Genetic Determinants of Periosteum Mediated Craniofacial Bone Regeneration: A Systematic Review

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ABSTRACT

Background: Periosteum-mediated bone regeneration (PMBR) is a known mandibular reconstruction. Though poorly understood and unpredictable, the concerns of developmental changes to donor and recipient tissues shared by other treatment options appear nonexistent. The definitive role of the periosteum during bone regeneration in any mammal remains poorly understood.

Objective: To characterise genetic determinants of PMBR in mammals through a systematic review.

Methods: Our search methodology was modeled after the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. The quality assessment of each publication was undertaken and the differences in gene expression at time points in weeks 1 and 2 were appraised

Results: A total of 4 studies met the inclusion criteria. The study subjects and tissues studied were 3 rat calvaria and 1 calf calvaria transplanted on mice. One out of the 4 studies had a quality score of the requisite ≥3. The gene expression results showed an upregulation of genes responsible for angiogenesis, cytokine activities, and immune-inflammatory response in week-1, and skeletal development and signaling pathways, in week-2

Conclusion: The results suggest that skeletal morphogenesis regulated by skeletal developmental genes and pathways may characterise the gene expression patterns of PMBR

Keywords: Craniofacial; Genetics; Regenerated bone; Periosteum mediated

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INTRODUCTION

Reconstruction of the young mandible is reported to be uncommon and described as intricate. [1,2] To date, about 29 cases of paediatric mandibular reconstruction have been reported in the literature of which, 13 were free flap reconstructions, 11 were non-vascularised reconstructions, and 5 used both techniques. [2-8] Its intricacy emanates from the need for a requisite understanding of developmental changes in bone and soft tissue of donor and recipient sites. [9] As a study, the restorative options of a mandibular defect, (an integral aspect of jaw tumour management) vary depending on which geo-developmental divide one view. Western centers often utilize primary or secondary reconstruction with vascularised osseous flaps and distraction osteogenesis, while developing healthcare systems like ours take advantage of the high frequency of childhood, benign mandibular lesions to utilize non-vascularised bone grafts. [9-12] A third treatment option often used in developing healthcare systems and gradually gaining traction in Western centers is the mandible's periosteum-mediated bone regeneration (PMBR). [13,14] Till date, a total of 32 case series with 63 cases, [13-44] has been reported and 44% (28/63) of these cases were reported from Africa, [14,15,22,31,33,35,36,38] an observation probably conditioned by the limited facilities mitigating against immediate or vascularised reconstruction. Despite its poor understanding and unpredictability, there are no concerns about changes in donor and recipient tissues during growth and development. In a previous clinical work on PMBR in humans, [14] it was reported that the regenerative potential of the mandibular periosteum begins as early as between 7 – 10 days and a reported bi-mandibular regenerative span of ~8cm in length, but another group had earlier reported new bone regeneration of the entire mandible. [33] Following reports of adult periosteum undergoing bone regeneration despite PMBR preference for young periosteum, [18,20] it was suggested that this probably inferred that young periosteum had the capacity to retain its osteocompetency with increasing age. [14] While there has been research on bone repair and regeneration, the definitive role of periosteum and the molecular pathways that regulate bone regeneration in mammals remains largely unknown. [45] The aim of this study is to review and catalogue the current evidence on the genetic determinants of PMBR in mammals.

METHODOLOGY

Search strategy

The search methodology was on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. [46] A Cochrane style MeSH (Medical Subject Headings) terms and keywords comprising; periosteum, craniofacial and (or) bone regeneration, and associated gene expression studies, were used for the initial search using the search tools; PubMed, Ovid Medline and Web of science. English only publications were selected and additional publications from the reference list of this initial search, were retrieved and reviewed to identify potential papers that met this study criteria.

Eligibility criteria

Titles and abstracts of selected publications were reviewed to identify suitable publications. Studies considered were - cross sectional studies, case control studies and controlled clinical trials. The full texts of these retrieved articles were proofread to identify those suitable for study inclusion. Purely clinical or pathological papers, conference papers and abstract only articles were excluded.

