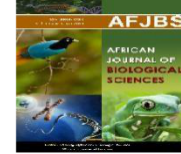# African Journal of Biological Sciences

Research Paper   **Open Access**

Gene Expression Variations associated with Oral and Maxillofacial Defects: an Updated Review

Saeed Nezafati[1], Tannaz Pourlak[1*]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran.
* Corresponding author: Tannaz Pourlak

Abstract

Most adult males or females suffer from oral and maxillofacial (M-F) defects. Serious diseases or injuries caused extensive damage to the oral and maxillofacial region. These types of injuries can destroy cell structure in hard and soft tissues of jaws, oro-nasal area, eyes, and facial skeleton. Many studies have been reported on the causative factors and therapeutic approaches of maxillofacial defects. One of the important reasons for oral and M-F defects is dysregulation of different mRNAs in various types of M-F defect. Also, the effect of some molecules, materials, and proteins on the expression of mRNAs can result in elevation or inverse inhibition of M-F defects. This chapter reviews and discusses the expression of some mRNAs across different oral and M-F defects, examines the expression of mRNAs associated with oral and M-F after transferring various mesenchymal stem cells, along with the impact of some materials or molecules on mRNAs expression, and some available therapeutic approaches in this area.

Keywords: Gene expression, mRNA, Oral, Maxillofacial Defect, Bone

Introduction

One of the leading causes of death in people is trauma. Maxillofacial (M-F) defects are one of the important traumatic injuries and most adult males or females suffer from it [1]. So far, many studies have been carried out on the causes and therapeutic approaches to the maxillofacial defects. Depending on the origin of these defects, various factors make different injuries in the maxillofacial defects. Different causes including growth factors, extracellular matrix molecules, transcription factors, and cytokines can increase angiogenesis and osteogenesis in bone tissue engineering [2]. Dysregulation of mRNAs expression has a critical role in the generation of maxillofacial defects and various studies have been reported on the effect of mRNA expression in oral and maxillofacial defects. Identifying and regulating the expression of mRNAs related with oral and maxillofacial defects can be considered for treatment with novel methods such as miRNAs. Also, some studies have demonstrated that use of some materials or molecules can affect the expression of mRNAs related to oral and M-F bones. The aim of this chapter is to show the impact of mRNA expression on maxillofacial injuries and also to examine the effect of some types of stem cell therapy on different mRNA as associated with oral and M-F bones.

Categories of maxillofacial defects

Serious injuries or diseases cause many damages in the maxillofacial region. The M-F injuries can destroy the entire structure - hard and soft tissues of oral, oro-nasal area, jaws, nose, eyes, facial skeleton, and cheeks [3]. Further, M-F defects are aggravated by congenital malformations, oncologic diseases, and injuries [4]. Considering the location and cause, the M-F has different categories; in terms of origin, it includes congenital, acquired, surgical, and traumatic cases. However, in terms of locality, it is classified as intraoral (mandibular, velo-pharyngeal, maxillary), extra-oral (auricular, ocular, orbital, nasal, lip) and composite defects. Congenital M-F defects have different etiologies such as drugs, infections, genetic factors, poor diet, and hormonal imbalance [5]. Surgical resection of some tumors such as salivary grand tumors, malignant mesenchymal tumors, benign mesenchymal tumors, and epidermoid carcinoma can lead to most acquired maxillary defects.

Dysregulation of expression of different genes involved in various maxillofacial defects

Adenoid cystic carcinoma

Cylindroma or Adenoid Cystic Carcinoma (ACC) is a type of maxillary and salivary gland tumor. ACC can develop in different sites such as the lung, brain, breast, Bartholin gland, and paranasal sinuses. ACC has some features including highly invasive and slowly growing [6, 7]. An importance sign of ACC is a lump inside the mouth, under the tongue and inside the cheek. The Epithelial – to – Mesenchymal Transition (EMT) is a procedure during which a change in cells occurs from an epithelial phenotype, polarized to non-polarized and highly motile mesenchymal phenotype [8]. In hepatocellular carcinoma [9], invasive lobular breast cancer [10], tongue squamous cell carcinoma, and patients with lymph node metastasis or local recurrence, the expression of TWIST2 and SIP1 increases. SIP1 and TWIST2 are two representative EMT regulators. Hypoxia-inducible factors-alpha (HIF-α) are three

homologues' subunits including (HIF-1 α, HIF-2 α, HIF-3 α). In these subunits, the HIF-2 expression is correlated with colorectal carcinoma, ovarian cancer, melanoma, and poorer prognosis in head and neck squamous cell cancer (HNSCC) [11]. The mRNA and protein levels of SIP1, TWIST2, and HIF-2 α have been significantly higher in ACC cell lines. Also, the increased expression of HIF-2 α has been correlated with metastasis and invasion in ACC. This finding proves that hypoxia microenvironment may have a critical role in EMT of ACC followed by M-F injuries [12]. SOX2 is a transcription factor in the sex-determining genome and has an essential role in protecting the anti-apoptotic properties of tumor cells [13]. Survivin or baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) is a one of the members of inhibitor apoptosis proteins (IAPs) [14]. By inhibiting the activity of Caspase-7 and Caspase-3 apoptotic effector, the Survivin can increase cell proliferation [15, 16]. Lu O et al. demonstrated that the expression of SOX2 and survivin increased in ACC patients. So, it was postulated that the survivin is a downstream regulatory gene of SOX2 and a correlation between them may elevate the resistance of ACC cancer cells and cause M-F injuries [17].

Mesenchymal stimulation therapy and expression of osteogenesis associated genes in intraoral MSPCs

