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Review Article

Application of Tissue Engineering and Biomaterials in Nose Surgery

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ABSTRACT

Surgery of the nose involves a series of operations that are directed at restoring the nasal anatomy and physiology. The extent or degree of reconstruction needed is dependent on the appearance-based requirement of the patients and the procedure exploited for the correction such that nasal airflow is preserved. Standard surgical approach includes the use of autologous tissue or implantation alloplastic bio or synthetic/fabricated construct materials to correct the defects. Over the years, tissue engineering has been proven to be a promising technique for reconstructing tissue and organ defects, including the nose. Recently, there has been keen interest in fabricating new tissues and organ scaffolds using 3D printing technology with good control over the micro-architecture and excellent interior architecture suitable for cell seeding. Unviability of the tissue and harvest-associated complications have increased the need for the investigation of tissue engineering based methods for nasal reconstruction using biomaterials, stem cells, and growth factors combined with 3D bioprinting. However, there are only a handful of studies vis-à-vis the application of cartilage tissue engineering, stem cells, and growth factors for the purpose. This review provides highlights about the available studies based on the application of stem cells, biomaterials, and growth factors for nasal reconstruction surgery, as there is limited recent information on the use of these entities in nasal surgeries.

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Introduction

Tissue engineering approaches are based on modifying the shape and functionality of cartilages by targeting their main cells, the chondrocytes. The typical cartilage tissue-engineering process involves seeding chondrocyte precursor cells onto a 3D scaffold matrix and transferring the construct either in vitro and in vivo into the patient over a defined period.[1] Several reports have shown that neocartilage constructs are comparable to typical human cartilage in terms of anatomical, histological, and mechanical properties.[2,3] One of the foremost pioneered works on tissue engineering and cartilage was done by Cao et al[4] when they reported the seeding of chondrocytes onto a synthetic biodegradable polymer fabricated to mimic the shape of human auricle; however, Greene & Watson demonstrated the clinical application of this approach by seeding precursor chondrocytes onto scaffolds to fabricate tissue-engineered cartilage (TEC).[3] Presently, there are several tissue engineering techniques to artificially fabricate human organs or tissue constructs similar in terms of biological and physical properties to the native tissues with three-dimensional (3D) matrix structures;[5] hence, recent approaches to artificially design human organ and tissue focus on 3D printing technology to fabricate scaffolds with excellent micro-architecture.[6] The 3D bioprinting has allowed considerably cells to be bioprinted directly into potential 3D structures of interested organ.[6] The 3D bioprinting is preferred over other conventional cell-seeding methods as it offers a high cell-seeding efficiency[7] and excellent control over the micro-matrix fabricated for the bioprinted cells.[8]

In addition, another novel technique, computer-assisted methods, bio-computer-aided-manufacturing (Bio-CAM), plays a significant part before and after bio printing.[9] Its main function is to anticipate the viability of the fabrication by simulating several computers-based paradigms. The nose is a complex body organ made up of 3 basic parts namely: a bony framework of cartilage, an internal mucosal, lining and the skin. Damages as a result of of trauma, skin and nasal cancers, and genetic deformities can occur to the nose. Reconstruction of the nose involves the harvest of cartilage from the appropriate region of the body, such as ribs and ear, that can also increase the odds of donor site morbidity and possibly inadequacies in regards with function and the appearances.[10] The principal purpose of nasal reconstruction is to achieve treated the deformity without compromising the structure and the physiology. Modern surgery enables the harvest and implantation of autologous cartilage by means of a skin flap, with or without the rearrangement of mucosal flaps reconstructed nose.[11]

