Chapter 11

Applied Basic Science of the Auricular Cartilage

Mohamed Khamis Tolba Mahmoud Abdalla

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72479

Abstract

Cartilage is an essential component of human body, and it is present in any region of the body. Auricular cartilages play an essential role in esthetic aspect and shape of the face. Therefore, comprehensive understanding of the applied basic science of the cartilage of the ear is essential to understand the pathophysiology of diseases that occur in this region, how much it is resistant to infections and invasion by malignancies and how postsurgical and postinfection healing happen.

Keywords: cartilage, auricular, ossification, invasion, malignancies

1. Introduction

In this chapter, the practical aspects of the applied basic surgical science of the auricular cartilage are discussed on an evidence-based level according to the most recent researches in the literature.

Ear pinna (auricle) is an extremely important organ not only for the facial aesthesis but also plays a major role in hearing physiology. Both functions rely primarily on the biomechanical nature of the cartilage. Degrees of inclination and angles at its attachment to the skull determine the shape of the head and the auditory function especially the ability to localize the direction of sound.

In addition, auricular cartilage is vulnerable to many congenital and acquired diseases that require cartilage replacement or excision; this has opened the door for many advances in tissue engineering to happen. Moreover, healthy cartilage of the auricle is a plentiful source of cartilage for reconstruction of the nose, skull base and facial defects.

Consequently, comprehensive knowledge about recent advances in literature about basic science of this critical piece of cartilage is of paramount importance. In this chapter, précised, focused and between lines pieces of information will be mentioned, but old and repeated ones will not. The chapter aims to know how basic physiology, pathology, biomechanics and biochemists of the auricular cartilage can be applied to the clinical perspectives. It is not a pure clinical chapter; only related points that can be applied to the clinical practice are discussed.

Based on the abovementioned perspectives, the reader of this chapter is expected to acquire detailed knowledge about:

- Microarchitecture of the auricular cartilage and applied physiological aspect of the chondrocyte and matrix,
- Response of auricular cartilage to relapsing polychondritis as the most common autoimmune disorder affects the auricular cartilage,
- Effect of ischemia on the cartilage,
- Pathophysiology of infective chondritis and perichondritis,
- Molecular biology of invasion of the cartilage by malignancies,
- Effect of surgical intervention and trauma on the cartilage,
- Healing of auricular cartilage after surgery and trauma,
- Healing of the graft in auricle and
- Aberration of healing.

Reader also will be provided, at the end of the chapter, with an "at a glance section" that summarizes the most important advances in understandings.

2. Microstructure of auricular cartilage

The auricle is a funnel-shaped cartilaginous structure consists of a single thin plate of elastic fibrocartilage covered by skin and it is continuous with the meatus of the external auditory. It is also characterized by ridges and depressions formed by the auricular cartilage; there are five regions caused by this molding such as helix, antihelix, tragus, antitragus and concha [1].

Auricular cartilage consists of cartilage cells fill small lacunar spaces in the matrix. Young cells, called chondroblasts, are relatively small and flat and have an irregular edge with pseudopodic-type extensions lodged in the matrix. Postmitotic chondroblasts have intercellular contact and are absorbed with matrix synthesis. The chondrocytes are mature cells that grow and become spheroid with age and lose the extensions [2].

The matrix is composed chiefly of water, proteoglycans, lipids and collagens. The substance is a firm gel, positive to periodic acid-Schiff reaction, and metachromatically to toluidine blue.

The glycoproteins are a series of mucoprotein copolymers, conjoined in large lateral chains without rami, of condroitin-4-sulfate glycosaminoglycans, condroitin-6-sulfate and keratin sulfate. The proportions are modified with age, keratan sulfate increases with age [3].

The resistance to compression and the viscoelasticity are referred to their content of glycosaminoglycans, and the resistance to tension of the collagen and elastic fibers content.

2.1. Applied surgical physiology of human chondrocytes

However, porcine and bovine chondrocytes were used for many years in the tissue engineering of human auricular cartilage; human auricular chondrocytes have become the procedures of production of elastic cartilage in vitro. This has changed the future of auricular reconstruction via its marked ability to grow in tissue culture and marked ability to produce matrix of both hyaline and elastic cartilage. Human chondrocytes have the following criteria in the tissue cultures:

1. They have ability to lay down large amount of elastic cartilage under certain circumstances. Alginate-suspended aggregated chondrocytes produce matrix that contained elastin (the hallmark of the original elastic cartilage) and this amount of auricular elastic cartilage increase markedly with the alginate/collagen-containing hydrogen and enriched with k-elastin [4].
2. It can also be stimulated with insulin, dexamethasone, or growth factors such as bFGF, PDGFbb, EGF, and IGF(2.3), what is more is their ability to continue growth in the subcutaneous pocket.
3. The neo-cartilage, produced by cultured chondrocytes, does not dedifferentiate or degenerate after long cultivation time (12 weeks) and it has the same immunohistochemistry properties as the native auricular cartilage.
4. Cartilages can be created in predetermined shapes and dimensions using chondrocyte transplantation on appropriate polymer templates [4].

