J Maxillofac Oral Surg 8(4):348–356

REVIEW

Craniofacial surgery, from past pioneers to future promise

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Received: 23 May 2008 / Accepted: 21 November 2009

Abstract
Objectives As a surgical subspecialty devoted to restoration of normal facial and calvarial anatomy, craniofacial surgeons must navigate the balance between pathologic states of bone excess and bone deficit. While current techniques employed take root in lessons learned from the success and failure of early pioneers, craniofacial surgery continues to evolve, and novel modalities will undoubtedly arise integrating past and present experiences with future promise to effectively treat craniofacial disorders.
Methods This review provides an overview of current approaches in craniofacial surgery for treating states of bone excess and deficit, recent advances in our understanding of the molecular and cellular processes underlying craniosynostosis, a pathological state of bone excess, and current research efforts in cellular-based therapies for bone regeneration.
Results The surgical treatment of bone excess and deficit has evolved to improve both the functional and morphological outcomes of affected patients. Recent progress in elucidating the molecular and cellular mechanisms governing bone formation will be instrumental for developing improved therapies for the treatment of pathological states of bone excess and deficit.
Conclusions While significant advances have been achieved in craniofacial surgery, improved strategies for addressing states of bone excess and bone deficit in the craniofacial region are needed. Investigations on the biomolecular events involved in craniosynostosis and cellular-based bone tissue engineering may soon be added to the armamentarium of surgeons treating craniofacial dysmorphologies.

Keywords Craniofacial surgery · Craniosynostosis · Distraction osteogenesis · Bone tissue engineering · Fibroblast growth factor · Bone morphogenetic protein · Transforming growth factor beta

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Introduction

The discipline of craniofacial surgery is dynamic yet replete with a rich history dating back to prehistoric times [1–3]. Throughout the world, evidence for intentional skull deformation and trephination in the treatment of premature cranial synostosis has been identified as far back as the Neolithic age [1–4]. Today, craniofacial surgery sits at the intersection of varied fields including plastic surgery, neurosurgery, head and neck surgery, and maxillofacial surgery, continually evolving through fundamental contributions from each other. As a surgical subspecialty devoted to the restoration of normal facial and calvarial anatomy, contemporary surgeons must navigate the balance between pathologic states of bone excess and bone deficit. While current techniques employed take root in lessons learned from the success and failure of early pioneers, craniofacial surgery continues to evolve, and novel modalities will undoubtedly arise integrating past and present experiences with future promise to effectively treat craniofacial disorders.

Past pioneers and contemporary philosophy

The foundations for modern craniofacial surgery can be traced back to the nineteenth century, where Otto provided the first written accounts of craniosynostosis in 1830 [5]. Two decades later, studies by Virchow led to the proposal of compensatory growth in a plane parallel to that of the fused suture, providing a cogent explanation for scaphocephalic, or boat-shaped, skulls as a consequence of sagittal synostosis [6]. Early published reports on the surgical correction of premature suture fusion can be found around the turn of the century by Lane and Lannelongue, which rapidly popularized the removal of affected sutures through a variety of strip craniectomy procedures [7,8]. Boundless enthusiasm, however, was promptly tempered by high complication rates, with

several physicians denouncing such surgeries as harmful, excessively used, and of dubious benefit [3].

Outbreak of the First and Second World Wars furnished the next backdrop for evolution of craniofacial surgery, with primary treatment and secondary reconstruction of trauma-related maxillofacial injuries providing ample opportunity for refinement of practice principles. Concepts learned from the battlefield were then applied by surgeons for correction of congenital malformations of the face and orbit. Integrating these lessons with those of Rene LeFort, who earlier described facial fracture patterns, Sir Harold Gillies performed the first midface advancement for treatment of syndromic maxillary hypoplasia in 1949 [3,9]. This attempt, however, employed osteotomies anterior to the orbital rim, lacrimal sac, and medial canthal ligament, limiting the ability to correct exophthalmos. As neither rigid fixation nor bone grafting was incorporated, postoperative relapse ensued [3].