Mesenchymal stromal cells (MSCs) have opened new perspectives in regenerative medicine for tissue engineering. MSCs promote the regeneration of different tissues such as tendon, cartilage, muscle tissue, and ligament [18, 19]. Dental tissue-derived mesenchymal stem cell-like population have different types such as stem cells from exfoliated deciduous teeth (SHED) (Miura,MSC1), post-natal dental pulp stem cells (DPSCs) [20], periodontal ligament stem cells (PDLSCs), intraoral mesenchymal stromal, progenitor cells (MSPCs), and stem cells from apical papilla (SCAP) [21]. Dental stem cells are more committed to odontogenesis, and they have been used for regenerative medicine. The cells isolated from maxillary and mandibular bone, dental pulp, and periosteum from the oblique line are described as MSPCs [22]. Different deficiencies in the expression of intraoral MSPCs genes can cause M-F defects. Studies have revealed that the decrease in osteogenesis related genes including Alkaline phosphatase (ALPL), bone morphogenetic protein 2 (BMP2), type I collagen (Col1A1), osteonectin (SPARC), osteocalcin (BGLAP), and osteopontin, can engender M-F defects [23, 24]. Mechanical stimulations have been used for bone regeneration through distraction osteogenesis [25, 26]. They also have a critical role in differentiation of MSPCs via an osteogenic pathway and then, the bone remodeling process is initiated by sensing mechanical stimulations and osteocytes via turning osteoblasts signal to form bone matrix [27]. Flexcell FX5K tension system has been used to evaluate the impacts of mechanical strain on the expression of osteogenesis related transcription factors and differentiation of osteoblast-like cells. Lohberge et al. [28] demonstrated that flexcell FX5K tension system therapy can be employed for osteogenic differentiated (OG) human intraoral MSPCs. After 14 days of mechanical stimulation with FX5K, the expression of osteogenesis specific markers such as runt-related transcription factor 2 (RUNX2), Col1A1, osteopontin (SPP1), BMP2, and SPARC were enhanced in OG group. However, a significant difference was observed in the mRNA expression of BGLAP between OG and control group [28]. So,

mechanical stimulation can be a regulator of osteogenic differentiation in intraoral MSPs and consequently in M-F defects [28]. Application of MSCs from the dental site in engineering approaches for oral and maxillofacial surgery can help reduce the need for an additional surgical intervention and also reduce morbidity [29]. Other studies have shown that Intraoral tissue-derived MSCs have an important potential for treatment of soft and hard connective tissue defects [30]. Periodontal ligaments include collagen-forming stem cells that express mesenchymal stem cell markers and differentiate into adipocytes, and cementoblast-like cells when transplanted into a pig periodontitis model or immunocompromised mice. It can promote periodontal tissue repair by increasing the capacity of generation a cementum/periodontal ligament-like structure [31]. Human dental pulp stem cells could differentiate into neural-like and adipocytes cells and have the ability of forming ectopic dentin and pulp tissue in vivo [32]. In a study, human maxilla-derived bone cells were positive for CD44, CD13 CD73 and CD90 but negative for CD31 [33]. Payer et al. [34] proved the potential of maxillary bone-derived cells in adipogenic and osteogenic differentiation by in vitro experiments. Pekovits et al. [35] used human alveolar bone-derived cells (hABDCs) and human bone marrow mesenchymal stromal cells (hBMSCs) to elucidate some mRNAs related osteogenic as well as chondrogenic and adipogenic markers. The mRNA expression of BGLAP (bone gamma-carboxy glutamate gla protein osteocalcin) increased in both hABDCs and hBMSCs induced group; also, the mRNAs expression of adipocyte-related gene FABP4 (fatty acid binding protein4), LPL (lipoprotein lipase), and chondrogenic differentiation marker ACAN (aggrecan) were higher in both hABDCs and hBMSCs group. However, insignificant difference was observed for SPARC (secreted protein acidic cysteine-rich osteonectin) mRNA expression between induced and non-induced group with hBMSCs and hABDCs [35]. This study can open an important avenue on using various mesenchymal stromal cells therapy in maxillofacial defects by changing the expression of related mRNAs.

Effect of the maxillofacial prosthesis on different gene expressions

Maxillofacial prosthesis is used to repair severe tissue, bone loss, and rehabilitation of facial mutilation in patients [36, 37]. Some studies have proven that the acrylic resin as an intermediary layer can improve the connection between implants and prosthesis [38, 39]. Acrylic resin is covered with silicone, with the resultant resin/silicon junction being a weak linkage. So, some studies have used primers and adhesion to improve the resin/silicone junction [40, 41]. In general, it is necessary to know how to safely use maxillofacial prosthesis. Rocha Bonatto et al. [42] demonstrated that the mRNA expression of IL-6 in RDCpS (resin + DC1205 primer + silicone) group was higher than in the control group. Nonetheless, regarding the mRNA levels of Col IV (collagen type IV), MMP-9 (matrix metalloproteinase-9), and TGF-β, there was no significant difference between treatment with primer and adhesive group and control group [42]. This study may prove the hypothesis that when the primer is used, an inflammatory process can occur by elevating the IL-6 level and subsequently M-F defects.

Dysregulation of inflammatory and anti-inflammatory cytokines related genes

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory defect in nasal obstruction, nasal mucosa, and growth of nasal polyps (NP) [43]. The CRSwNP is categorized in M-F defects. Type 2 cytokines have a major role in NP. Multiple inflammatory cells inducing neutrophils, eosinophils, innate lymphoid cells (ILC), lymphocytes, and mast cells are infiltrated in NP [44]. Programmed cell death-1 (PD-1) is a member of the immunoglobulin superfamily and has a critical role in immune tolerance, cell proliferation, cytokine production, and anti-inflammatory function of T cell function [45]. PD-1 expression in CRSxNP disease can promote tissue infiltrating T cells [46]. T lymphocyte activation is negatively regulated by the interaction between PD-1 and its receptors (PD-L1 and PD-L2) [47, 48]. In a study, PD-1 mRNA expression was significantly higher in CRSwNP compared with control nasal tissue. However, the mRNA expressions of the ligands PD-L1 and PD-L2 were remarkably lower in CRSwNP group [49]. TGF-β and IL-10 are the major anti-inflammatory cytokines and have an essential role in the regulation of the immune cell. Another study found that the mRNA levels of TGF-β and IL-10 were lower in NP tissue compared with control nasal tissue group. Reduction of the TGF-β levels in NP leads to a lower capacity for local induction of Treg [49]. Krohn et al. [49] demonstrated a higher positive correlation with enhanced PD-1 expression in NP, IL-5 mRNA, and CT scan scores and degree of sinus opacity.