Ability of human auricular chondrocytes to proliferate in tissue cultures to produce auricular cartilage molds with the same histological and mechanical criteria, and the same predetermined configuration have changed surgical approaches in clinical situations such as anotia, microtia, traumatic loss and cauliflower ears. This also has replaced old-fashioned methods such as costal cartilage grafting, which was mandating the timing of surgery to be delayed until the age of 6–10 [5], and carry the risk of pneumothorax and chest wall deformities [6].

2.2. Applied surgical physiology of auricular cartilage matrix

As mentioned earlier, the biochemical composition of matrix is the factor that determines the biomechanical properties such as wear resistance, load bearing and shock absorption [7]. The mechanical properties of the auricular cartilage have not been extensively studied to date, but the Young's modulus was determined by tension calculating a modulus value for concha and tragal cartilage to be 3.4 and 2.8 MPa, respectively, but the difference was not significant [8]; however, the concha was found to demonstrate a greater Young's elastic modulus in comparison to the helix [9].

In addition, the final stress relaxation rate was similar for all five regions of the auricular cartilage, suggesting that all regions of the auricle had the ability to reach similar load equilibrium over 15 min (helix $1.78 \times 10^{-4} \pm 0.32$ MPa/s, antihelix $1.62 \times 10^{-4} \pm 0.31$ MPa/s, concha MPa/s $1.52 \times 10^{-4} \pm 0.23$ MPa/s, antitragus $1.46 \times 10^{-4} \pm 0.23$ MPa/s and tragus $1.46 \times 10^{-4} \pm 0.15$ MPa/s). The final absolute relaxation was also similar between the five regions of the auricular cartilage, demonstrating that the auricular cartilages could relax to a similar final stress level (helix 0.21 ± 0.02 MPa, antihelix 0.24 ± 0.04 MPa, concha 0.23 ± 0.04 MPa, antitragus 0.21 ± 0.03 MPa and tragus 0.23 ± 0.03 MPa) [8–10]. Therefore, surgeons can harvest any anatomical part of the auricle for reconstruction.

Such biomechanical properties are mainly due to collagen II fibers in the matrix because Dahl et al. analyzed the bimolecular composition of endogenous auricular cartilage in normal adults, pediatric patients with microtia and pediatric patients with preauricular appendages. Immunohistochemical analysis demonstrated similar levels and distribution of elastin and collagens I and X in all three groups of patients, and reduced expression of collagen II in children with microtia [11]. Collagen II is, also, the main target affected in several diseases and malignancies, which is discussed in the following paragraphs.

As mentioned earlier, reconstructive surgeon should use synthetic or tissue engineered cartilage that provides the anatomical and biomechanical properties of the human auricle to achieve good biocompatibility with the skin [12], adequate mechanical properties prevent deformation of the implant when implanted beneath the skin providing definition of the auricle shape. Also, similar mechanical properties to the surrounding tissue prevent stress at the interface [1]; mechanical mismatch can lead to micromovement between the skin and the implant when subcutaneously implanted [13], thus implant failure and extrusion.

3. Applied pathophysiology of conditions affecting auricular cartilage

3.1. Inflammatory conditions

3.1.1. Noninfective conditions

The most common disease of this type is the relapsing polychondritis (RP) that results from autoimmune reaction against collagen fibers of the cartilage. In addition, there is a condition that must be known to differentiate it from malignancies of the skin and cartilage, it is the "chondrodermatitis nodularis chronica helicis" or "Winkler's disease," which results from ischemia of the cartilage.

3.1.1.1. Relapsing polychondritis

Relapsing polychondritis (RP) is a rare multisystem autoimmune disease characterized by recurrent episodes of inflammation and progressive destruction of cartilaginous tissues, elastic cartilage of the ears and nose, hyaline cartilage of peripheral joints, vertebral fibrocartilage

and tracheobronchial cartilage [14, 15]. Auricular chondritis occurs in 20% of patients at presentation and in 90% at some point during the course of the disease [15]; therefore, its applied pathophysiology will be discussed with some details in the following context. Etiology of RP is unknown but the pathogenesis is mostly due to an immunologic reaction to type II collagen in all human tissues [16, 17].