During the following decades, Paul Tessier revolutionized the field of craniofacial surgery with the introduction of new ideas and techniques based on the application of intentional fracture osteotomies learned from the work of his predecessors. Originally trained in general surgery, orthopedics, and ophthalmology, Tessier acquired substantial experience at the end of World War II with facial trauma at the Center for Maxillofacial Surgery of the Military Region of Paris in Hospital Puteaux [3,10]. He also spent additional time working with both Archibald McIndoe and Gillies in Great Britain. Through such experiences, and from that gained by cadaveric study, Tessier established the need for post-osteotomy rigid fixation and the incorporation of bone grafting for stabilization of surgical gaps [10]. Several additional principles were also elaborated by Tessier, including the importance for wide subperiosteal exposure of the face, the ability to reposition the orbit without injury to its contents, and the advantages of repositional osteotomy over onlay bone grafting [10]. Many of these tenets led to development of treatment paradigms for not only craniosynostosis, but also orbital hypertelorism, Treacher Collins syndrome, and oro-ocular clefts.

As an extension of Tessier's pioneering work, Fernando Ortiz-Monasterio introduced the concept of monoblock advancement in 1978 [11]. Over the course of three years, Ortiz-Monasterio and colleagues performed seven simultaneous fronto-orbito-facial advancements in patients with Crouzon's syndrome at the Plastic Surgery Unit of the Hospital General de Mexico. This technical leap yielded more aggressive correction of exorbitism in all cases, with concurrent repositioning of orbital roof, floor, medial, and lateral walls producing greater anatomical correction when compared to other, more limited procedures [11]. Like Tessier, Ortiz-Monasterio used rigid fixation and bicortical iliac bone grafting around the pterygoid processes and lateral orbital walls to minimize risk of relapse. In addition, advancement of the frontal bone yielded similarly good results in contour of both the forehead and calvarium. While further modifications have since been made on this technique of fronto-orbito-facial advancement, the fundamental principles of monobloc advancement nonetheless remain in frequent use today.

The foundations for contemporary strategies and surgical approach were clearly laid in these landmark exploits of early pioneers, but the field of craniofacial surgery remains in constant evolution. The distinct mark of Tessier and others, however, is still undeniably palpable in present day treatment paradigms. Modern craniofacial surgery can be broadly grouped into procedures designed to address either bone excess, such as in the case of craniosynostosis, or bone deficit whether acquired or congenital in etiology. While dramatic advancements have been made in our understanding of these conditions, surgical intervention based on controlled osteotomies along well defined fracture patterns and rigid bony fixation remains the best recourse for treatment of the morphologic and functional abnormalities seen with various craniofacial disorders.

Craniosynostosis, the premature fusion of one or more cranial sutures, represents a pathologic state in which a surfeit of bone at growth centers of the skull results in dramatic dysmorphology of the vault and face. Current techniques for correction of sagittal synostosis, the most common form of craniosynostosis, must, by design, address the disproportionate anteroposterior growth characteristic of the scaphocephalic skull [12–15]. In addition, premature fusion of the sagittal suture results in a distinctive frontal and occipital prominence, further complicating any plans for calvarial reconstruction [13]. Where early procedures failed to exact an acceptable and lasting correction of these skull deformities, however, more aggressive approaches today have succeeded in undertaking a more complete remodeling of the entire vault through multiple planned osteotomies in concert with mini-plate fixation and autogenous bone grafting [12,13,16]. Such techniques have incorporated the separation of both bifrontal and biparieto-occipital fragments to allow for more precise calvarial contouring [12,13]. Use of laterally oriented temporal barrel staves and wire fixation has added to the ability to stably increase parietal and temporal width while decreasing anteroposterior length. Alternatives to this approach have included the pi procedure, originally introduced by Jane and colleagues in 1978 [17]. Subsequently modified by Vollmer and Persing, this technique allows for immediate correction of scaphocephaly while minimizing widespread skull defects through the replacement of bone flaps [12,18]. Resorbable mini-plate fixation adds to the stability of this procedure without restricting future growth. Importantly, concerns over the risk for greater surgical complications with the pi and reverse pi procedures have not been borne out in large clinical studies [19]. Mean blood loss, dural injury, air embolism, and postoperative seizure rates have compared favorably with other various craniectomy techniques [19]. Though no single procedure for the correction of sagittal synostosis has proven universally successful in all children, the pi and reverse pi procedures are frequently employed by many craniofacial surgeons today.