Oral squamous cell carcinoma

One of the most common malignancies in the world is oral cancer. Some factors and biomarkers including alcohol, genetic predisposition, tobacco, and betel quid chewing, as well as use of some biomaterials for healing processes and recovery of the human body during surgery can be correlated with initiation and development of cancers [50, 51]. Oral squamous cell carcinoma (OSCC) is one of the predominant fractions of head and neck squamous cell carcinoma (HNSCC). It is one of the most common disorders in the oral and maxillofacial region [52]. In addition, HNSCC is the 7th most common cancer in the world. Understanding the pathways of oncogenesis and exploiting the molecular profile are necessary for targeted therapy of some cancers such as OSCC [53, 54]. Platelet-derived growth factor-alpha (PDGFRA) gene encodes tyrosine kinase receptor for PDGFs. Physiologically, PDGFRA promotes wound healing and organ development [55]. However, in pathological cases, PDGFRA activation may induce kinase phosphorylation and increases cancer cell invasion and growth [56, 57]. Shan Ong et al. [58] showed that the PDGFRA mRNA levels were high in primary OSCC group, and the risk of regional lymph node metastasis was directly correlated with the mRNA levels of PDGFRA. This study suggests that use of anti-PDGFRA drugs can be suggested as targeted therapy for OSCC. In dentistry, application of dental implants in hard tissue reconstruction can cause oral cancer [59, 60]. Bone morphogenetic protein-2 (BMP-2) is a useful drug for dental treatment and orthopedic surgery to form bone graft membranes, solutions, or osteogenesis [61]. In normal cells, BMPs regulate epithelial-to-mesenchymal transition (EMT) such as cardiac morphogenesis and neural crest migration [62]. Studies suggested that the overexpression of BMP-2 increased cell invasiveness and motility in oral squamous carcinoma cells [63]. Up-regulation of BMP-2 by inducing CCL5

release increased the invasion of OSCC [63]. Kim et al. [63] also demonstrated that use of CCL5 neutralizing antibodies inhibited the OSCC cell invasion; this result can be a therapeutic approach for oral cancer and maxillofacial defects. The spread of neurotropic carcinomatous or perineural invasion (PNI) has an important role in cancer cells expanding the tissues surrounding the tumor through nerve bundles [64]. PNI is involved in the movement of neoplastic cells to remote areas from the primary lesion along the nerve tract [65]. Studies have shown that the possible occurrence of PNI in OSCC ranges from 6% to 30% [66]. Activation of various signaling pathways, involving extracellular matrix adhesion proteins, trophic factors, and chemotaxis regulation may cause tumor cell invasion towards nerves and then along the trunk via the perineural space [67, 68]. In OSCC, some molecules such as neural cell adhesion molecules (N-CAM) [69], Claudin1 [70], Claudin4 [71], nerve growth factor (NGF) [72], snail [73] and activin A [74] have been detected in surgical specimens of cases showing PNI. The PNI is critical in evaluating the prognosis of OSCC. Nevertheless, it is not appropriate in the correct planning of surgical management of patients and PNI may be evaluated only in surgical specimens [75]. Insulin-like growth factor-II binding protein-3 (IMP3) is one of the members of the IMP family. IMP3 is a necessary biomarker for numerous malignancies which affects cellular adhesion, proliferation, invasion of malignant neoplasms [76], and for predicting PNI of gastric cancer [77]. Laminin-5 is one of the different proteins correlated with PNI and is a valid predictor of the neural spread of adenoid cystic carcinoma of head and neck [78]. So, the early detection of PNI can help to modify the treatment especially neck treatment plans [79]. In a study, the mRNA expression of IMP3, Laminin-5 was enhanced in OSCC preoperative incisional biopsy samples [80]. Also, 84.8% of the IMP3 positive and 67.2% of the laminin-5 positive in preoperative biopsy demonstrated evidence of PNI in the postoperative surgical specimens [80]. This study proved a positive association between IMP3 as well as Laminin-5 expression with PNI. Therefore, it is hypothesized that it may possible to reduce the function of PNI in OSCC patients by inhibiting the expression of IMP3 and laminin-5. Early diagnosis of OSCC can help to reduce metastasis of these cancer cells. Some cultured human squamous cell carcinomas generate cytokeratin 19 (CK19) [81]. It is a component of cytoskeleton proteins whose gene consists of six introns and six exons [82]. The translation product of this gene is CK19 protein with 400 residues that is a type I cytokeratin [83]. Some studies have reported that the CK19 protein is measurable in the basal layer of normal oral mucosa; however, the presence of CK19 in OSCC tissue has been reported in invasive carcinoma tissue as well as in all mucosal layers [84]. Some previous studies have demonstrated various positive rates of CK19. For example, according to Hamakawa et al. [85], a strongly positive rate of CK19 in OSCC tissue showed only 24% of tissue. In contrast, Vara et al. [86] reported that only 29% of tongue squamous cell carcinoma (SCC) tissues were positive for CK19. Zhong et al. [81] proved the fact that the mRNA expression of CK19 was higher in OSCC tissue. Also, this study indicated that there is no a significant difference for the CK19 expression between cancerous and para-cancerous tissues from OSCC patients. However, the correlation between the pathological differentiation grade and the level of CK19 mRNA in OSCC was significant [81].

Effect of hemokinin A, sonic hedgehog, intermittent hypoxia, SCPC, and RESV on maxillofacial bone

Tachykinins act as neuromodulators and neurotransmitters [87]. Tachykinins are a family including neurokinin A (NKA), Substance P (SP), hemokinin A (HK-1), and neurokinin B (NKB). The TAC1 gene encodes for SP, the TAC3 and NKA gene encodes for NKB, and the TAC4 gene encodes for HK-1 [88]. These members of tachykinins bind to G protein-coupled neurokinin receptors and affect cellular responses. HK-1 and SP are the preferred ligands of neurokinin receptor 1 (NK-1). HK-1 has important roles in hematopoiesis by supporting the survival and maturation of pre-B cells [88]. HK-1 is expressed in immune and inflammatory cells, glial cells, placenta, and human endothelial cells [89]. Previous studies have suggested that SP encourages the formation and resorption of maxillofacial bones' activity via NK1-R [90]. The mRNA expression of TAC4 and NK1-R was detected in the osteoclast-rich cell population in teeth and maxillofacial bones [91]. Fukuda et al. [91] demonstrated that total resorption of bone was higher in a group treated with SP than in the group subjected to HK-1. Also, HK-1 competitively inhibited SP-induced function and formation of osteoclasts via NK1-R which has high affinity to both SP and HK-1. Hedgehog (Hh) signaling plays a critical function in the development of vertebrate embryos and drosophila such as regulation of craniofacial development [92]. There are three Hh ligands including Indian hedgehog (Ihh), desert hedgehog (Dhh), and sonic hedgehog (Shh) which bind to the patched-1 (PTCH1) and patched-2 (PTCH2) (transmembrane receptors) [93]. Smoothened (Smo) is a seven-transmembrane protein necessary for Hh signaling [94]. So, it is implicated in the mediation of Shh signaling in the early mouse embryo and rheostat tin of graded Shh signals into distinct responses and it begins a series of downstream events that control the expression of Shh target genes [95]. Shh signaling has a role in cell differentiation and proliferation in the normal development of maxillofacial [96]. Defect in Shh signaling can cause a number of congenital defects and human diseases such as polydactyly, basal cell carcinoma, and holoprosencephaly that is correlated with maxillofacial regions [96]. Du et al. [97] observed that the mRNA smo levels were higher on 11 days postcoitum (dpc) in mouse maxillofacial development. However, on 14.5 dpc, the expression level of smo decreased considerably. Intermittent hypoxia (IH) in children with obstructive sleep apnea (OSA) cause morphological changes in the maxillofacial bones [98]. IH exposure induces the impaired of maxillofacial bones, during growth, increased bone mineral density (BMD) in the intra-radicular alveolar bone in the mandibular first molar (M1) region and induces reduction in the volume of the nasal cavity [99]. Hypoxia is necessary for the repair and remodeling of the damaged bones through hypoxia-inducible factor (HIF). HIF is a critical stimulator of angiogenesis and vessel formation [100]. Vascular endothelial growth factor (VEGF) is a popular angiogenic factor, and also is the primary target for HIF-α [101]. Previous studies have reported that the VEGF and HIF have important roles in the coupling between osteogenesis and angiogenesis during repair and bone formation of maxillofacial area [102]. Periodontal ligament (PDL) is a specialized soft connective tissue which connects the alveolar bone socket and tooth, thereby promoting the maintenance and development of periodontium