Collagen type II is the main target of the autoantibodies in RP; therefore, it is the initial step that induces the chondritis; this is approved by the fact that titers against the native type II collagen were substantially higher than titers against constituent alpha-1 (II) chains and antibodies are positive in 30% of cases [17]. This observation suggests that the antibodies were not formed after destruction of cartilage and denaturation of collagen [16]. However, not only autoantibodies against type II collagen have been detected in patients with RP but also autoantibodies against type IX and XI collagen have been found in a patient with RP [18]. In addition, recently auto antibodies against other cartilage proteins such as cartilage oligomeric matrix proteins(COMP) and matrilin-1 have been found; matrilin-1 is a cartilage matrix protein expressed at high levels in the tracheal, nasal, auricular and chondrosternal cartilage [19, 20]. Such antibodies activate both humoral and cellular immunoreaction; there are several evidences to support this [21]:

1. Damaged cartilage is infiltrated by CD4 + T-cells and plasma cells and contains immune deposits and perichondral infiltrate of lymphocytes and plasma cells with loss of basophilic staining of the cartilage matrix indicating loss of proteoglycans [22].
2. A T-cell response specific to peptides found in collagen type II (which contributes 95% of all cartilage collagen) or of matrilin-1 is found in some patients [23].
3. Over half the patients with RP carry the HLA-DR4 antigen [24, 25].
4. In one patient, oral administration of collagen type II for desensitization was apparently effective [26].

These reactions lead to severe chondritis by recruiting inflammatory cells to the cartilage, such recruitment is orchestrated by a complex cytokine network [27] such as interferon-ϒ, interleukin [IL]-2, and IL-12 [28] in addition to soluble triggering receptor (sTREM-1) expressed on myeloid cells 1, chemokine (C-C motif) ligand 4 (CCL4), vascular endothelial growth factor (VEGF) and matrix metalloproteinases-3 (MMP-3) [29].

As a result of this autoimmune reaction, many proteases are released from the inflammatory cells [21] and by chondrocytes that undergo apoptosis by the effect of MMP-3 [30], causing destruction of cartilage matrix and leading to the characteristic features of RP of the auricle.

Because collagen II is responsible for biomechanical criteria of the auricle, after repeated attacks or sometimes after a single prolonged episode, the cartilaginous structure of the ear is damaged and the pinna not only feels flabby but also may droop or even flop up and down when the patient walks [15]. Pinna also may hardened by calcifications or ossification of the connective scar tissue that replaces the cartilage. Cauliflower ear deformity occurs in about 10% of patients [22].

3.1.1.2. Chondrodermatitis nodularis chronica helicis (Winkler's disease)

Another noninfective inflammatory reaction related to the unique criteria of the cartilage in general and auricular cartilage in specific is an inflammatory lesion called chondrodermatitis nodularis chronica helicis. It is a chronic perichondritis, which is thought to be related to limited vascularity at the lateral and anterior aspect of the auricle. The skin is tightly stretched over the underlying cartilage with minimal subcutaneous tissue, which results in limited vascularity and ischemia which is thought to promote the development of this lesion [31]. Another related theory is the perichondrial vacuities which narrows the blood vessels and induce ischemia of the cartilage, leading to the clinical picture of the given disease [32]. Mostly located on the helix, this disease is characterized by a hard nodule which involves the skin and the cartilage of the ear.

Ischemia also can result from compression on the cartilage as in infection and hematoma, which are discussed in the following paragraphs.

3.1.2. Infective inflammatory conditions (perichondritis and chondritis)

Perichondritis and chondritis represent infections of the auricular perichondrium or cartilage. It is caused by blunt or penetrating trauma to the ear or by direct extension from an otitis externa. Penetrating trauma may result from various injuries, including ear piercing, assaults, bites and iatrogenic injuries. Iatrogenic infection occurs when the cartilage and soft tissues of the ear are employed as donor sites for tissue used in the repair of defects of the nose and external ear [33]. The increasingly popular piercing of the ear cartilage as opposed to the lobule may predispose to infection [34], and outbreaks have been reported and Pseudomonas is the most frequent causative organism [35]. Burn of the auricle is the most aggressive form because it makes the cartilage most vulnerable to infective chondritis due to presence of large amount of dead cartilage tissues.

Whatever the reason of chondritis, cartilage becomes intensely infiltrated with polymorphonuclear leukocytes and phagocytes, which damage the cartilage via its cytokines and inflammatory mediators [36] such as auricular cartilage, like any cartilage, lack of vascular supply; it is only supplied from the overlaying perichondrium that makes it vulnerable to ischemia and necrosis. In addition, intact perichondrium adds to the problem because it does not allow the inflammatory edema of the cartilage to expand, increasing the pressure on the cartilage which causes more necrosis and end up with cauliflower ear [37]. This pathophysiology must be applied clinically by immediate drainage of abscess and hematoma, and adequate debridement of any dead cartilage [38].

3.2. Auricular cartilage and malignancy

Cancer of the auricle accounts for around 6% of all cutaneous malignancies, out of which 50–60% are squamous cell carcinoma, 30–40% is basal cell carcinoma (BCC) and 2–6% is malignant melanomas. [39] These malignancies can invade the cartilage of the auricle via several mechanisms but the most recent mechanism rather than the direct tissue pressure effect is the role played by mediators released by the tumors.