Study quality appraisal

The quality assessment of each publication was undertaken through a modification of the pre-existing tool, STrengthening the REporting of Genetic Association studies (STREGA). [47] This was achieved by evaluating in each article characteristics comprising – accurate description of a periosteum mediated craniofacial bone regeneration, description of case and control screening population, inclusion of gene or variant ID (e.g., NCBI rs identification, evaluation of gene function or gene ontology identifiers) and measure of genetic association that is risk odd ratio. Each publication was appraised using these characteristics, and each characteristic allowed a score of 0 or 1, to add up to a maximum overall score of 5. A quality score of ≥ 3/5 was deemed an acceptable study quality.

Data extraction and analysis

All results were extracted onto a data form for tabulation. Descriptive statistical information on case types in addition to sample sizes, gene expression methods and genetic associations was captured. In addition, significant differential in gene expression between defect and control periosteal at

1st and 2nd week (*time points*) and differential expression between weeks 1 and 2, were reviewed, and this was due to report of bone regeneration commencing as early as between 7 – 10 days. [14] Upregulated and downregulated genes were catalogued, and a gene expression was adjudged significant if the fold change between expression time points was ≥ 2.0 or ≤ -2.0. SPSS 27 software package (IBM Company, Armonk, NY, USA) was used for statistical analysis.

RESULTS

As shown in the flow diagram [Appendix I], the collective search yielded 69 citations; of which 57 publications were removed for reasons ranging from study duplicity to no correlation with craniofacial bone regeneration, thus 12 publications were selected for full-text review. Upon proofread, 8 additional studies were removed for being purely clinical related and having no gene expression correlation, resulting in 4 studies, [48-51] meeting the inclusion criteria.

One of the four studies had a modified STREGA score of ≥3 and additional details are shown in Table 1. The study subjects and tissues were 3 rat calvaria and 1 calf calvaria transplanted on mice. The gene expression techniques used were microarray, and rt-PCR and their results were reviewed at first and second weeks as *time points*. The results of the gene expression evaluation over these time points (see tables 2 & 3), showed a significant upregulation of genes associated with inflammation and immune response that is angiogenesis, immune - inflammatory response genes like cytokines (IL-1beta, IL-6), cathepsin K (*CTSK*) and receptor activator of nuclear factor kappa-B ligand (*RANKL*), and few skeletal development genes) prevailing on the week 1 (table 2) while, significant upregulation of functional related genes responsible for bone and skeletal development, regulation of ossification and osteoblast specific genes like; runt related transcription factor 2 (*Runx2*), *collagen type 1, osteonectin, osteocalcin / osteopontin genes*, prevailing at week 2 (Table 3). Genes related to decreased intracellular metabolic activity was also observed in week 1 while several biological signaling pathways like BMP-2, Hedgehog, PDGF, NOTCH and Wnt were implicated in week 2 (Tables 2 & 3). Further analysis of the differential gene expression for the inflammatory and immune response genes showed a higher count of significant gene expression in week 1 compared to week 2 (table 4 & 5). Specific genes related to inflammatory and immune responses were grouped in 3 of the 4 papers due to the volume as reviewed in the gene ontology resource tool. [52,53]

Table 1. Modified STREGA quality score per publication

No.	Publications	PMBR Description	Use of Controls	NCBI ID No. / Variant types	Validation of results	Reported data as risk ratio	Quality score (0 to 5)
1	Li et. al. (67)	Yes	Yes	Yes	No	Yes	4
2	Al-Kattan et al. (68)	Yes	No	Yes	No	No	2
3	Ivanovski et al.(69)	Yes	No	Yes	No	No	2
4	Matsushima et al. (70)	Yes	Yes	No	No	No	2

NCBI = National Center for Biotechnology Information

Table 2. Percentage of significant differential expressed genes at week 1.

