although patient's history may differentiate between traumatic and degenerative lesions, in clinical practice it often remains difficult to find the cause of cartilage defects. Small or early superficial cartilage defects may present with only (minor) effusion of the affected joint or even without symptoms or pain, as cartilage lacks nerve fibres. A study of Hjelle and co-workers showed that in more than 60% of arthroscopies for different indications (e.g meniscus lesion), cartilage lesions were found along [23]. In addition, diagnosis of structures likely to be damaged upon trauma (e.g. subchondral bone, ligaments or menisci), by Magnetic Resonance Imaging (MRI) may reveal an even higher general incidence of cartilage lesions. Important developments in the field of MRI are protocols such as delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) and T1Rho. Both techniques are designed to visualize cartilage on the collagen and GAG content level [24]. Overall MRI is expected to replace cartilage biopsies for evaluation of (novel) cartilage repair strategies and thus becomes more important in evaluation of progression of cartilage degeneration and cartilage repair techniques in a non-invasive manner. Both biopsies and MRI's have shown that cartilage repair may be hampered by unwanted hypertrophy and ossification. Peterson was the fist to describe this unwanted hypertrophy during ACT, while interlesional osteophytes are reported after microfracture procedures, minced cartilage procedures, and perichondrium arthroplasty [25,26]. Interlesional osteophytes can seen as a consequence of ossification of the repaired cartilage.

Periosteal and perichondrium arthroplasty

Periosteal progenitor cells capable to undergo chondrogenesis reside in their own matrix. This not only gives periosteum good handling properties but some even regard periosteum as a natural scaffold with its own progenitor cells. As such periosteum transplantation is a potentially interesting approach for the treatment cartilage defects. Many researchers have reported on the chondrogenic potential of periosteum [2,27-29]. In a rabbit study *de novo* formatted hyaline cartilage with collagen type II (COl2A1) was found in more than 90 percent of the cartilage defects treated with autologous periosteal grafts [2]. However studies in human subjects never showed such successful results [30]. Many factors may impact the clinical results when applying periosteum in humans for cartilage repair; (i) a decreasing number of progenitor cells with increasing age, (ii) the method of harvesting periosteum is essential to include the cambium layer with its progenitors, (iii) ossification of subchondral bone by factors released by the transplanted periosteum or ossification of the transplanted periosteum itself [31]. An alternative method is the use of perichondrium. This tissue resembles periosteum, but in contrast to periosteum does not cover bones but covers cartilage of the ribs. Perichondrial arthroplasty used for human cartilage repair was first described by Skoog et al. [32]. This technique has been reported to give an initial cartilage repair in the defect [33,34]. On the long term poor results related to overgrowth of the graft and ossification are reported by Bouwmeester et al. [26]. This report of Bouwmeester was one of

the first reports illustrating the need to prevent ossification of the repaired cartilage and the need to maintain cells in their chondrogenic phase. These authors concluded that a better fixation of the graft might improve the results. However, the underlying biology causing the poor outcome of the technique is not understood. In a study comparing periosteum with perichondrium, chondrogenesis was significantly more observed when using periosteal grafts [35]. Lack of control of the amount of progenitor cells prior to transplantation, graft fixation and control of unwanted ossification post-transplantation, remain an issue of concern, especially when using progenitor cells for Tissue Engineering of cartilage.