Matrix metalloproteases (MMP) play an integral role in tumor growth and metastasis; MMPs are a family of zinc-dependent endopeptidases. They allow tumors to grow by degrading

matrix barriers of the underlying cartilage and promoting angiogenesis as well as releasing active growth factors and modulating apoptosis; therefore, they are used as tumor markers malignant transformation of keratinocytes [40, 41]. Specifically, MMP-13 is associated with greater metastatic capacity and MMP-11 is linked to increased local invasiveness of SCC of the head and neck. MMP-13 (collagenase 3) preferentially degrades type II collagen found in cartilage [42]. In cSCC, MMP-13 collocates with laminin-5, which is normally founded in the basement membrane to promote keratinocyte motility to the edge of the lesion and subsequently degrades nearby tissue, allowing tumor invasion [43, 44]. Therefore, matrix of the cartilage in the auricle is an important risk factor for the squamous cell carcinoma which releases many proteolytic enzymes to facilitate invasion and spread.

4. Healing of auricular cartilage

4.1. Normal healing

Cartilage injuries can be caused by several reasons because it is liable to trauma and several surgical procedures; it is capacious source of highly resistant cartilage, it is also liable to several disfiguring congenital anomalies that necessitate plastic surgeries that require grafts to the auricle to close defects [45]. Despite the widely spread use of those grafts in auricular cartilage defects, insufficient union and loss of grafting material through absorption in the long run has regularly been reported [46].

In addition, damage associated with traumatic injuries or extensive surgical manipulation is characterized by catastrophic disruption of cartilage matrix integrity and structure, extensive chondrocyte death in the area of cartilage injury, and expansion of this "zone of injury," which is facilitated by diffusible mediators such as nitric oxide [47]. The main reason behind this is that the body does not heal isolated cartilage damage effectively because blood supply necessary for the initiation and support of the repair process is absent, a lack of sufficient stem cells to repopulate and repair the defect, and chondrocyte cell death in the surrounding cartilage which compromises tissue integrity and interferes with repair tissue integration [47]. Viable chondrocytes near the injury may proliferate, form clusters of new cells, and synthesize new matrix, but chondrocytes cannot migrate readily through cartilage tissue to the site of the injury, and the matrix components they synthesize usually are not sufficient to fill the defect [47]. To conclude, any cartilage wound healing response that does not lead to replacement of type II collagen and proteoglycan synthesis will result in tissue with abnormal morphologic and mechanical properties [48]. Unfortunately, this is the case when the basic healing process of the cartilage was studied.

Pathophysiology of healing of hyaline cartilage (auricular) can be classified according to the reason of injury:

i. Postsurgical and posttraumatic healing

General healing process of the cartilage is in the young rabbit, traumatization of cartilage perpendicular to its surface resulted within 3 days in regression and necrosis of the tissue, lining the cut end, which is neighbored by a zone of hyperactivity and increased mitosis. On the seventh day, filaments present in the matrix are arranged in bundles, which demarcate the border between the viable cartilage and the regressive zone; they are continuous with the

perichondrial fibers [49], the necrotic material is invaded by macrophages and polymorphonuclear cells from the contiguous exudate. In later stages, this zone has developed into a firm layer of fibrous tissue. After 4–6 weeks, the demarcating fibers will cover the rounded stump, protecting the cartilage fragment. However, all these reactions are absent in adult rabbits making the cartilage not to heal [50].

ii. Healing of grafting to the auricle (healing at interface between graft and auricular cartilage)

Wound healing of the incision surface of the graft was similar to the reaction in the pre-existent cartilage, described earlier. Thus, the scarring occurred on both sides of the junction and therefore, the junction was in most cases, fibrous and not cartilaginous. In addition, the subcutaneous transplant site in the head and neck lead to strong inflammatory reactions and resorption of the bioartificial cartilage in contrast to orthopedic and trauma surgery where the engineered constructs or autologous chondrocytes are placed in the immunoprivileged region of joints [51].

To conclude, the end result of healing depends on the age of the patient, direction and depth of the wound as the following:

1. Large, complete-thickness defects do not heal easily; normal healing time for ear cartilage piercing is 2 months to 1 year, so intervention is a must [52].
2. Partial-thickness defects are normally repaired by deposition of fibrous scar tissue.
3. Small, full-thickness cartilage defects are replaced by fibrocartilage. The mechanism of fibrocartilaginous repair appears to be mediated by proliferation and differentiation of mesenchymal cells of the marrow [53].