[103]. Alkaline phosphatase (ALP) and bone morphogenetic protein-2 (BMP-2) induce osteogenesis and the osteogenic transformation of PDL cells [104]. The BMP-2 upregulation and ALP activation could elevate periodontium osteogenesis in PDL cells in response to growth hormones [105]. PDL tissues via BMP-2 and ALP maintain proper alveolar bone homeostasis [106]. Oishi et al. [107] examined the mRNAs expression of HIF-α and VEGF that are osteogenesis-angiogenesis coupling markers and also the mRNAs expression of ALP and BMP-2. They found that the osteogenic marker was higher in PDL tissues induced with IH compared with the control. Furthermore, the IH increased BMD in alveolar bone proper, changing the bone microstructure as well as important risk factors for homeostasis in a disturbance in alveolar bone proper in growing IH rats. So, it is hypothesized that IH can induce mRNA expression of VEGF, HIF-α, ALP, and BMP-2 in the maxillofacial bones in children with obstructive sleep apnea (OSA). On the other hand, porous scaffolds guide and support new tissue formation by providing a physical and three-dimensional template. Porous scaffolds have some advantages including facilitation of cellular vascularization and colonization, removal of metabolic waste products, and provision of channels for tissue-fluid circulation [108]. Porous material may act as a bone graft in a load-bearing position in orthopedic and craniomaxillofacial surgical operations [81]. Adversely, low or high rates of degradation can cause limitation of porous bioactive materials, although porous tricalcium phosphate has a capacity to bend to bone [109]. Silica-calcium phosphate nanocomposite (SCPC) has regeneratively and superior bone restorability than other porous bioactive materials [110]. Gupta et al. [111] have reported that the expressions of collagen-I (Col-I)/glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA and osteocalcin mRNA/GAPDH mRNA were higher in the group stimulated with SCPC50. Also, the expression of osteonectin (OSN)/GAPDH mRNA was higher in the group stimulated with SCPC30. This study suggests that SCPC can be used to enhance the osteoblast-related gene expressions in maxillofacial defects. The use of resveratrol (RESV), definitely influenced bone repair in animals with induced diabetes mellitus. As well, the combination of insulin therapy plus RESV was necessary for the modulation of BMP-2 gene expression [112]. Long-term intake of RESV could be a beneficial therapeutic approach in the rehabilitation of patients with dental implants, by modulation of bone morphogenetic proteins and osteopontin gene expression [113]. Because of immunomodulatory effects of resveratrol, and its ability to reduction levels of proinflammatory cytokines, appears to be as an additional element to improve regenerative progression of alveolar bone [114]. So, RESV could be remarkable in view of applications in the field of maxillofacial surgery.

Table 1. Variations in mRNAs related to maxillofacial defects or tissues

Direction of changes	mRNAs name	effect	Disease or target	Ref.
upregulation	SIP1, TWIST2	Increase EMT	ACC	[12].
upregulation	HIF-1α	Increase metastasis and invasion	ACC	[12].

upregulation	BIRC5	Inhibits the activity of caspase-3 and Caspase-7	ACC	[17].
upregulation	SOX2	Anti-apoptotic of cancer cells	ACC	[17].
upregulation	RUNX2, Col1A1, BMP-2, SPP1	Induced by FX5K, - osteoblast cells differentiation	Human intraoral MSPCs	[28]
upregulation	FABP4, LPL, ACAN	Induced by hABDCs, increase adipocyte and osteogenic	-	[35].
Not a significant difference	SPARC	Induced by hABDCs, increase- adipocyte and osteogenic	-	[35].
upregulation	IL-6	Induced by acrylic resin and increase the inflammatory process	M-F prosthesis group	[42]
Not a significant difference	MMP-9, Col1 IV, TGF-β	Induced by acrylic resin	M-F prosthesis group	[42]
upregulation	PDGFRA, BMP-2, IMP3, Laminin-5	Increase- invasive, motility, spreading of tumor cell	OSCC	[58, 63, 80]
upregulation	CK19	Increases invasive of carcinoma tissue in all mucosal layer	OSCC	[81]
upregulation	Smo	Differentiation and proliferation in the normal development of M-f	Mouse M-F development	[97]
upregulation	HIF-α, VEGF, ALP, BMP-2	Induced by IH, increase- osteogenesis and angiogenesis	PDL tissue	[107]

upregulatio n	Col-I, OSN, osteocalcin	Induced by SCPC, increase osteoblast in M-F bones	M-F bones	[111]

EMT: Epithelial – to – Mesenchymal Transition, SIP1: Smad interacting protein 1, TWIST2: Twist family BHLH transcription factor2, ACC: adenoid cystic carcinoma, HIF-1α: Hypoxia-inducible factors-alpha, BIRC5: baculoviral inhibitor of apoptosis repeat-containing 5, RUNX2: runtrelated transcription factor 2, Col1A1: type I collagen, BMP-2: bone morphogenetic protein 2, SPP1: osteopontin, MSPCs: mesenchymal stromal and progenitor cells, FABP4: fatty acid binding protein4, LPL: lipoprotein lipase, ACAN: aggrecan, hABDCs: human alveolar bone-derived cells, SPARC: secreted protein acidic cysteine-rich osteonectin, IL-6: interleukin 6, M-F: maxillofacial, MMP-9: matrix metalloproteinase-9, CK19: cytokeratin 19, OSCC: Oral squamous cell carcinoma, VEGF: Vascular endothelial growth factor, ALP: alkaline phosphatase, OSN: osteonectin, SCPC: Silica-calcium phosphate nanocomposite