Similar to the treatment of sagittal synostosis, contemporary approaches for treatment of metopic and coronal synostosis have also embraced aggressive vault remodeling through multiple controlled osteotomies, replacement of bone, and temporary rigid fixation. Objectives for correction of metopic synostosis include enlargement of the anterior cranial fossa, restoration of normal contour to the frontal bone and supraorbital rim, and normalization of interdacryon distance [20]. To accomplish this, bifrontal craniotomy is frequently performed along with radial osteotomies and advancement of lateral supraorbital rims [12,20]. When combined with resorbable plate fixation and calvarial bone grafting, simultaneous improvement of orbit position can be achieved [21]. Coronal synostosis can likewise be corrected through controlled fractures along the frontal bone and supraorbital rim [13]. To remedy frontal bossing and compensatory temporal bulge,

surgeons may perform a unilateral or bilateral frontal craniotomy with forehead reconstruction and supraorbital rim advancement [13,22]. Replacement of remodeled calvarial bone grafts with rigid fixation may then yield a more conventional contour. Finally, harkening back to practices of our prehistoric ancestors with intentional skull deformation, passive deformation – in the form of postoperative molding helmet therapy – is now routinely performed to promote proper contouring of the skull following surgery.

While large strides have been made in the treatment of many calvarial vault deformities, similar evolution has occurred in the management of various midface and mandibular disorders, where bone deficit, as opposed to excess, is of often greater concern. Whether post-traumatic or congenital in etiology, challenging deficiencies in bone have been largely addressed by the application of new modalities to the craniofacial skeleton. Traditional approaches at reconstruction using osteotomies and bone grafting have been associated with unsatisfactory outcomes and both significant short and long term morbidities, particularly when large advancements are necessary for normalization of bone position [23–25]. Since the adoption of distraction osteogenesis, more favorable results have been obtained, making this modality the current treatment of choice for several midface and mandibular bone deficiencies [23].

As a powerful form of endogenous tissue engineering, distraction osteogenesis promotes bone formation through the gradual separation of osteogenic fronts. Despite its recent application to the craniofacial skeleton, the basic tenets of distraction osteogenesis were elaborated nearly a century earlier. In 1956, Ilizarov demonstrated this technique could be employed for long bone reconstruction with acceptable morbidity and consistent results [26–28]. The first translation to intramembranous bone was described by Snyder in 1972, using a canine model to study gradual mandibular lengthening through distraction [29]. And in 1989, Joseph McCarthy made a landmark contribution to craniofacial surgery, performing the first human mandibular distraction at the Institute of Reconstructive Plastic Surgery in New York [30,31]. Since that time, distraction osteogenesis has become a standard tool for surgeons to clinically achieve significant mandibular advancement.

Similar to the mandible, distraction osteogenesis has also been applied to the midface with equally promising results. Controlled LeFort III-type midface advancement by osteotomy and gradual distraction was first demonstrated in sheep by Rachmiel, achieving over 40 mm of lengthening [32,33]. Subsequent work by Ortiz-Monasterio and others have since confirmed that distraction osteogenesis can be safely utilized in patients with midface hypoplasia secondary to Crouzon's or Apert syndrome [34–36]. Studies by Cedars and colleagues have shown midface distraction to eliminate or significantly reduce airway obstruction allowing for decannulation or avoidance of tracheostomy entirely [36]. Furthermore, effects on speech and extraocular muscle function were minimal [36]. Such results, in combination with success observed in mandibular lengthening, have highlighted the clear utility of distraction osteogenesis for the treatment of facial bone deficit and have positioned this modality to be the current treatment of choice in many situations where large bone defects must be remedied.