Consequently, it is inevitable to find a method that enhances cartilage tissue healing or to replace the damaged cartilage as following:

1. Biologic grafts such as perichondrium have been successfully used to repair full-thickness defects, probably because the inner layer of the perichondrium, adjacent to the cartilage contains progenitor cells that can differentiate into chondroblasts [52]. However, the outer layer rapidly produces fibrous overgrowth, preventing the good cartilage-to-cartilage connection necessary to restore the mechanical function of the structure [54].
2. Tissue engineered cartilage molds can be used, as mentioned in Section 2.1.
3. Growth factors to enhance healing such as somatomedin-C have growth-promoting effect on cartilage [46]. In addition, such products that induce chondrogenesis can be produced via gene therapy. Gene therapy approaches to cartilage repair are encouraged by the ability of various gene products to enhance chondrogenesis [55]. Examples include growth factors [56] such as insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), fibroblast growth factors and various members of the BMP family, as well as transcription factors such as SOX-9 [57], certain signaling molecules such as SMADs [58], and molecules that inhibit apoptosis such as BCL-2 [59]. However, it is still difficult to administer them exogenously to sites of cartilage injury in a sustained and therapeutically useful manner.

4.2. Aberrant healing of the cartilage

Any surgical intervention, especially ear piercing, may complicate with keloid which represent one extreme of aberrant dermal wound healing that is observed only in susceptible individuals following cutaneous injury [60] with higher incidence during puberty and pregnancy, periods with hyperactivity of the pituitary gland [61]. Due to increased release of greater melanocyte stimulating hormone (MSH), keloid formation mainly occurs in parts of the body with high concentrations of melanocytes [62].

Histopathologically, keloid is included in the spectrum of fibroproliferative disorders and commonly affects the ears, it has been suggested that keloid scarring is caused by an inability to stop the wound healing process and abnormal response to inflammation by fibroblasts [63, 64]. Scar is densely populated by inflammatory cells, which release fibrogenic factors such as transforming growth factor (TGF)-β1 and -β2. This environment enhances accumulation of ECM, while its degradation is impaired (via decreased levels of TGF-β3 and matrix metalloproteinases [MMP], for example, (MMP-9) [65]. In addition, development of a Th-2 response stimulates fibrogenesis and Th-1 predominance attenuates the tissue fibrosis [66, 67].

To conclude, author summarizes this chapter in the following points, which include the latest research findings in literature about the above discussed issue.

5. At a glance

1. Both functions of the auricle, atheistic and hearing, rely primarily on the biomechanical nature of its cartilage.
2. Human auricular chondrocytes have become the procedures for the production of elastic cartilage in vitro because they lay down large amount of elastic cartilage under certain circumstances.
3. Cartilage of human chondrocytes culture is resistant to degeneration even after long time and it has the same immunohistochemistry properties the native auricular cartilage.
4. The final stress relaxation rate is similar for all five regions of the auricular cartilage; all regions of the auricle had the ability to reach similar load equilibrium over 15 min.
5. Biomechanical properties of the auricular cartilage are mainly due to collagen II fibers in the matrix which is defective in patients of congenital auricular malformations.
6. Implants must have the same mechanical properties of the cartilage otherwise mechanical mismatch can lead to micromovement between the skin and the implant thus implant failure and extrusion.
7. Collagen type II is the main target of the autoantibodies in relapsing polychondritis (RP); therefore, it is the initial step that induces the chondritis.
8. Recently, autoantibodies against cartilage oligomeric matrix proteins (COMP) and matrilin-1 have been found in patients of (RP).

9. However, not many experiments, oral administration of collagen type II for desensitization in (RP) is apparently effective.
10. Chondrodermatitis nodularis chronica helicis is proven to be partially due to ischemia of the cartilage.
11. Intact perichondrium in auricular perichondritis and hematoma adds to the problem because it does not allow the inflammatory edema or blood, respectively, to expand, increasing the pressure on the cartilage, which causes more necrosis and end up with cauliflower ear.
12. MMP-13 (collagenase 3) preferentially degrades type II collagen found in cartilage.
13. In cSCC, MMP-13 collocates with laminin-5, which is normally found in the basement membrane to promote keratinocyte motility to the edge of the lesion and subsequently degrades nearby tissue, allowing tumor invasion.
14. Chondrocytes cannot migrate readily through cartilage tissue to the site of the injury, and the matrix components they synthesize usually are not sufficient to fill the defect.
15. Healing of the cartilage depends on the age of the patient, direction and depth of the wound; large, complete-thickness defects do not heal easily and intervention is a must.
16. Subcutaneous transplant site in the head and neck lead to strong inflammatory reactions and resorption of the bioartificial cartilage in contrast to orthopedic and trauma surgery where the engineered constructs or autologous chondrocytes are placed in the immunoprivileged region of joints.
17. Keloid is one extreme of aberrant dermal wound healing that is observed only in susceptible individuals following cutaneous injury.