Conclusions

It has been recognized for several years that variation in the expression profile of genes occurs in maxillofacial defects. Defects in oral and maxillofacial bones cause different diseases. Adenoid cystic carcinoma, oral squamous cell carcinoma, and chronic rhinosinusitis with nasal polyps (CRSwNP) are some related diseases. As mentioned in ACC disease, the expression of TWIST2 and SIP1 genes that increase EMT is high. Also, SOX2 mRNA, a transcription factor in the sex-determining genomes, and Survivin mRNA, an apoptosis protein, were higher in ACC. Therefore, subsequent studies are required to work on inhibiting the expression of these genes using miRNAs or different anti-drugs in the treatment of ACC. In OSCC cells, the expression of some mRNAs related to invasion, spreading, proliferation, and metastasis was higher. So, it is necessary to make significant advances in the future by carefully examining the expression of these genes in the diagnosis and treatment of OSCC. Use of different types of MSCs can affect the expression of some mRNAs related to osteogenesis and subsequently reduce morbidity or decrease additional surgical intervention in M-F bones. In the same way, application of some molecules such as Shh, HK-1, and SCPC can increase osteoblast-related genes expression and total resorption of oral and M-f bones. RESV as a promoter of osteoblasts' proliferation and antagonist of osteoclasts' differentiation, exposed novel perceptions on bone regeneration, in consideration of its future application in dentistry and maxillofacial surgery. It is possible to take more effective steps to reconstruct M-F bones by studying the effect of these molecules on the expression of related mRNAs in a more comprehensive statistical system. Future studies are required for recognized different molecules which are involved in the regulation of gene expression pattern associated with maxillofacial (M-F) defects.

Ethical Approval

Not applicable.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

References

[1] Maas CS, Merwin GE, Wilson J, Frey MD, Maves MD. Comparison of biomaterials for facial bone augmentation. Arch Otolaryngol Head Neck Surg 1990;116:551-6.

[2] Cui M, Kanemoto S, Cui X, Kaneko M, Asada R, Matsuhisa K, et al. OASIS modulates hypoxia pathway activity to regulate bone angiogenesis. Sci Rep 2015;5:16455.

[3] Ortegon SM, Martin JW, Lewin JS. A hollow delayed surgical obturator for a bilateral subtotal maxillectomy patient: a clinical report. J Prosthet Dent 2008;99:14-8.

[4] Hubálková H, Holakovský J, Brázda F, Diblík P, Mazánek J. Team approach in treatment of extensive maxillofacial defects–Five case report serie. Prague Med Rep 2010;111:148-57.

[5] Boyne, P.J. Restoration of osseous defects in maxillofacial casualties. J Am Dent Assoc 1969;78:767-76.

[6] van der Wal JE, Becking AG, Snow GB, van der Waal I. Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. Head Neck 2002;24:779-83.

[7] Rapidis AD, Givalos N, Gakiopoulou H, Faratzis G, Stavrianos SD, Vilos GA, et al. Adenoid cystic carcinoma of the head and neck.: Clinicopathological analysis of 23 patients and review of the literature. Oral Oncol 2005;41:328-35.

[8] Kalluri, R. EMT: when epithelial cells decide to become mesenchymal-like cells. J Clin Invest 2009;119:1417-9.

[9] Yang MH, Chen CL, Chau GY, Chiou SH, Su CW, Chou TY, et al. Comprehensive analysis of the independent effect of twist and snail in promoting metastasis of hepatocellular carcinoma. Hepatology 2009;50:1464-74.

[10] Fackler MJ, McVeigh M, Evron E, Garrett E, Mehrotra J, Polyak K, et al. DNA methylation of RASSF1A, HIN-1, RAR-β, Cyclin D2 and Twist in in situ and invasive lobular breast carcinoma. Int J Cancer 2003;107:970-5.

[11] Koukourakis MI, Giatromanolaki A, Sivridis E, Simopoulos C, Turley H, Talks K, et al. Hypoxia-inducible factor (HIF1A and HIF2A), angiogenesis, and chemoradiotherapy outcome of squamous cell head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;53:1192-202.

[12] Zhou C, Liu J, Tang Y, Zhu G, Zheng M, Jiang J, et al. Coexpression of hypoxia-inducible factor-2α, TWIST2, and SIP1 may correlate with invasion and metastasis of salivary adenoid cystic carcinoma. J Oral Pathol Med 2012;41:424-31.

[13] Alvi M.A., Ahmad S, Aqib AI, Tayyab MH, Murtaza A, Ashfaq KH, et al. Diagnosing post parturient hemoglobinuria in goat on the basis of hematology, serum biochemistry and treatment response. Mat Sci Med 2018;2:34-6.

[14] Xiang R, Liao D, Cheng T, Zhou H, Shi Q, Chuang TS, et al. Downregulation of transcription factor SOX2 in cancer stem cells suppresses growth and metastasis of lung cancer. Br J Cancer 2011;104:1410-7.

[15] Jia X, Li X, Xu Y, Zhang S, Mou W, Liu Y, et al. SOX2 promotes tumorigenesis and increases the anti-apoptotic property of human prostate cancer cell. J Mol Cell Biol 2011;3:230-8.

[16] Mehvish S, Barkat M.Q. Phytochemical And Antioxidant Screening Of Amomum Subulatum, Elettaria Cardamomum, Emblica Officinalis, Rosa Damascene, Santalum Album And Valeriana Officinalis And Their Effect On Stomach, Liver And Heart. Mat Sci Med (MSM) 2018;2:28-33.

[17] Luo Y, Liu T, Fei W, Yue XG. Correlation between SOX2 and Survivin clinical features in patients with salivary adenoid cystic carcinoma. J Infect Public Health 2019 12:847-53.

[18] Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-7.

[19] Yang Y, Rossi FM, Putnins EE. Periodontal regeneration using engineered bone marrow mesenchymal stromal cells. Biomaterials 2010;31:8574-82.

[20] Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A 2000;97:13625-30.

[21] Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. J Endod 2008;34:166-71.

[22] Lohberger B, Payer M, Rinner B, Kaltenegger H, Wolf E, Schallmoser K, et al. Tri-lineage potential of intraoral tissue-derived mesenchymal stromal cells. J Craniomaxillofac Surg 2013;41: 110-8.