Despite dramatic progress made in the treatment of various craniofacial disorders, however, several limitations still remain with contemporary techniques. Considering the extensive nature of procedures designed to remodel the calvarial vault, postoperative mortality rates have still been reported to be as high as 2.3% [13,37]. Examining 793 craniofacial operations at six major centers, Whitaker and colleagues noted an overall complication rate of 16.5%, with significant hemorrhage, infection, and neurologic events constituting the most frequent adverse events [37,38]. Current figures suggest infection to occur in approximately 2 to 5% of patients, with potentially catastrophic sequelae if not promptly diagnosed and treated [37,39,40]. Like infection, neurologic complications such as cerebrospinal fluid leak and seizures can also be potentially devastating if not expeditiously addressed [39]. Lastly, the specter of suturectomy site reossification remains plainly extant, with an incidence as high as 20% [41]. In such instances, reoperation, with all its attendant risks, becomes an option that must be entertained.

Enthusiasm surrounding the potential for distraction osteogenesis as a means to engineer novel bone has similarly been tempered by numerous complications which have plagued craniofacial surgeons performing this procedure. Despite increasing experience over the last two decades, a pronounced learning curve still exists and cumulative complication rates still reside in the neighborhood of 35% [23]. Most commonly, soft-tissue and pin-tract infections have been reported, along with osteomyelitis and hardware loosening secondary to daily manipulation of the distraction device [23]. Fibrous non-union, permanent inferior alveolar nerve injury, and bony relapse also remain significant considerations in the postoperative period. Though overall results of distraction osteogenesis have been acceptable, with good or excellent results reported in 86% of patients, significant improvement can still be made to minimize complications and optimize clinical outcomes for the treatment of craniofacial bone deficit [23].

Molecular genetics and cellular-based therapies

The evolution of craniofacial surgery has witnessed a multitude of milestones, with the development of several novel approaches effecting continual improvement in patient care. Given the advancements made in the surgical treatment of craniofacial dysmorphologies, however, continued efforts at minimizing morbidity and mortality remain imperative. Present day strategies remain disconcertingly limited, rendering the biomedical burden of some craniofacial pathologies nearly unmanageable. Significant room therefore exists for progress to made, and recent work in molecular genetics and cellular-based therapies hold promise for future treatment of craniosynostosis and various facial skeletal hypoplasias.

Molecular genetics and the development of targeted therapy

Though the etiology of craniosynostosis remains largely unknown, a more comprehensive understanding of the biomolecular events surrounding premature fusion has recently emerged through clinical genetic studies and use of murine models for suture synostosis. Several investigations have evaluated the roles of growth factors and various cytokines in the governance of suture fate, with Fibroblast Growth Factors (FGFs) notably implicated in a multitude of craniosynostosis syndromes. Of the four known FGF Receptors (FGFRs), mutations in three have been clinically linked to premature pathologic suture fusion [42–45]. Gain of

function mutations localized to the IgII-IgIII linker region have been well characterized, as x-ray crystallographic analysis has demonstrated enhanced ligand-receptor interactions and receptor dimerization [46]. Well recognized mutations include the Ser252Trp and Pro253Arg substitutions in FGFR-2 associated with Apert syndrome and the FGFR-1 Pro252Arg mutation associated with Pfeiffer syndrome [42,43]. Analogous mutations have also been identified in FGFR-3 for patients with Muenke syndrome and type I thanatophoric dysplasia [47].