Author details

Mohamed Khamis Tolba Mahmoud Abdalla[1,2]*

*Address all correspondence to: mohamed_khameess@yahoo.com

1 Department of Otorhinolaryngology, Head and Neck Surgery, Alexandria University, Royal College of Surgeon of England, London, UK

2 University of South Wales, Pontypridd, UK

References

[1] Griffin MF, Premakumar Y, Seifalian AM, Szarko M, Butler PE. Biomechanical characterisation of the human auricular cartilages; implications for tissue engineering. Annals of Biomedical Engineering. 2016;**44**(12):3460-3467

[2] Quatela VC, Sherris DA, Rosier RN. The human auricular chondrocyte: Responses to growth factors. Archives of Otolaryngology – Head & Neck Surgery. 1993;**119**(1):32-37

[3] Quarto R, Campanile G, Cancedda R, Dozin B. Modulation of commitment, proliferation, and differentiation of chondrogenic cells in defined culture medium. Endocrinology. 1997;**138**(11):4966-4976

[4] Sivayoham E, Woolford TJ. Current opinion on auricular reconstruction. Current Opinion in Otolaryngology & Head and Neck Surgery. 2012;**20**(4):287-290

[5] Kawanabe Y, Nagata S. A new method of costal cartilage harvest for total auricular reconstruction: Part I. Avoidance and prevention of intraoperative and postoperative complications and problems. Plastic and Reconstructive Surgery. 2006;**117**(6):2011-2018

[6] De Chalain T, Phillips JH, Hinek A. Bioengineering of elastic cartilage with aggregated porcine and human auricular chondrocytes and hydrogels containing alginate, collagen, and kappa-elastin. Journal of Biomedical Materials Research. 1999;**44**(3):280-288

[7] Lu XL, Mow VC. Biomechanics of articular cartilage and determination of material properties. Medicine & Science in Sports & Exercise. 2008;**40**(2):193-199

[8] Zahnert T, Hüttenbrink KB, Mürbe D, Bornitz M. Experimental investigations of the use of cartilage in tympanic membrane reconstruction. Otology & Neurotology. 2000; **21**(3):322-328

[9] Griffin MF, Premakumar Y, Seifalian AM, Szarko M, Butler PE. Biomechanical characterisation of the human nasal cartilages; implications for tissue engineering. Journal of Materials Science: Materials in Medicine. 2016;**27**(1):11

[10] Kluger N, Guillot B. Body-piercing complications. Annales de Dermatologie et de Vénéréologie. 2010;**137**:153

[11] Dahl JP, Caballero M, Pappa AK, Madan G, Shockley WW, Van Aalst JA. Analysis of human auricular cartilage to guide tissue-engineered nanofiber-based chondrogenesis: Implications for microtia reconstruction. Otolaryngology – Head and Neck Surgery. 2011;**145**(6):915-923

[12] Walton RL, Beahm EK. Auricular reconstruction for microtia: Part II. Surgical techniques. Plastic and Reconstructive Surgery. 2002;**110**(1):234-252

[13] Nayyer L, Birchall M, Seifalian AM, Jell G. Design and development of nanocomposite scaffolds for auricular reconstruction. Nanomedicine: Nanotechnology, Biology and Medicine. 2014;**10**(1):235-246

[14] Gergely P, Poór G. Relapsing polychondritis. Best Practice & Research Clinical Rheumatology. 2004;**18**(5):723-738

[15] Letko E, Zafirakis P, Baltatzis S, Voudouri A, Livir-Rallatos C, Foster CS. Relapsing polychondritis: A clinical review. In: WB Saunders, editor. Seminars in Arthritis and Rheumatism. 2002 Jun;**31**(6):384-395

[16] Ebringer R, Rook G, Swana GT, Bottazzo GF, Doniach D. Autoantibodies to cartilage and type II collagen in relapsing polychondritis and other rheumatic diseases. Annals of the Rheumatic Diseases. 1981;**40**(5):473-479

[17] Foidart JM, Abe S, Martin GR, Zizic TM, Barnett EV, Lawley TJ, Katz SI. Antibodies to type II collagen in relapsing polychondritis. New England Journal of Medicine. 1978; **299**(22):1203-1207

[18] Alsalameh S, Mollenhauer J, Scheuplein F, Stöss H, Kalden JR, Burkhardt H, Burmester GR. Preferential cellular and humoral immune reactivities to native and denatured collagen types IX and XI in a patient with fatal relapsing polychondritis. The Journal of Rheumatology. 1993;**20**(8):1419-1424

[19] Buckner JH, Wu JJ, Reife RA, Terato K, Eyre DR. Autoreactivity against matrilin-1 in a patient with relapsing polychondritis. Arthritis and Rheumatism. 2000;**43**(4):939-942

[20] Hansson AS, Heinegård D, Piette JC, Burkhardt H, Holmdahl R. The occurrence of autoantibodies to matrilin 1 reflects a tissue-specific response to cartilage of the respiratory tract in patients with relapsing polychondritis. Arthritis & Rheumatology. 2001;**44**(10):2402-2412

[21] Trentham DE, Le CH. Relapsing polychondritis. Annals of Internal Medicine. 1998; **129**(2):114-122

[22] Longo L, Greco A, Rea A, Vasco VR, De Virgilio A, De Vincentiis M. Relapsing polychondritis: A clinical update. Autoimmunity Reviews. 2016;**15**(6):539-543