Three-dimensional bioprinting of nasal cartilage

There have been several applications of 3D bioprinting, such as metal 3D printed devices[12] as well as 3D printed tools[13] and, most importantly, 3D bioprinting of bones and cartilages. Several the studies have revealed the use of bioprinting techniques to construct 3D scaffolds that are similar to native organs and tissues. Yao et al reported the 3D printing of polycaprolactone-hydroxyapatite scaffolds, which were efficient in supporting physiological and mechanical loads in rabbits.[14] Similarly, Wang et al reported the bioprinting propylene fumarate porous scaffolds and concluded that the fabricated scaffold displayed excellent qualities for bone tissue engineering applications.[15] In another study, Pati et al seeded 3D printed PCL/PLGA/ß-TCP scaffolds with human nasal inferior turbinate tissue-derived mesenchymal stromal cells to build up bone-like extracellular matrix (ECM) and improve its osteogenic abilities, leading to the revelation that the decellularized scaffolds exhibited improved and excellent osteoinductive and osteoconductive properties.[16] Similarly, Kundu et al have demonstrated

bioprinting of cartilages using alginate-encapsulated chondrocytes with PCL serving as mechanical support and confirmed cartilage production via in vivo experiments.[17] PEG and PCL construct containing chondrocytes have been demonstrated to be an excellent biomaterial to bioprint ear-shaped constructs.[18]

D'Lima and Cui et al in their studies, showed that direct bioprinting of human chondrocytes or hMSCs-seeded structures in an effort to repair cartilage defects using PEG dimethacrylate (PEGDMA) as the bioink. The result of the experiment revealed that the construct exhibited greater cell viability and integration into the defective cartilage.[19,20] From a recent finding by, Zenobi-Wong et al it was seen that effective 3D bioprinting of complex cartilaginous constructs can be successfully achieved using bio-inks to print scaffold-like organs such as auricle and nose.[21] The application of bioprinting techniques has so far presented a few limitations; however, its working principle of layer-by-layer printing method is still not commonly applicable to printing complex hollow constructs like heart and intestines. Bertassoni et al[22] have suggested a answer to this problem can be the incorporation of a sacrificial material to provide mechanical support between each fabricated layer.

Tissue-engineering of nasal structure

Tissue engineering is a multidisciplinary field encompassing biology, medicine, and engineering. It utilizes biological or synthetic frameworks and various cell differentiation procedures to fabricate functional substitute tissues, thereby decreasing the reliance on donated tissue and/or organs.[23] Tissue engineering of cartilage encompasses a combination of 3 entities, namely the scaffold, a biocompatible synthetic or natural material that possess the ability to maintain a 3D structural integrity and biointegration while supporting the growth of cells like chondrocyte that can either.[24]

Stem cells and nasal reconstruction surgery

Stem cells have a very high capability to replicate and differentiate into numerous different cell types. Chondrocytes are derived from the embryonic mesenchymal stem cells wherease MSCs are found to have reduced tumorigenic tendencies than the embryonic or fetal stem cells. Furthermore, these can be easily accessible from tissues types like bone marrow,[25] adipose tissue,[26] umbilical cord blood synovium.[27] Table 1 gives a summary of the appliccation of adult mesenchymal stem cells (MSCs) in fabricating cartilages designed for nose reconstruction surgery.

Bone marrow-derived MSCs (BM-MSCs) are located in the bone marrow and are capable of differentiating into several different cell including chondrocytes, given the desired growth and differentiating conditions (Table 1 and Figure 1).[37,38] Erickson et al[28] also reported that human adipose-derived MSCs (AD-MSCs) can generate cartilage matrix proteins in the presence of growth factors. AD-MSCs are derivative of fat harvested in the course of liposuction and can differentiate into chondrocytes for nasal reconstruction (Table 1).[25,27,28–36]

Nasal surgery and biomaterials

According to Çakir et al, shaping of cartilage and continuous reassessment of the cartilage are important to maintain the appearance of the nose.[39] As such, there is a need to develop a bioengineered cartilage with comparable mechanical characteristics as that of native structures. Sajjadian et al reported that the most frequently used autologous sites for nasal reconstruction are the cartilaginous nasal septum, auricular conchal bowl, and costal cartilage.[40] Any fabricated bio-cartilage for rhinoplasty must-have properties mimic that of a nasal septal cartilage.[41,42] Fabrication of tissue-engineered cartilage undergoes 4 important steps, namely: a scaffold, chondrocytes to be seeded on the scaffold, growth factors for cell differentiation and maturation, and environmental settings that simulate the cartilage local biological niche.[43]

Scaffolds

Ideal scaffolding biomaterials should be a porous structure able to contain chondrocytes and stem cells, hydrophilic, biocompatible, biodegradable, and nonimmunogenic. Alginate hydrogels have

Table 1
Summary of methodologies used to differentiate human mesenchymal stem cells to chondrocytes in vitro. Table adapted from [1] with copyright permission.