With gain-of-function mutations in FGF receptors clearly linked to development of premature suture fusion, extensive research has been performed in the murine model examining the interplay between FGF ligands and their receptors. Most of these studies have focused specifically on FGF2 and its interactions with various receptor isoforms, as FGF2 has been shown to possess potent mitogenic and osteoinductive capacity [45,48–50]. Within fusing suture complexes in mice, FGF2 has been found to be abundant, whereas patent sutures express relatively low levels of this growth factor [51–53]. Ectopic expression of FGF2, however, has been demonstrated to result in premature pathologic suture fusion, providing a corollary to gain-of-function FGF receptor mutations observed in human craniosynostosis [54,55]. Extending these findings, investigators have developed transgenic mice carrying FGFR mutations analogous to those found in patients with Apert and Pfeiffer syndrome. Interestingly, mice with the FGFR-1 Pro250Arg mutation similar to the Pro252Arg mutation in Pfeiffer syndrome were found to demonstrate pathologic suture fusion with facial asymmetry and midface hypoplasia [56]. Transgenic mice carrying a FGFR-2 Ser250Trp mutation orthologous to that observed in Apert syndrome likewise displayed premature fusion, highlighting the significance of fibroblast growth factors and their receptors in the pathogenesis of craniosynostosis [57].

Similar to FGFs, several studies have also evaluated the role of transforming growth factor (TGF)-β and other members of the TGF-β superfamily in pathologic suture fusion. Unlike FGFs, however, only recently has an autosomal dominant gain-of-function mutation in TGF-β receptors been reported in conjunction with a craniosynostotic phenotype [58]. Members of the TGF-β family have nonetheless been found to be ubiquitously involved in bone and skeletal biology, and a multitude of investigations have demonstrated TGF-β isoforms to be critical in suture development and the maintenance of patency [59–63]. "Observations by Opperman in rats have shown increased levels of TGF-β2 during active fusion, and this has been confirmed by microarray and immunohistochemical analyses in mice [64–66]". Paralleling these observations, examination of synostotic suture samples from 10 infants revealed an increase in TGF-β2 isoform immunoreactivity relative to control patent sutures [67]. Given these findings, the distinct possibility may therefore exist to develop future strategies targeting these growth factors for the treatment of craniosynostosis.

Bone Morphogenetic Proteins (BMPs), additional members of the TGF-β superfamily, have also received increasing attention of late with respect to the regulation of suture fate. Although BMPs were originally identified in demineralized long bone extracts, recent investigations have suggested that there may be an intricate balance between BMP agonists and BMP antagonists dictating ultimate levels of BMP signaling and subsequent cranial suture fate [54,68–70]. While abundant levels of this pro-osteogenic cytokine have been found in all sutures, differential expression of their antagonists have been identified in the calvarium [54]. Most notably, antagonists such as noggin and BMP3 have been predominantly localized to patent sutures in mice, presumptively downregulating the signaling capacity of endogenously produced BMPs [54,71]. When these antagonists were ectopically expressed, increased levels of noggin were found to downregulate BMP signaling activity, thereby arresting normal suture fusion [54]. While further studies into the underlying biomolecular mechanisms of craniosynostosis are necessary, these reports afford yet another potential approach for the development of future targeted therapeutics.

Based on the recent body of knowledge garnered from both clinical genetic and animal model studies, the stage has been set for development of future strategies aimed at modulating prospective suture fate. Given the strong association between aberrant FGF signaling and craniosynostosis, downregulation of either membrane receptors or intracellular signaling events may afford the opportunity to alter subsequent suture development [72]. Multiple reports have demonstrated FGF signal transduction to occur through ligand-induced receptor homo- and hetero-dimerization activating intracellular tyrosine kinase domains [73]. Interestingly, Ueno and colleagues have recently described a truncated form of FGFR-1 lacking its cytoplasmic domain to inhibit signal transduction in wild-type FGFR-1, -2, and -3, the same receptor isoforms implicated in human craniosynostosis [74]. Furthermore, studies have already shown expression of this truncated receptor in osteoblasts to inhibit subsequent differentiation and bone deposition [55,74]. And when dominant-negative FGF receptors were transfected in utero into fetal rat calvarial sutures, Greenwald and colleagues noted inhibition of normal suture fusion [55]. As an alternative to manipulation of signaling at the receptor level, a variety of studies have also evaluated the ability to block the down-stream signaling events of various FGFs. The FGF signal transduction machinery has been found to employ several components of the Mitogen-Activated Protein Kinase (MAPK) pathway, allowing the ability to potentially manipulate FGF signaling through cytoplasmic intermediaries [73]. Most notably, treatment of Apert osteoblasts with either SB203580, a specific inhibitor of p38 MAPK, or PD98059, a specific inhibitor of MAPK kinase (MEK), was found to reduce IL-1 alpha and RhoA expression, along with osteogenic differentiation, as demonstrated by a reduction in alkaline phosphatase activity [75]. Direct application of PD98059 to cultured mouse calvariae has also been reported to dampen not only osteopontin expression, but also FGF-2 accelerated suture fusion [76]. These findings therefore highlight the potential utility in downregulating FGF activity, either through alteration in ligand-receptor activation at the cellular membrane level or through the application of various intracellular signaling inhibitors, in the future treatment of pathologic suture fusion. Incorporation of such strategies may engender a more physiologic level of FGF activity, thereby altering the course of syndromic craniosynostosis.