No.	Publications	Subjects	Mean age	Assay	Gene types upregulated at day 7	Genes Upregulated (%)
1.	Li et. al. (67)	6 Mini pigs	18 months	Microarray (APGA)	Inflammatory & immune response	297 (68%)
2.	Al-Kattan et al. (68)	6 Wistar Rats	6 months	Microarray (ARGA)	Angiogenesis, NF/Kappa *β* pathways, Inflammatory & immune response	ND
3.	Ivanovski et al. (69)	6 Wistar Rats	6 months	Microarray (ARGA)	Inflammatory and immune response	1296 (34%)
4.	Matsushima et al. (70)	3 Calves & Mice	<6 months	RT-PCR	ND	ND

APGA = Agilent porcine gene array; ARGA = Affymetrix rat genome array, RT-PCR = Reverse transcriptase polymerase chain reaction; ND = Not disclosed

Table 3. Percentage significant differential expressed genes at 2nd week.

No.	Publications	Subjects	Mean age	Genes upregulated over 2nd week	Genes Upregulated (%)
1.	Li et. al. (67)	6 Mini pigs	18 months	SDG, Tgf*β* /Bmp, Wnt & Notch pathways	1065 (55%)
2.	Al-Kattan et al. (68)	6 Wistar Rats	6 months	SDG, Tgf*β* /Bmp, Wnt pathways	361 (67%)
3.	Ivanovski et al. (69)	6 Wistar Rats	6 months	SDG, Tgf*β* /Bmp & Wnt pathways	92 (76%)
4.	Matsushima et al. (70)	3 Calves & Mice	<6 months	SDG	4

SDG = Skeletal Developmental Gene; ND = Not disclosed

Table 4. Week 1 upregulated genes with high fold change of ≥ 2.0 or ≤ -2.0 and gene count in parenthesis

No.	Publications	Cytokine & inflammatory and immune response genes
1	Li et. al. (67)	Cellular component (196)
		Biological process (100)
		Molecular function (62)
2	Al-Kattan et al. (68)	*IL6, IL1a, IL1b, TNF*
3	Ivanovski et al. (69)	Cellular component (1909)
		Cell growth & apoptosis (151)
		Immune response (154)
		Biological process (1558)
4	Matsushima et al. (70)	ND

Table 5. Week 2 upregulated genes with high fold change of ≥ 2.0 or ≤ -2.0

No.	Publications	Cytokine & inflammatory and immune response genes	Skeletal developmental genes	Wnt signaling pathway genes	Tgfβ /Bmp signaling pathway related genes	Notch signaling pathway related genes
1	Li et. al. (67)	Cellular component (95), Biological process (300), Molecular function (185)	*THBS3, DMP1, PTHLH, Osteocalcin, MSX1, RUNX2, Collagen XI, XIII,*	*FZRB, CPZ, WISP2, WIFI, APC2*	*THBS3, MAP3K1, FRZB, TGFB3, DLX5*	*NOTCH4, CFD, FOXC1*
2	Al-Kattan et al. (68)	PDGF	*BGLAP2, DMP1, BMP3, COL11A2,*	*FRZB, DKK3*	ND	ND
3	Ivanovski et al.(69)	Cellular component (168) Cell growth & adhesion (183)	*Osteocalcin, DMP1, COL13A1, OMD, IGFBP5, MEPE, SATB2, RUNX2, PTHR1, ACAN*	*CPZ, WIF1, FZRB, DKK3, FZD6,8, LRP4,*	*THBS4, BAMBI, LTBP3, PDGFRB, BMP2*	ND
4	Matsushima et al. (70)		*Collagen I & II, RUNX, BSP*	ND	ND	ND

DISCUSSION

The bones in the craniofacial and appendicular regions develop differently, that is the former is derived from ectodermal neural crest cells of the closing neural tubes, which ensures a different characteristic to its periosteum and ossification patterns, compared to the appendicular bones. [54-56] The bone matures through an intramembranous