Cell source	Methodologies	Scaffold	Inducing factors	Outcome
Adipose tissue [28]	A genetically engineered ELP may potentially promote chondrocyte differentiation of AD-MSC without exogenous chondrogenic supplements.	Transwell membrane	ELP	ELP could promote chondrogenesis for AD-MSC cells in the absence of exogenous TGF-b1 and dexamethasone under low oxygen tension conditions.
Adipose tissue [29]	To examine the chondrogenic potential of adipose tissue-derived stromal cells.	Alginate culture		After 2 weeks, AD-MSCs expressed Col II, VI, and Chondroitin 4-sulfate. In vivo, cells expressed Col II, VI, and Aggrecan, indicating chondrogenic differentiation.
Amniotic fluid [30]	To assess the chondrogenic potential of AM-MSC.	Collagen scaffold in vivo	Recombinant human BMP-2	AM-MSC has the potential to differentiate into chondrocytes in vitro and in vivo.
Amniotic fluid [25]	To investigate the chondrogenic potential of AM-MSC cells in pellet and alginate-hydrogel culture.	Pellet culture and alginate-hydrogel culture	TGF-b1, TGF-b3, BMP-2, IGF-1, and dexamethasone	AM-MSC expressed Col II and sGAG, indicating chondrogenic differentiation. However, compared to BMSCs, less cartilaginous matrix was produced after 3 weeks in pellet culture.
Bone marrow [31]	To assess the effect that BMP-2 has on the chondrogenic differentiation of BMSCs under serum-free conditions.	Pellet culture	BMP-2 and TGF-b1	BMP-2 induced a chondrogenic linage development.
Bone marrow [32]	To examine the chondrogenic potential of human BMSCs encapsulated in alginate beads.	Alginate beads	TGF-b1 and Dexamethasone	
Bone marrow [33]	To differentiate BMSCs from chondrocytes on 3D nanofibrous scaffold.	Electrospun PCL	TGF-b1	After 21 days, Col II and IX were detected.
Bone marrow [34]	To examine the chondrogenic potential of BMSCs encapsulated in fibrin-based hydrogels.	Fibrin alginate-hydrogel pellets	TGF-b1 and Dexamethasone	The fibrin-encapsulated cells expressed collagen type II and aggrecan, indicating their differentiation. into chondrocytes.
Bone Marrow [35]	To investigate the effect of reduced oxygen environment micro-pellet culture on chondrogenic differentiation.	A reduced oxygen environment micro-pellet culture		Aggrecan and Col II gene expression were increased in pellet cultures differentiated under 2% O2 relative to 20% O2 pellets.
Bone marrow and adipose tissue [27]	To examine the differential expression pattern of ECM molecules in BMSCs and AM-MSCs following chondrogenic differentiation.	Cells were encapsulated in alginate	TGF-b1	Collagen type II and X were secreted more strongly by BMSCs than AM- MSCs. BMSCs expressed a more mature phenotype than AM-MSCs after chondroinduction.
Bone marrow and synovium [36]	To relate the chondrogenic potential of SMSCs to BMSCs and evaluate the ideal conditions for SMSCs chondrogenesis.	Pellet culture	BMP-2, TGF-b, and dexamethasone	SMSCs and BM-MSCs displayed a similar morphology; however, cartilage pellets from SMSCs were significantly larger than those from BMSCs.