The role of periosteum in autologous chondrocyte transplantation

The work of Brittberg and co-workers showed that chondrocytes can be harvested from the patient, cultured *ex vivo* and then successfully transplanted for the repair of articular cartilage defects using a gel carrier [36]. This technique, commonly referred to as Autologous Chondrocyte Transplantation or Implantation (ACT of ACI), is one of the first examples to successfully espouse the principles of tissue engineering for cartilage repair. In the early years of ACT, transplanted chondrocytes were kept in the cartilage defect by suturing an autologous periosteal flap over the treated defect with no additional augmentation using artificial structures. It was expected that the combination of the chondrogenic potential of periosteum together with the transplanted chondrocytes would be essential and would generate a chondrogenic unit leading to cartilage repair [37]. However, since the chondrogenic effect of the periosteum declines drastically with age [14], the stimulatory effect of the periosteum might only be relevant in younger patients. On the other hand, periosteum alone could be used to treat younger patients [37]. But the combination of chondrocytes and periosteum may better be reserved for older patients. Because of the substantial risk of periosteal hypertrophy, the technology requires refinement with the inclusion of new bioactive biomaterials that can secure the cells in the defect area and enhance their proliferation and differentiation. This optimization effort has led to the introduction of collagen meshes in ACI procedures. Since ACI demands the harvesting of autologous cartilage donor tissue from a non load bearing site at the articular cartilage surface, one might argue that this technique intrinsically causes extra damage to the already damaged joint. As an alternative, mesenchymal progenitor cells can be harvested from other donor sites. This is appealing as the use of these cells in cartilage repair would not further damage the joint. Mesenchymal progenitor cells in cartilage repair are therefore the subject of investigation by several groups including ours. However, the implementation of these cells can pose several challenges. Our group reported that periosteal progenitor cells implanted into an osteochondral defect have a poor survival compared to chondrocytes [38]. Ball et al. [39] demonstrated increased viability of differentiated, allogenic perichondrium cells upon implantation compared to non-differentiated ones [39]. When using progenitor cells for cartilage repair, ossification of the repaired tissue may impair clinical results. Examples hereof are ossification and formation of interlesional osteophytes when applying techniques such as microfracture and periosteum or perichondrium plasty [25,26]. These findings illustrate that maintaining differentiated progenitor cells in their chondrogenic state is a challenging task in cartilage repair. In contrast to native chondrocytes, it seems that progenitor cells have the tendency to follow the different phases of endochondral ossification towards hypertrophy and mineralisation after being triggered to differentiate into chondrocytes. As such, it is of utmost importance to maintain cells in their desired differentiation state when applying these cells for cartilage TE purposes. Work of Hendriks and co-workers showed that chondrocytes stimulate mesenchymal progenitor cells towards chondrogenesis when both cell types are co-cultured [40]. Importantly, the resulting cartilage constructs remains in its chondrocyte phase. The underlying mechanism was later described by Fisher et al. who suggested that human articular cartilage-derived soluble factors such as parathyroid hormone related peptide (PTHrP) are potent means of improving chondrogenesis and suppressing the hypertrophic development of mesenchymal stem cells [41] as they differentiate into chondrocytes. Furthermore, we have recently shown that cyclooxygenase-2 (COX-2) inhibitors are also able to decrease chondrocyte hypertrophy (manuscript in preparation). Taken together, studying periosteal chondrogenic differentiation may improve the use of mesenchymal progenitor cells for cartilage TE purposes. In conclusion, cartilage defects remain challenging to treat and TE approaches are being extensively evaluavated to overcome the inability of cartilage to repair itself. Both the past experience of periosteum transplantations into the cartilage defect and studying cartilage formation by periosteal progenitor cells both *in vitro* as in *ex vivo* models give important clues how to further optimize cartilage TE.

Periosteum as a model to study and improve cartilage te

As mentioned above, periosteum can be harvested and cultured as an *ex vivo* model [8]. After harvesting, periosteum is embedded in a sandwich of agarose. TGF-β is used to induce chondrogenesis of progenitor cells in the cambium layer. The advantage of such a model is that mesenchymal progenitor cells remain in their own surrounding matrix and time consuming and demanding cell culture techniques are bypassed. Such an *ex vivo* model enables the investigation of factors controlling chondrocyte terminal differentiation and ossification. In follow-up, these factors may be tested for their ability of maintaining differentiated progenitor cells for cartilage TE engineering purposes *in vivo*. Next to biochemical factors also biomechanical factors impact the outcome of articular cartilage repair. As such periosteal arthroplasty was one of the first models which confirmed the essential role of Continous Passive Motion (CPM) for maturation of cartilage repair strategies. Since periosteum cultured as an *ex vivo* model can be loaded with different mechanical loading regimes, this also enables us to unravel biomechanical factors which improve collagen type II-content of TE engineered cartilage [42]. Especially engineering cartilage with the appropriate amount of Collagen type II (and other essential extra cellular matrix components such as glycosaminoglycans) remains challenging and has not been fully achieved yet. Periosteum as a source for mesenchymal tissue formation has been investigated in literature for several species such as minipig, chicken, etc., although rabbit periosteum is most frequently used. Harvesting periosteum for (fundamental) research purposes or periosteum transplantations should be performed not only under sterile conditions, but should also aim to harvest a maximum yield of progenitor cells. While the group of O'Driscoll describes a specifically designed periosteal elevator, the Shastri-group has described hydraulic elevation of periosteum as a safe and reliable method for harvesting [43,44]. Interestingly, subperiosteal injection of TGF-β *in vivo* enhances the quality of harvested periosteal tissue prior to use for *ex vivo* or *in vivo* cartilage TE purposes [45].