[23] Buckner JH, Van Landeghen M, Kwok WW, Tsarknaridis L. Identification of type II collagen peptide 261-273-specific T cell clones in a patient with relapsing polychondritis. Arthritis & Rheumatology. 2002;**46**(1):238-244

[24] Lang B, Rothenfusser A, Lanchbury JS, Rauh G, Breedveld FC, Urlacher A, Albert ED, Peter HH, Melchers I. Susceptibility to relapsing polychondritis is associated with hla-dr4. Arthritis & Rheumatology. 1993;**36**(5):660-664

[25] Zeuner M, Straub RH, Rauh G, Albert ED, Schölmerich J, Lang B. Relapsing polychondritis: Clinical and immunogenetic analysis of 62 patients. The Journal of Rheumatology. 1997;**24**(1):96-101

[26] Navarro MJ, Higgins GC, Lohr KM, Myers LK. Amelioration of relapsing polychondritis in a child treated with oral collagen. The American Journal of the Medical Sciences. 2002;**324**(2):101-103

[27] Arnaud L, Mathian A, Haroche J, Gorochov G, Amoura Z. Pathogenesis of relapsing polychondritis: A 2013 update. Autoimmunity Reviews. 2014;**13**(2):90-95

[28] Kraus VB, Stabler T, Le ET, Saltarelli M, Allen NB. Urinary type II collagen neoepitope as an outcome measure for relapsing polychondritis. Arthritis & Rheumatology. 2003;**48**(10):2942-2948

[29] Sato T, Yamano Y, Tomaru U, Shimizu Y, Ando H, Okazaki T, Nagafuchi H, Shimizu J, Ozaki S, Miyazawa T, Yudoh K. Serum level of soluble triggering receptor expressed on myeloid cells-1 as a biomarker of disease activity in relapsing polychondritis. Modern Rheumatology. 2014;**24**(1):129-136

[30] Ouchi N, Uzuki M, Kamataki A, Miura Y, Sawai T. Cartilage destruction is partly induced by the internal proteolytic enzymes and apoptotic phenomenon of chondrocytes in relapsing polychondritis. The Journal of Rheumatology. 2011;**38**(4):730-737

[31] Rickli H, Hardmeier T. Winkler's chondrodermatitis nodularis chronica helicis. Der Pathologe. 1988;**9**(1):25-29

[32] Upile T, Patel NN, Jerjes W, Singh NU, Sandison A, Michaels L. Advances in the understanding of chondrodermatitis nodularis chronica helices: The perichondrial vasculitis theory. Clinical Otolaryngology. 2009;**34**(2):147-150

[33] Kaplan AL, Cook JL. The incidences of chondritis and perichondritis associated with the surgical manipulation of auricular cartilage. Dermatologic Surgery. 2004;**30**(1):58-62

[34] Keene WE, Markum AC, Samadpour M. Outbreak of Pseudomonas aeruginosa infections caused by commercial piercing of upper ear cartilage. Journal of the American Medical Association. 2004;**291**(8):981-985

[35] Kent SE, Rokade AV, Premraj K, Butcher C. "High" ear piercing and perichondritis of the pinna. BMJ: British Medical Journal. 2001;**323**(7309):400

[36] Martin R, Yonkers AJ, Yarington CT. Perichondritis of the ear. The Laryngoscope. 1976; **86**(5):664-673

[37] Stroud MH. A simple treatment for suppurative perichondritis. The Laryngoscope. 1963;**73**(5):556-563

[38] Dowling JA, Foley FD, Moncrief JA. Chondritis in the burned ear. Plastic and Reconstructive Surgery. 1968;**42**(2):115-122

[39] Vuyk HD, Cook TD. Auricular reconstruction after Moh's surgery. A review. Faces. 1997;**5**:9-21

[40] Boisen J, Malone CH, Kelly B, Wagner RF. Cutaneous squamous cell carcinoma with invasion through ear cartilage. Case Reports in Dermatological Medicine. 2016;**16**:2016

[41] Martinez JC, Cook JL. High-risk cutaneous squamous cell carcinoma without palpable lymphadenopathy: Is there a therapeutic role for elective neck dissection? Dermatologic Surgery. 2007;**33**(4):410-420

[42] Reunanen N, Kähäri VM. Matrix metalloproteinases in cancer cell invasion. In: Madame Curie Bioscience Database. Austin, TX: Landes Bioscience; 2000. pp. 1-35

[43] Airola K, Johansson N, Kariniemi AL, Kähäri VM, Saarialho-Kere UK. Human collagenase-3 is expressed in malignant squamous epithelium of the skin. Journal of Investigative Dermatology. 1997;**109**(2):225-231

[44] Ash JE, Beck MR, Wilkes JD. Tumors of the Upper Respiratory Tract and Ear. Washington, DC: Armed Forces Institute of Pathology; 1964