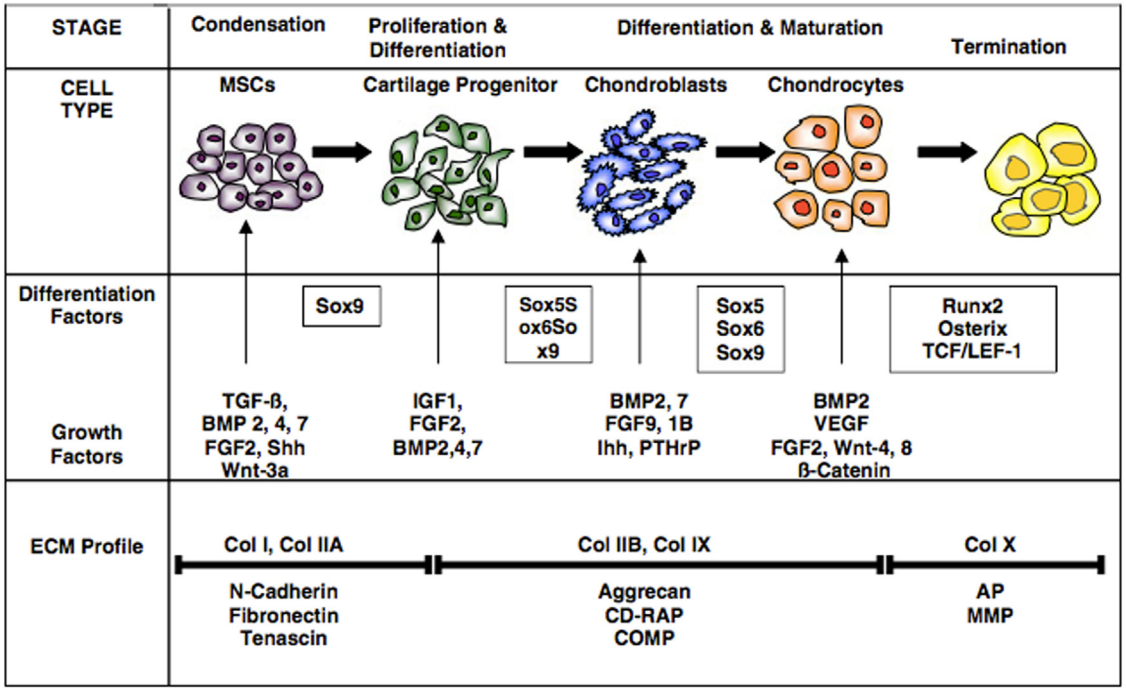

Figure 1. Showing summary of the different stages involved in differentiating MSCs into chondrocytes. Abbreviations: alkaline phosphatase (AP), cartilage-derived retinoic acid-sensitive protein (CD-RAP), collagen (Col), cartilage oligomeric protein (COMP), matrix metalloprotease (MMP), vascular endothelial growth factor (VEGF). This figure was adapted from [1] with copyright permission.

Table 2
Summary of nasal mucosal Bioengineering Efforts. Adapted from [48] with copyright permission.

Study type	Biomaterial used	Type of cells	Bioactive factors	Results	References
In vitro	Human amnion	Pig tracheal epithelial cells and pig tracheal fibroblasts	HGF, EGF, and TGF-b	Interactions with the amnion scaffold and fibroblasts	[49]
In vitro	Polyethylene terephthalate membrane coated with collagen gel	Human bronchial epithelial cells and human lung fibroblasts	EGF, insulin	Fibrin glue was useful in joining bioengineered epithelium and bioengineered cartilage	[50]
In vitro	Transwell polycarbonate membrane	Human bone marrow stem cells and human bronchial epithelial cells	TGF-b3	Co-culturing of respiratory epithelium and mesenchymal stem cells in chondrogenic culture	[51]
In vitro	Collagen gel	Rat tracheal epithelial cells and rat tracheal, dermal, nasal, and gingival fibroblasts	EGF, insulin	Gingival fibroblasts and tracheal fibroblasts can stimulate respiratory epithelium differentiation healing	[52]
In vitro	HYAFF benzyl ester of hyaluronic acid covered with collagen	Mature respiratory epithelial cells	EGF, insulin	HYAFF promotes mucociliary differentiation comparable to collagen	[53]
In vivo, nude mice	Nonionic, surfactant polyol (Pluronic F-127)	Sheep nasal septal respiratory epithelia	EGF, insulin	Nasal epithelium and cartilage cells are applicable to regenerate native airway-like tissues	[54]
In vivo, dogs	Hydrated porcine decellularized matrix	Cells likely differentiated from naturally present basal cells in the scaffold	None	Hydrated decellularized matrix results in growth of mature airway epithelium but not cartilage	[55]
In vivo, Sprague-Dawley normal rats	Collagen sponge and polypropylene mesh	Gingival fibroblasts and adipose tissue-derived stem cells	EGF, insulin	Adipose stem cells and fibroblasts have a synergistic effect on respiratory epithelial regeneration	[56]
In vivo, human	Crystalline polypropylene and high-density polyethylene mesh lined by collagen sponge	Autologous venous blood injected into the sponge intraoperatively	None	Collagen sponge provided scaffold over which complete defect re-epithelialization happened over 2 months	[57]
In vivo, human	Decellularized human donor trachea	Bronchial respiratory cells	Bovine pituitary extract, EGF	Bronchial respiratory epithelial cells formed normal tracheal mucosa on the inner surface of a decellularized tracheal graft	[53]