In vivo differentiation of periosteum to generate cartilage

In vivo stimulation of periosteal progenitor cells (e.g. by damaging periosteum or by subperiosteal injection of a gel) can also be used to engineer ectopic cartilage. An interesting approach designed by

Takahashi et al. [46] used early fracture callus, induced at the iliac crest [46]. The early fracture callus was implanted into osteochondral defects of rabbit knees and yielded excellent results in terms of cartilage repair. Later work showed that periosteum stimulation by partial resection of periosteum without inducing a true fracture also generated cartilage. After harvesting and transplantation of this ectopically generated cartilage osteochondral defects were successfully repaired with this tissue [47]. Shastri and co-workers published an interesting concept of inducing osteogenesis in an artificially created subperiostal space they refer to as the "in vivo bioreactor" (IVB). They also went on to demonstrate chondrogenesis within the IVB by the injection of a hyaluronic acid-based gel containing the anti-angiogenic factor Suramin. In this system the inhibition of angiogenesis provided the hypoxic character to the biogel-environment which was likely to favour the formation of cartilage that resembles early fracture callus [48,49]. Following the initial report, which focused on bone, we aimed to achieve controlled chondrogenesis within the IVB and control the local subperiosteal environment by simply injecting a gel to initiate the endochondral process. In a seminal study Emans and Shastri demonstrated that both agarose and polysaccharide gels loaded with liposomes containing TGF-β1 were equally successful in triggering the formation of ectopic cartilage, thus paving the way for using simply a biomaterial as a trigger for chondrogenesis *in vivo*. The hypercellular cartilage induced within the IVB, was harvested during its early chondrogenic phase and successfully implanted into an osteochondral defect where excellent lateral integration into the subchondral bone as well as in the articular cartilage was observed. Importantly, absence of ossification of the transplanted ectopically produced cartilage was observed in a long term follow-up study [48].

In cartilage repair techniques such as ACT and Matrix Assisted Chondrocyte Transplantation (MACT), cells are harvested from articular cartilage [36]. This may affect joint homeostasis and implies expensive culture techniques. Thus alternative cell sources which do not interfere with the joint (homeostasis) and finding methods which bypass expensive and time consuming culture techniques are important goals to further optimize cartilage repair techniques. The main advantage of the herein described approach is that the body is used as its own "*in situ incubator*"; thereby omitting the above summarized drawbacks of currently used techniques. This approach also provides a donor tissue that already carries a certain degree of cartilaginous micro architecture and optimally integrates into the subchondral bone/articular surface and remodels via endochondral pathways at the anatomically desired sites. Scotti et al. [50] showed that if early non-hypertrophic endochondral tissue is harvested and implanted the transplanted graft would not further ossify [50]. As such it seems that in contrast to transplant periosteum directly after harvesting, ossification of repaired cartilage does not occur when periosteum is differentiated into cartilage prior to transplantation [46-48].

Conclusion

Early on, periosteum was recognised for its chondrogenic capacity and as such has been explored as an autologous tissue for cartilage repair. Periosteum is a source of mesenchymal progenitor cells, which are capable of forming cartilage and bone and participating in natural repair mechanisms such as repair of bone fracture through ossification of a cartilage callus via endochondral ossification. Since periosteum can be harvested and cultured using organ culture techniques, wherein it serves as a matrix for the directed chondrogenesis of its progenitor cells, periosteum is well suited as a model system to study the factors that influence chondrogenesis. One can envisage that using periosteum organ culture models biophysical and biochemical variables that impact chondrocyte fate, lineage choices and maintenance can be identified. This knowledge can then be translated into viable clinical treatment strategies such as ACI but also for cartilage repair strategies which make use of progenitors cells (e.g. the *in vivo* bioreactor) since chondrogenesis of progenitor cells may be followed by unwanted hypertrophy and ossification.

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