[23] Sumanasinghe RD, Bernacki SH, Loboa EG. Osteogenic differentiation of human mesenchymal stem cells in collagen matrices: effect of uniaxial cyclic tensile strain on bone morphogenetic protein (BMP-2) mRNA expression. Tissue Eng 2006;12:3459-65.

[24] Peters A, Toben D, Lienau J, Schell H, Bail HJ, Matziolis G, et al. Locally applied osteogenic predifferentiated progenitor cells are more effective than undifferentiated mesenchymal stem cells in the treatment of delayed bone healing. Tissue Eng Part A 2009;15:2947-54.

[25] Loboa EG, Fang TD, Warren SM, Lindsey DP, Fong KD, Longaker MT, et al. Mechanobiology of mandibular distraction osteogenesis: experimental analyses with a rat model. Bone 2004;34:336-43.

[26] Smith-Adaline EA, Volkman SK, Ignelzi MA Jr, Slade J, Platte S, Goldstein SA. Mechanical environment alters tissue formation patterns during fracture repair. J Orthop Res 2004;22:1079-85.

[27] Meyer U, Wiesmann HP, Kruse-Lösler B, Handschel J, Stratmann U, Joos U. Strain-related bone remodeling in distraction osteogenesis of the mandible. Plast Reconstr Surg 1999;103:800-7.

[28] Lohberger B, Kaltenegger H, Stuendl N, Payer M, Rinner B, Leithner A. Effect of cyclic mechanical stimulation on the expression of osteogenesis genes in human intraoral mesenchymal stromal and progenitor cells. Biomed Res Int 2014; 2014.

[29] Shi S, Bartold PM, Miura M, Seo BM, Robey PG, Gronthos S. The efficacy of mesenchymal stem cells to regenerate and repair dental structures. Orthod Craniofac Res 2005;8:191-9.

[30] Rodríguez-Lozano FJ, Bueno C, Insausti CL, Meseguer L, Ramírez MC, Blanquer M, et al. Mesenchymal stem cells derived from dental tissues. Int Endod J 2011;44: 800-6.

[31] Ding G, Liu Y, Wang W, Wei F, Liu D, Fan Z, et al. Allogeneic periodontal ligament stem cell therapy for periodontitis in swine. Stem cells 2010;28:1829-38.

[32] Gronthos S, Brahim J, Li W, Fisher LW, Cherman N, Boyde A, et al. Stem cell properties of human dental pulp stem cells. J Dent Res 2002;81:531-5.

[33] Clausen C, Hermund NU, Donatsky O, Nielsen H. Characterization of human bone cells derived from the maxillary alveolar ridge. Clin Oral Implants Res 2006;17:533-40.

[34] Payer M, Lohberger B, Stadelmeyer E, Bartmann C, Windhager R, Jakse N. Behaviour of multipotent maxillary bone-derived cells on β-tricalcium phosphate and highly porous bovine bone mineral. Clin Oral Implants Res 2010;21:699-708.

[35] Pekovits K, Kröpfl JM, Stelzer I, Payer M, Hutter H, Dohr G. Human mesenchymal progenitor cells derived from alveolar bone and human bone marrow stromal cells: a comparative study. Histochem Cell Biol 2013;140:611-21.

[36] Chung RW, Siu AS, Chu FC, Chow TW. Magnet-retained auricular prosthesis with an implant-supported composite bar: a clinical report. J Prosthet Dent 2003;89:446-9.

[37] Leonardi A, Buonaccorsi S, Pellacchia V, Moricca LM, Indrizzi E, Fini G. Maxillofacial prosthetic rehabilitation using extraoral implants. J Craniofac Surg 2008;19:398-405.

[38] Aydin C, Karakoca S, Yilmaz H. Implant-retained digital prostheses with custom-designed attachments: a clinical report. J Prosthet Dent 2007;97:191-5.

[39] Lemon JC, Chambers MS. Locking retentive attachment for an implant-retained auricular prosthesis. J Prosthet Dent 2002;87:336-8.

[40] Chang PP, Hansen NA, Phoenix RD, Schneid TR. The effects of primers and surface bonding characteristics on the adhesion of polyurethane to two commonly used silicone elastomers. J Prosthodont 2009;18:23-31.

[41] Goiato MC, Garcia-Júnior IR, Magro-Filho O, dos Santos DM, Pellizzer EP. Implant-retained thumb prosthesis with anti-rotational attachment for a geriatric patient. Gerodontology 2010;27:243-7.

[42] Bonatto LDR, Goiato MC, da Silva EVF, Oliveira SHP, Haddad MF, Chaves Neto AH, et al. Biocompatibility of primers and an adhesive used for implant-retained maxillofacial prostheses: An in vitro analysis. J Prosthet Dent 2017;117:799-805.

[43] Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012;50:1-12.

[44] Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl 2007;20:1-136.

[45] McGee HS, Yagita H, Shao Z, Agrawal DK. Programmed Death-1 antibody blocks therapeutic effects of T-regulatory cells in cockroach antigen-induced allergic asthma. Am J Respir Cell Mol Biol 2010;43:432-42.

[46] Zhang LP, Lin L, Zheng CQ, Shi GY. T-lymphocyte subpopulations and B7-H1/PD-1 expression in nasal polyposis. J Int Med Res 2010;38:593-601.

[47] Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.

[48] Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2:261-8.

[49] Kortekaas Krohn I, Bobic S, Dooley J, Lan F, Zhang N, Bachert C, et al. Programmed cell death-1 expression correlates with disease severity and IL-5 in chronic rhinosinusitis with nasal polyps. Allergy 2017;72:985-93.

[50] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

[51] Brzak BL, Mravak-Stipetić M, Canjuga I, Baricević M, Balicević D, Sikora M, et al. The frequency and malignant transformation rate of oral lichen planus and leukoplakia--a retrospective study. Coll Antropol 2012;36:773-7.

[52] Scully, C. and S.R. Porter. Referrals in oral medicine. Dent Update 2007;34:340-2, 5-6, 8-50.

[53] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.

[54] Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011;11:9-22.

[55] Reichardt P, Demetri GD, Gelderblom H, Rutkowski P, Im SA, Gupta S, et al. Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. BMC Cancer 2016;16:22.

[56] Pauls K, Merkelbach-Bruse S, Thal D, Büttner R, Wardelmann E. PDGFRalpha- and c-kit-mutated gastrointestinal stromal tumours (GISTs) are characterized by distinctive histological and immunohistochemical features. Histopathology 2005;46:166-75.