EGF 1/4 epidermal growth factor; HGF 1/4 human growth factor; TGF 1/4 transforming growth factor

Table 3
Showing summary of bioengineered cartilage for nasal surgery. Adapted from [48] with copyright permission.

Study type	Scaffold material	Cell types	Bioactive materials	Study period	Study results	References
In vitro	PLGA with acrylic sheets	Bovine articular cartilage	Ham F12 medium with fetal bovine serum	12 weeks	Mature neocartilage constructs can be fabricated into specific shapes entirely in vitro	61
In vitro	Alginate-reconstituted chondrocytes on polyester membrane inserts	Human nasal septal chondrocytes	TGF-b1, FGF-2, FGF-10, PDGF-BB	10 weeks	Neocartilage constructs had shape fidelity comparable to nasal septal cartilage	42
In vivo, nude mice	PLGA	Bovine articular cartilage	RPMI medium, withoutgrowth factors	12 weeks	Neocartilage constructs had mechanical properties similar to human nasal septal cartilage after 12 wk of in vivo incubation	62
In vivo, nude mice	Alginate-reconstituted chondrocytes on polyester membrane inserts	Human nasal septal chondrocytes	TGF-b1, FGF-2, PDGF-BB	2 months	Histologic, biochemical, and biomechanical features of neocartilage resemble native human septal tissue	60
In vivo, Sprague-Dawley rats	Alginate gelatin on PLGA	None	TGF-b3	10 weeks	Empty scaffolds loaded with growth factors induce chondrogenesis by cell homing when implanted into the nose	41
In vivo, nude mice	PLGA	Human adipose tissue-derived stem cells	Basic FGF, TGF-b1	8 weeks	Adipose tissue-derived stem cells can successfully form cartilage in vivo	63
In vivo, nude mice	Alginate gel	Human adipose tissue-derived stem cells	Insulin, TGF-b1	20weeks	Predifferentiated adipose tissue-derived stem cells maintain differentiation and form cartilage in vivo	64
In vivo, nude mice		Human adipose tissue-derived stem cells	Insulin, TGF-b1	16weeks	Predifferentiated adipose tissue-derived stem cells maintain differentiation and form cartilage in vivo	44
In vivo, nude mice		Rabbit articular cartilage	none	12weeks	PHBV/bioglass scaffold makes superior cartilage in vivo compared with PHBV alone	45
In vivo, human		Human auricular chondrocytes	none	2-34months	Auricular chondrocytes expanded in vitro form mature cartilage when injected in vivo into the nasal dorsum	65
In vivo, human		none	PDGF	22-27months	Demineralized bone matrix and PDGF can be used to augment small osseous nasal dorsum defects	66

been stated to possess good chondrogenic properties but are not suitable for suturing, and they lack the properties precluding their direct implantation. Liu and Wu, in 2 separate studies, reported a new scaffold fabricated using poly(3-hydroxybutyrate-co-3-hydroxyvalerate), a biocompatible and biodegradable plastic derived from bacteria with a unique capacity for formation of new cartilages and structural integrity.[44,45] However, poly(3-hydroxybutyrate-co-3-hydroxyvalerate) fabricated scaffolds are costly and fragile. Collagen sponges and polyvinyl alcohol have also been demonstrated by Gonzalez et al to be efficient in promoting cartilage growth[46] and additionally suitable for the application of electro-spinning and 3-dimensional printing design of scaffolds with precise control.[47] Table 2 gives a summary of available biomaterials used for nasal reconstruction surgery.