[45] Sand M, Sand D, Brors D, Altmeyer P, Mann B, Bechara FG. Cutaneous lesions of the external ear. Head & Face Medicine. 2008;**4**(1):2

[46] Duncan MJ, Thomson HG, Mancer JK. Free cartilage grafts: The role of perichondrium. Plastic and Reconstructive Surgery. 1984;**73**(6):916-921

[47] Shantz JS, Marcucio R, Kim HT, Miclau III T. Chapter 4: Bone and Cartilage Healing, Section 1: General Principles: Basics, pp. 109-124

[48] Silver FH, Glasgold AI. Cartilage wound healing. An overview. Otolaryngologic Clinics of North America. 1995;**28**(5):847-864

[49] Izumi T, Scully SP, Heydemann A, Bolander ME. Transforming growth factor β1 stimulates type II collagen expression in cultured periosteum-derived cells. Journal of Bone and Mineral Research. 1992;**7**(1):115-121

[50] Zalzal GH, Cotton RT, McAdams AJ. Cartilage grafts – Present status. Head & Neck. 1986;**8**(5):363-374

[51] Rotter N, Haisch A, Bücheler M. Cartilage and bone tissue engineering for reconstructive head and neck surgery. European Archives of Oto-Rhino-Laryngology and Head & Neck. 2005;**262**(7):539-545

[52] Prudden JF, Nishihara G, Baker L. The acceleration of wound healing with cartilage. I. Surgery, Gynecology & Obstetrics. 1957;**105**(3):283-286

[53] Duynstee ML, Verwoerd-Verhoef HL, Verwoerd CD, Van Osch GJ. The dual role of perichondrium in cartilage wound healing. Plastic and Reconstructive Surgery. 2002; **110**(4):1073-1079

[54] Evans CH, Ghivizzani SC, Smith P, Shuler FD, Mi Z, Robbins PD. Using gene therapy to protect and restore cartilage. Clinical Orthopaedics and Related Research. 2000; **379**:S214-S219

[55] O'Connor WJ, Botti T, Khan SN, Lane JM. The use of growth factors in cartilage repair. Orthopedic Clinics. 2000;**31**(3):399-409

[56] Uusitalo H, Hiltunen A, Ahonen M, Gao TJ, Lefebvre V, Harley V, Kähäri VM, Vuorio E. Accelerated up-regulation of L-Sox5, Sox6, and Sox9 by BMP-2 gene transfer during murine fracture healing. Journal of Bone and Mineral Research. 2001;**16**(10):1837-1845

[57] Fujii M, Takeda K, Imamura T, Aoki H, Sampath TK, Enomoto S, Kawabata M, Kato M, Ichijo H, Miyazono K. Roles of bone morphogenetic protein type I receptors and Smad proteins in osteoblast and chondroblast differentiation. Molecular Biology of the Cell. 1999;**10**(11):3801-3813

[58] Feng L, Precht P, Balakir R, Horton WE. Evidence of a direct role for bcl-2 in the regulation of articular chondrocyte apoptosis under the conditions of serum withdrawal and retinoic acid treatment. Journal of Cellular Biochemistry. 1998;**71**(2):302-309

[59] Bran GM, Brom J, Hörmann K, Stuck BA. Auricular keloids: Combined therapy with a new pressure device. Archives of Facial Plastic Surgery. 2012;**14**(1):20-26

[60] Aköz T, Gideroğlu K, Akan M. Combination of different techniques for the treatment of earlobe keloids. Aesthetic Plastic Surgery. 2002;**26**(3):184-188

[61] Bayat A, Arscott G, Ollier WE, McGrouther DA, Ferguson MW. Keloid disease: Clinical relevance of single versus multiple site scars. British Journal of Plastic Surgery. 2005; **58**(1):28-37

[62] Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;**453**(7193):314-321

[63] Sandulache VC, Parekh A, Li-Korotky H, Dohar JE, Hebda PA. Prostaglandin E2 inhibition of keloid fibroblast migration, contraction, and transforming growth factor (TGF)-β1–induced collagen synthesis. Wound Repair and Regeneration. 2007;**15**(1):122-133

[64] Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: Pathomechanisms and current and emerging treatment strategies. Molecular Medicine. 2011;**17**(1-2):113

[65] Brown JJ, Bayat A. Genetic susceptibility to raised dermal scarring. British Journal of Dermatology. 2009;**161**(1):8-18

[66] Wynn TA. Fibrotic disease and the TH1/TH2 paradigm. Nature Reviews Immunology. 2004;**4**(8):583-594

[67] Doucet C, Brouty-Boyé D, Pottin-Clémenceau C, Canonica GW, Jasmin C, Azzarone B. Interleukin (IL) 4 and IL-13 act on human lung fibroblasts. Implication in asthma. Journal of Clinical Investigation. 1998;**101**(10):2129

IntechOpen