[57] Feng H, Hu B, Liu KW, Li Y, Lu X, Cheng T, et al. Activation of Rac1 by Src-dependent phosphorylation of Dock180(Y1811) mediates PDGFRalpha-stimulated glioma tumorigenesis in mice and humans. J Clin Invest 2011;121:4670-84.

[58] Ong HS, Gokavarapu S, Tian Z, Li J, Xu Q, Zhang CP, et al. PDGFRA mRNA overexpression is associated with regional metastasis and reduced survival in oral squamous cell carcinoma. J Oral Pathol Med 2018; 47: 652-9.

[59] Siddiqi A, Payne AGT, De Silva RK, Duncan WJ. Titanium allergy: could it affect dental implant integration? Clin Oral Implants Res 2011;22:673-80.

[60] Pfammatter C, Lindenmüller IH, Lugli A, Filippi A, Kühl S. Metastases and primary tumors around dental implants: A literature review and case report of peri-implant pulmonary metastasis. Quintessence Int 2012;43:563-70.

[61] Lópiz-Morales Y, Abarrategi A, Ramos V, Moreno-Vicente C, López-Durán L, López-Lacomba JL, et al. In vivo comparison of the effects of rhBMP-2 and rhBMP-4 in osteochondral tissue regeneration. Eur Cell Mater 2010;20:367-78.

[62] Thiery JP, Sleeman JP. Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol 2006;7:131-42.

[63] Kim MJ, Kim KM, Kim J, Kim KN. BMP-2 promotes oral squamous carcinoma cell invasion by inducing CCL5 release. PLoS One 2014;9:e108170.

[64] Tarsitano A, Tardio ML, Marchetti C. Impact of perineural invasion as independent prognostic factor for local and regional failure in oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:221-8.

[65] Rapidis AD, Givalos N, Gakiopoulou H, Faratzis G, Stavrianos SD, Vilos GA, et al. Adenoid cystic carcinoma of the head and neck. Clinicopathological analysis of 23 patients and review of the literature. Oral Oncol 2005;41:328-35.

[66] Kurtz KA, Hoffman HT, Zimmerman MB, Robinson RA. Perineural and vascular invasion in oral cavity squamous carcinoma: increased incidence on re-review of slides and by using immunohistochemical enhancement. Arch Pathol Lab Med 2005;129:354-9.

[67] Binmadi NO, Yang YH, Zhou H, Proia P, Lin YL, Batista De Paula AM, et al. Plexin-B1 and semaphorin 4D cooperate to promote perineural invasion in a RhoA/ROK-dependent manner. Am J Pathol 2012;180:1232-42.

[68] Koide N, Yamada T, Shibata R, Mori T, Fukuma M, Yamazaki K, et al. Establishment of perineural invasion models and analysis of gene expression revealed an invariant chain (CD74) as a possible molecule involved in perineural invasion in pancreatic cancer. Clin Cancer Res 2006;12:2419-26.

[69] Solares CA, Brown I, Boyle GM, Parsons PG, Panizza B. Neural cell adhesion molecule expression: no correlation with perineural invasion in cutaneous squamous cell carcinoma of the head and neck. Head Neck 2009;31:802-6.

[70] Dos Reis PP, Bharadwaj RR, Machado J, Macmillan C, Pintilie M, Sukhai MA, et al. Claudin 1 overexpression increases invasion and is associated with aggressive histological features in oral squamous cell carcinoma. Cancer 2008;113:3169-80.

[71] Lourenço SV, Coutinho-Camillo CM, Buim ME, Pereira CM, Carvalho AL, Kowalski LP, et al. Oral squamous cell carcinoma: status of tight junction claudins in the different histopathological patterns and relationship with clinical parameters. A tissue-microarray-based study of 136 cases. J Clin Pathol 2010;63:609-14.

[72] Kolokythas A, Cox DP, Dekker N, Schmidt BL. Nerve growth factor and tyrosine kinase A receptor in oral squamous cell carcinoma: is there an association with perineural invasion? J Oral Maxillofac Surg 2010;68:1290-5.

[73] Mendelsohn AH, Lai CK, Shintaku IP, Fishbein MC, Brugman K, Elashoff DA, et al. Snail as a novel marker for regional metastasis in head and neck squamous cell carcinoma. Am J Otolaryngol 2012;33:6-13.

[74] Chang KP, Kao HK, Liang Y, Cheng MH, Chang YL, Liu SC, et al. Overexpression of activin A in oral squamous cell carcinoma: association with poor prognosis and tumor progression. Ann Surg Oncol 2010;17:1945-56.

[75] Varsha BK, Radhika MB, Makarla S, Kuriakose MA, Kiran GS, Padmalatha GV. Perineural invasion in oral squamous cell carcinoma: Case series and review of literature. J Oral Maxillofac Pathol 2015;19:335-41.

[76] Nielsen J, Christiansen J, Lykke-Andersen J, Johnsen AH, Wewer UM, Nielsen FC. A family of insulin-like growth factor II mRNA-binding proteins represses translation in late development. Mol Cell Biol 1999;19:1262-70.

[77] Damasceno EA, Carneiro FP, Magalhães AV, Carneiro Mde V, Takano GH, Vianna LM, et al. IMP3 expression in gastric cancer: association with clinicopathological features and HER2 status. J Cancer Res Clin Oncol 2014;140:2163-8.

[78] Kumamoto M, Kuratomi Y, Yasumatsu R, Nakashima T, Masuda M, Inokuchi A. Expression of laminin 5 basement membrane components in invading and recurring adenoid cystic carcinoma of the head and neck. Auris Nasus Larynx 2006;33:167-72.

[79] Tai SK, Li WY, Yang MH, Chu PY, Wang YF. Perineural invasion in T1 oral squamous cell carcinoma indicates the need for aggressive elective neck dissection. Am J Surg Pathol 2013;37:1164-72.

[80] Tarsitano A, Asioli S, Morandi L, Monti V, Righi A, Morselli Labate AM, et al. Laminin-5 and insulin-like growth factor-II mRNA binding protein-3 (IMP3) expression in preoperative biopsy specimens from oral cancer patients: Their role in neural spread risk and survival stratification. J Craniomaxillofac Surg 2016;44:1896-902.

[81] Zhong LP, Zhao SF, Chen GF, Ping FY, Xu ZF, Hu JA. Increased levels of CK19 mRNA in oral squamous cell carcinoma tissue detected by relative quantification with real-time polymerase chain reaction. Arch Oral Biol 2006;51:1112-9.