Similar to manipulation of FGF signaling, therapeutic approaches modifying activity levels of TGF-β and members of the TGF-β superfamily may likewise yield fruitful modalities to effect changes in cranial suture fate. As elevated levels of TGF-β2 have been described in

sutures undergoing both physiologic and premature pathologic fusion, investigators have examined the utility of applying neutralizing antibodies to delay or prevent suture synostosis [59,62]. Opperman and colleagues have demonstrated that the application of exogenous TGF-β2 antibodies to an ex vivo calvarial organ culture system prevents expected suture fusion [62]. Similarly, subperiosteal delivery of TGF-β2 antibodies by Moursi was found to also significantly reduce suture bridging in rats [77]. Such observations may be potentially extended to future approaches aimed at preventing not only primary suture fusion but also postoperative resynostosis.

As a final approach for cytokine based treatment of premature suture fusion, recent investigations have focused on relative levels of BMPs and their antagonists. Studies have shown noggin upregulation to impair osteogenic differentiation and bone deposition both in vitro and in vivo [54,78]. Translating this observation to the calvarium, Warren demonstrated ectopic expression of noggin through an adenoviral vector to prevent expected suture fusion in mice [54]. In addition, recent investigations have shown exogenous delivery of Noggin through a slow release collagen vehicle to limit suture resynostosis following strip suturectomy in rabbits [79]. These findings thus highlight the potential for manipulation of BMP signaling, through upregulation or direct application of antagonists, to be used as a future modality to modify suture fate. In combination, or used as separate entities, manipulation of FGF signaling, TGF-β2 antibodies, and upregulation of BMP antagonists each therefore hold promise to one day enhance our ability to treat craniosynostosis.

Cellular-based therapies and bone tissue engineering

In contrast to modalities being developed to treat bone excess and premature suture fusion observed in craniosynostosis, design of future approaches for craniofacial skeletal hypoplasias and post-traumatic bone deficit have instead focused on the immense potential of cellular-based tissue engineering. Over the last two decades, the need for alternative strategies has driven the creative application of various autogenous, allogeneic, and prosthetic materials to reconstruct the craniofacial skeleton. Unfortunately, use of these techniques have been met by variable success, and furthermore have been beset by numerous shortcomings, including infection, immunologic rejection, graft vs host disease, and relapse [80–85]. With recent advances in bone tissue engineering, however, researchers have been afforded a new avenue to develop novel methods to generate bone in the craniofacial skeleton.

Significant work has been focused on defining the consummate cellular building block with which to base future strategies for bone generation. While considerable controversy continues to hamper further investigations with human embryonic stem cells, post-natal progenitor cells have recently emerged as an attractive candidate for use in tissue engineering applications [86]. Though the true nature of these post-natal cells remains to be clarified, their capacity to differentiate into a multitude of cell types has been well documented and their promise for use in tissue repair remains high [87–89]. Early investigations with these cells focused on the Mesenchymal Stem Cell (MSC) fraction naturally residing within bone marrow. Several reports have demonstrated adult bone marrow derived MSCs to be capable of undergoing lineage specific differentiation into fat, cartilage, and bone under appropriate conditions [87,90–92]. In addition, animal models have documented use of MSCs in repair of critical-sized calvarial defects in rabbits and orbital defects in pigs [93–95]. Several factors, however, have tempered enthusiasm for use of these cells in strategies for bone repair. With a frequency as low as 1 in 27,000 cells, large volumes of bone marrow aspirate would be necessary to obtain numbers large enough for clinical use [96]. Concerns have also been raised related to donor-age associated changes in cellular biology and the need for selective sera and growth factor supplements for culture expansion prior to in vivo use [97–99]. Given these limitations, several hurdles still remain for use of marrow-derived MSCs in the treatment of craniofacial skeletal deficits.