process that is characterised by different mesenchymal cells differentiating into bone-depositing osteoblasts or ossification centers and eventually to compact bone. [57] Conversely, appendicular bones develop by endochondral ossification which is characterised by cell differentiation into chondrocyte-synthesized collagen which matures by proliferation and then templatizes the shape of the future (ossified) bone. [58,59] Despite, intramembranous and endochondral bone developments differing in many aspects, they share similar regulatory mechanisms. [57,60] While bone repair or regeneration is believed to be periosteal driven, there remains a void on the precise role of periosteum in bone regeneration. [57,58] PMBR comprises 4 successive phases; an initial inflammatory response and recruitment of osteo-progenitor cells, formation of a cartilaginous template, replacement of template with immature (spongy) bone and finally remodelling into mature bone, and the periosteum is the main driver throughout all four phases. [60] In the author's opinion, an improved understanding of the role of periosteum may proffer a clear resolution to bony repair and defect reconstruction option with advantages including low cost and reduced morbidity from a non-existent donor site. However, currently, its unpredictability and lack of consensus among clinicians remain its only drawback. [14] While little or no genetic association studies on PMBR have been undertaken in humans, a few have been undertaken in animal models and a review of this was the focus of this study. The number of studies that met this study's inclusion criteria suggest the dearth of publications on this topic even in animals, with additional search revealing no report on the underlying molecular mechanism of periosteum in bone regeneration. Only one of the four studies was adjudged to have met the requisite quality score and this was due to the improper study designs and absence of gene ontology (GO) identifiers. [51] Particularly, the absence of GO identifier prevented specific gene expression interpretation which would have aided in the comparison of the outcomes to other associations. Three of the studies used microarray technology which is an effective transcriptional profiling technique that has been used to characterise the processes of bone healing and guided regeneration. [49,50,61,62] While skeleto-developmental and immune-inflammatory responses were the major events implicated in bone regeneration according to this review and other studies, this report supports that inflammatory - immune response observed in bone healing and regeneration was different from that of the usual soft tissue wound healing. [63-65] Besides inflammatory and immune response activities, two other events in angiogenesis, and neurogenesis also occurred and while new vessel formation is a well-recognized requirement for bone regeneration, the observation of neurogenesis was somewhat surprising however there has been reports that suggest that new nerve fibre formation promotes osteogenesis. [66-68] Furthermore, references to gene expression in PMBR were made between the time points weeks 1 and 2 and this was due to the clinical manifestation of PMBR in as early as 7 -10 days. [14] The upregulation of Inflammatory and immune response was expected at 7 days as this supports the initial inflammatory phase of bone regeneration, but the added responses of I-kB kinase/NF-kB signaling pathway was interesting as this is a known pathway reported to induce inflammation-induced bone loss. [69] In week 2, the upregulated pathways; TGF beta/Bmp, Wnt and Notch are known to upregulate SDG. Of all these skeletal development pathways, Bmp signaling is the only strongly suggested pathway associated with bone regeneration as, BMP2 is suggested to regulate PMBR through periosteum-based target cells. [70,71] In converse, Wnt signaling pathway activity through its Wnt target cells which are present in fractured bones compared to bony defect, suggests they influence more of bone repair than regeneration albeit in a different mechanism from the Bmp signaling. [72,73]

While PMBR holds a lot of promise as bone reconstruction option especially in the mandible as is used today, [14] factors like developmental growth in paediatric mandibular reconstruction is an aspect that remains uncertain and in need of added research. This uncertainty stems from several factors that is the condyle is a mandibular growth spot, and its involvement or preservation may affect jaw growth post PMBR. While factors like a patient's age are known to affect the rate of growth, other known factors like radiotherapy and chemotherapy are not of concern as PBMR is not recommended for malignant lesion. [9,14,74]

In conclusion, this review tried to harmonize the various reports on the complex events of PMBR of the mandible through upregulation of genes and signaling pathways. This result suggests that skeletal morphogenesis regulated by skeletal developmental genes and pathways may characterise the gene expression patterns of PMBR. Immune –

inflammatory related genes appear to be mostly upregulated at week 1 while the SDG and signaling pathways upregulate in week 2. The limitations of this study would include characterisation of the events only in an up or down gene regulation between weeks 1 and 2. In addition, due to tissue heterogeneity in the periosteum, attributing specific phenotypic or molecular event to a particular cell type was impossible due to the absence of histological analysis. Thus the source of gene expression could not be localized. In addition, the analysis presented was present at transcription level that is actively expressed genes which may not correspond to the protein coded for or expressed. Thus, combining the assays used by these reports with Immunohistochemistry (IHC) or proteomics could provide a more accurate picture of bone regeneration events.