Growth factors

Mature chondrocytes, adipose tissue-derived stem cells, and bone marrow-derived stem cells, and growth factors are known to be applicable in producing cartilage (Table 2)[48–57] when loaded into scaffolds. In vitro cartilage researches need to regulate the micro-environmental parameters in order to mimic the in vivo conditions.

To support mature tissue formation, cells must be enhanced with growth factors, and some of the most generally used growth factors are the transforming growth factors (TGFs) b1, b2, or b3, fibroblast growth factors, and bone morphogenic proteins. They are all responsible for promotion of chondrogenesis process. Barry et al reported that all 3 families of TGFs promote chondrogenesis; however, TGF-b2 and TGF-b3 are the most potent.[58] Kim and Im[59] in a related study, reported that TGF-b2 and bone morphogenic protein 7 effectively stimulate the development of cartilage once co-cultured with adipose tissue-derived stem cells.[24] The use of bone, cartilage and biomaterial has enabled the strengthening of the nasal dorsum. Homologous and alloplastic constituents have also been utilized, each with its own merits and demerits. Nonetheless, alloplastic materials are associated with the greater risk of infection and extrusion, in comparision to the autologous implants. Conversely, autologous materials are scarcely available. With all these limitations, investigators have endeavored to produce as many as copies of autologous cartilage.

Yanaga et al[41] in a clinical study, carried out nasal dorsal expansion in 32 patients using chondrocytes from auricies combined with auto-serum. Gel was inserted into a subcutaneous space of the nasal dorsum and shaped by applying the finger pressure. A week later, a Solid cartilage formation was seen where, histological analysis confirmed matured cartilage with perichondrium after 6 months. Furthermore, the report noted that a nonsignificant donor site defect with successful aesthetic outcomes following of 17 months of follow-up. The method resulted in the in vitro expansion of mature chondrocytes. However, using adipose tissue-derived stem cells may reduce the risk of donor site defects in cartilage. Table 3 summarizes available studies showcasing the application of stem cells, growth factors, and biomaterials to rhinoplasty.[41,42,44,45,60,61-66]

In another report by Planas, collagen and glycosaminoglycan (GAG) were used to design a porous matrix loaded with platelet-derived growth factor. The implant was successfully used for small osseous nasal dorsum defects. They suggested the implant could also be used for larger defects.[66] Furthermore, this implant has also been well-documented for its application in rhinoplasty.[67] Tiengo et al also demonstrated the use of bovine tendon collagen with and GAG in combination with perichondrial flap, cartilage graft, and skin grafting of full-thickness nasal tip.[68,69]

Conclusuion

Regenerative medicine is an advancing field that has elicited promising results in nasal surgery. Owing to the complex nature of nasal cartilage, conventional approaches are shown to bring about unsatisfactory results. However, with tissue engineering and regenerative medicine have enabled nasal reconstruction when bettter aesthetic outcomes and reduceed complications and donor site morbidity. Recently, 3D bioprinting techniques have proven important and efficient in fabricating new cartilage and organs similar to native organs. However, this technique still presents some challenges as its layer-by-layer printing method does not efficiently work for printing complex hollow structures yet. Though introducing an extra material during fabrication has solved this problem, as reported by some studies,

it increases the complexity of the bioprinting process. Future development in advancing nasal surgery may include a combination of 3D bioprinting with stem cell technologies (stem cells seeded with 3D bioprinted scaffolds) and growth factors.

Conflict of interest

The authors deny any conflict of interest in any terms or by any means during the study.

Availability of data and material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Consent for publication

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Contributors' statement page

Dr. Parham Khoshdani Farahani: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript. Coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content.

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