As an alternative to MSCs found in bone, post-natal progenitor cells residing in the stromal fraction of adipose tissue have gained significant notoriety of late. Adipose-derived Stromal Cells (ASCs), have been shown to express UTF-1, Nodal, and Snail2, all genes once thought limited to embryonic stem cells, and possess similar growth kinetics and cell senescence with MSCs [100]. Unlike their bone marrow counterpart, however, ASCs are more easily accessible and represent an available, readily expandable building block for tissue engineering purposes [101]. Studies by Zuk and colleagues have shown the ability of ASCs to form fat, cartilage, muscle, or bone in the presence of precise induction factors [89,101]. And in animal studies, adult mouse-derived ASCs have been found to retain similar osteogenic potential when compared to ASCs harvested from juvenile animals [102]. This highlights a distinct advantage of ASCs over MSCs, which have been found to yield 41% fewer osteogenic progenitor cell colonies when harvested from bone marrow of older animals [103].

While investigators continue to refine our understanding of the biomolecular events involved in osteogenic differentiation of ASCs, several reports have already demonstrated the utility of ASCs in a variety of bone tissue engineering strategies. Lee et al. described in vivo bone formation from Lewis rat-derived ASCs implanted with polyglycolic acid constructs into subcutaneous pockets [104]. An equivalent capacity has also been demonstrated with human-derived ASCs seeded onto either three dimensional hydroxyapaptite/tricalcium phosphate cubes or polylactic-co-glycolic acid scaffolds and implanted into immunocompromised mice [105,106]. Extending these findings, human ASCs have recently been shown to be capable of repairing critical-sized femoral defects in nude rats [107]. Radiographic, histological, and biomechanical analyses all revealed bone healing in rat femurs following implantation of lipoaspirate cells seeded onto collagen-ceramic carriers [107]. From a craniofacial skeletal perspective, ASCs have been used to engineer bone in critical-sized calvarial defects. Cowan and colleagues demonstrated healing of 4 mm trephine defects using mouse-derived ASCs seeded onto apatite-coated polylactic-co-glycolic acid scaffolds, with complete bone bridging observed radiographically by 12 weeks [108]. Importantly, clinical translation of these findings has already been documented, as surgeons in Germany reported use of ASCs, in combination with iliac crest bone chips, to repair a large calvarial defect in a 7-year-old child [109]. Such results therefore engender significant enthusiasm for the use of ASCs in craniofacial bone tissue engineering. As a readily available and cost-effective building block, implementation of ASCs may herald significant advances in the treatment of various skeletal hypoplasias and bone deficits by craniofacial surgeons.

Conclusion

Craniofacial surgery has undergone significant evolution over the past two centuries. Faced with the treatment of disorders involving both bone excess and bone deficit, work by early pioneers helped to define several core principles guiding strategies employed by surgeons today. Craniofacial skeletal reconstruction, however, still remains a significant biomedical burden and limitations in contemporary approaches continue to highlight the need for development of novel modalities to either impair excess bone formation or promote osteogenesis in sites of need. With knowledge gained from investigations on the biomolecular events involved in craniosynostosis and with the promise of cellular-based bone tissue engineering, new approaches may soon be added to the armamentarium of surgeons treating craniofacial dysmorphologies. Integration of these modalities with contemporary techniques may one day yield innovative approaches to carefully control the balance between bone excess and bone deficit in the craniofacial skeleton.

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Source of Support: Nil, **Conflict of interest:** None declared.