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Nil
Conflict of interest
None Declared

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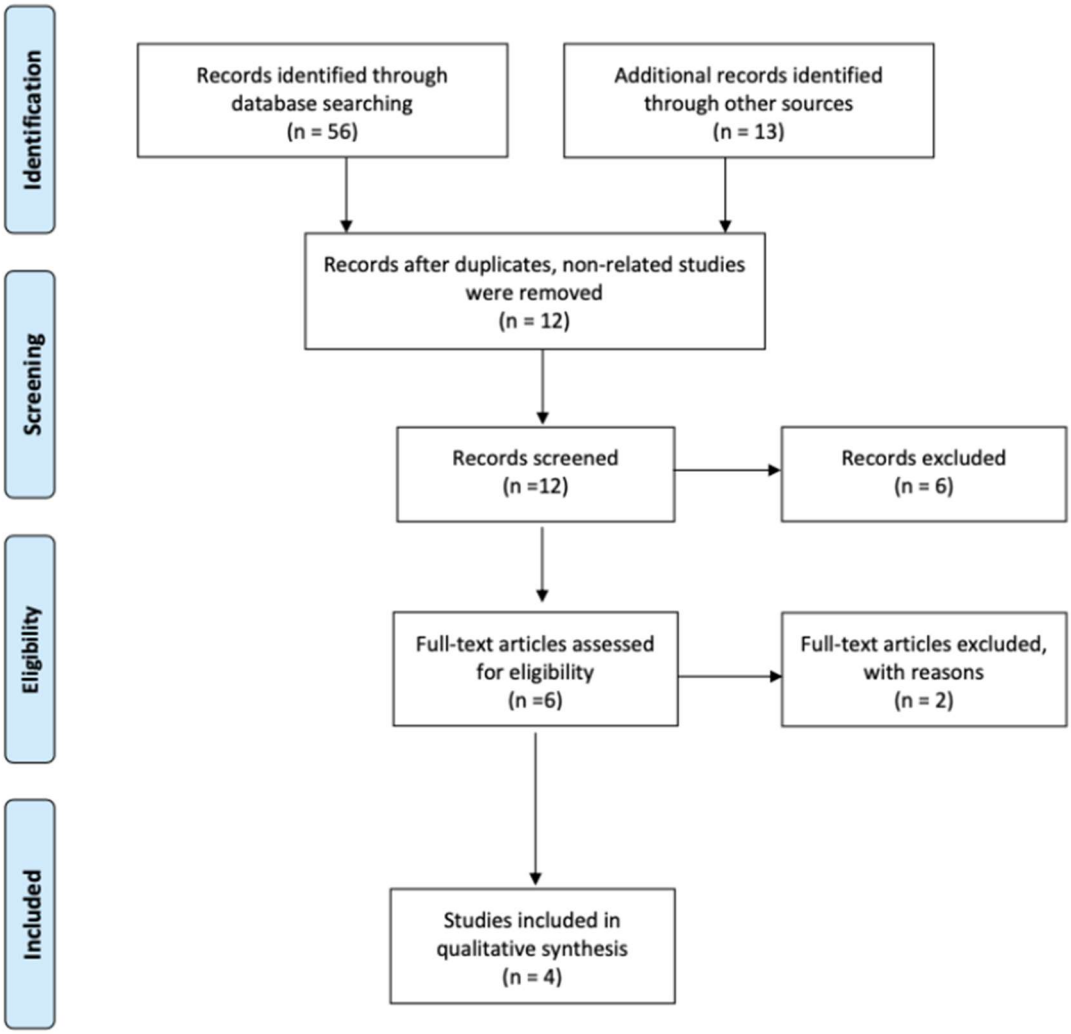
Appendix I



Search flow chart