[82] Wu YJ, Rheinwald JG. A new small (40 kd) keratin filament protein made by some cultured human squamous cell carcinomas. Cell 1981;25:627-35.

[83] Whittock NV, Eady RA, McGrath JA. Genomic organization and amplification of the human keratin 15 and keratin 19 genes. Biochem Biophys Res Commun 2000;267:462-5.

[84] Barrett AW, Morgan M, Nwaeze G, Kramer G, Berkovitz BK. The differentiation profile of the epithelium of the human lip. Arch Oral Biol 2005;50:431-8.

[85] Hamakawa H, Bao Y, Takarada M, Fukuzumi M, Tanioka H. Cytokeratin expression in squamous cell carcinoma of the lung and oral cavity: an immunohistochemical study with possible clinical relevance. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:438-43.

[86] Vora HH, Shah NG, Patel DD, Trivedi TI, Chikhlikar PR. Prognostic significance of biomarkers in squamous cell carcinoma of the tongue: multivariate analysis. J Surg Oncol 2003;82:34-50.

[87] Szymaszkiewicz A, Malkiewicz A, Storr M, Fichna J, Zielinska M. The place of tachykinin NK2 receptor antagonists in the treatment diarrhea-predominant irritable bowel syndrome. J Physiol Pharmacol 2019;70.

[88] Zhang Y, Lu L, Furlonger C, Wu GE, Paige CJ. Hemokinin is a hematopoietic-specific tachykinin that regulates B lymphopoiesis. Nat Immunol 2000;1:392-7.

[89] Page NM, Woods RJ, Gardiner SM, Lomthaisong K, Gladwell RT, Butlin DJ, et al. Excessive placental secretion of neurokinin B during the third trimester causes pre-eclampsia. Nature 2000;405:797-800.

[90] Goto T, Yamaza T, Kido MA, Tanaka T. Light- and electron-microscopic study of the distribution of axons containing substance P and the localization of neurokinin-1 receptor in bone. Cell Tissue Res 1998;293:87-93.

[91] Fukuda A, Goto T, Kuroishi KN, Gunjigake KK, Kataoka S, Kobayashi S, et al. Hemokinin-1 competitively inhibits substance P-induced stimulation of osteoclast formation and function. Neuropeptides 2013;47:251-9.

[92] Seppala M, Fraser GJ, Birjandi AA, Xavier GM, Cobourne MT. Sonic Hedgehog Signaling and Development of the Dentition. J Dev Biol 2017;5.

[93] Hooper JE, Scott MP. Communicating with Hedgehogs. Nat Rev Mol Cell Biol 2005;6:306-17.

[94] van den Heuvel M, Ingham PW. smoothened encodes a receptor-like serpentine protein required for hedgehog signalling. Nature 1996;382:547-51.

[95] Zhao Y, Tong C, Jiang J. Hedgehog regulates smoothened activity by inducing a conformational switch. Nature 2007;450:252-8.

[96] Hardcastle Z, Mo R, Hui CC, Sharpe PT. The Shh signalling pathway in tooth development: defects in Gli2 and Gli3 mutants. Development 1998;125:2803-11.

[97] Du J, Fan Z, Ma X, Wu Y, Liu S, Gao Y, et al. Expression of smoothened in mouse embryonic maxillofacial development. Biotech Histochem 2012;87:187-94.

[98] Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest 2012;141:1601-10.

[99] Kuma Y, Usumi-Fujita R, Hosomichi J, Oishi S, Maeda H, Nagai H, et al. Impairment of nasal airway under intermittent hypoxia during growth period in rats. Arch Oral Biol 2014;59:1139-45.

[100] Maes C, Carmeliet G, Schipani E. Schipani. Hypoxia-driven pathways in bone development, regeneration and disease. Nat Rev Rheumatol 2012;8:358-66.

[101] Daskalow K, Rohwer N, Raskopf E, Dupuy E, Kühl A, Loddenkemper C, et al. Role of hypoxia-inducible factor-1alpha in angiogenic-osteogenic coupling. J Mol Med (Berl) 2009;87: 583-90.

[102] Schipani E, Maes C, Carmeliet G, Semenza GL. Regulation of osteogenesis-angiogenesis coupling by HIFs and VEGF. J Bone Miner Res 2009;24:1347-53.

[103] Kaku M, Yamauchi M. Mechano-regulation of collagen biosynthesis in periodontal ligament. J Prosthodont Res 2014;58:193-207.

[104] Selvig KA, Sorensen RG, Wozney JM, Wikesjö UM. Bone repair following recombinant human bone morphogenetic protein-2 stimulated periodontal regeneration. J Periodontol 2002;73:1020-9.

[105] Li H, Bartold PM, Young WG, Xiao Y, Waters MJ. Growth hormone induces bone morphogenetic proteins and bone-related proteins in the developing rat periodontium. J Bone Miner Res 2001;16:1068-76.

[106] Mine K, Kanno Z, Muramoto T, Soma K. Occlusal forces promote periodontal healing of transplanted teeth and prevent dentoalveolar ankylosis: an experimental study in rats. Angle Orthod 2005;75:637-44.

[107] Oishi S, Shimizu Y, Hosomichi J, Kuma Y, Maeda H, Nagai H, et al. Intermittent Hypoxia Influences Alveolar Bone Proper Microstructure via Hypoxia-Inducible Factor and VEGF Expression in Periodontal Ligaments of Growing Rats. Front Physiol 2016;7:416.

[108] Tsuruga E, Takita H, Itoh H, Wakisaka Y, Kuboki Y. Pore size of porous hydroxyapatite as the cell-substratum controls BMP-induced osteogenesis. J Biochem 1997;121:317-24.

[109] Finkemeier, C.G. Bone-grafting and bone-graft substitutes. J Bone Joint Surg Am 2002;84:454-64.

[110] El-Ghannam, A.R. Advanced bioceramic composite for bone tissue engineering: design principles and structure-bioactivity relationship. J Biomed Mater Res A 2004;69:490-501.

[111] Gupta G, El-Ghannam A, Kirakodu S, Khraisheh M, Zbib H. Enhancement of osteoblast gene expression by mechanically compatible porous Si-rich nanocomposite. J Biomed Mater Res B Appl Biomater 2007;81:387-96.

[112] Pino DS, Casarin RC, Pimentel SP, Cirano FR, Corrêa MG, Ribeiro FV. Effect of resveratrol on critical-sized calvarial defects of diabetic rats: histometric and gene expression analysis. J Oral Maxillofac Surg 2017;75:2561. e1-. e10.
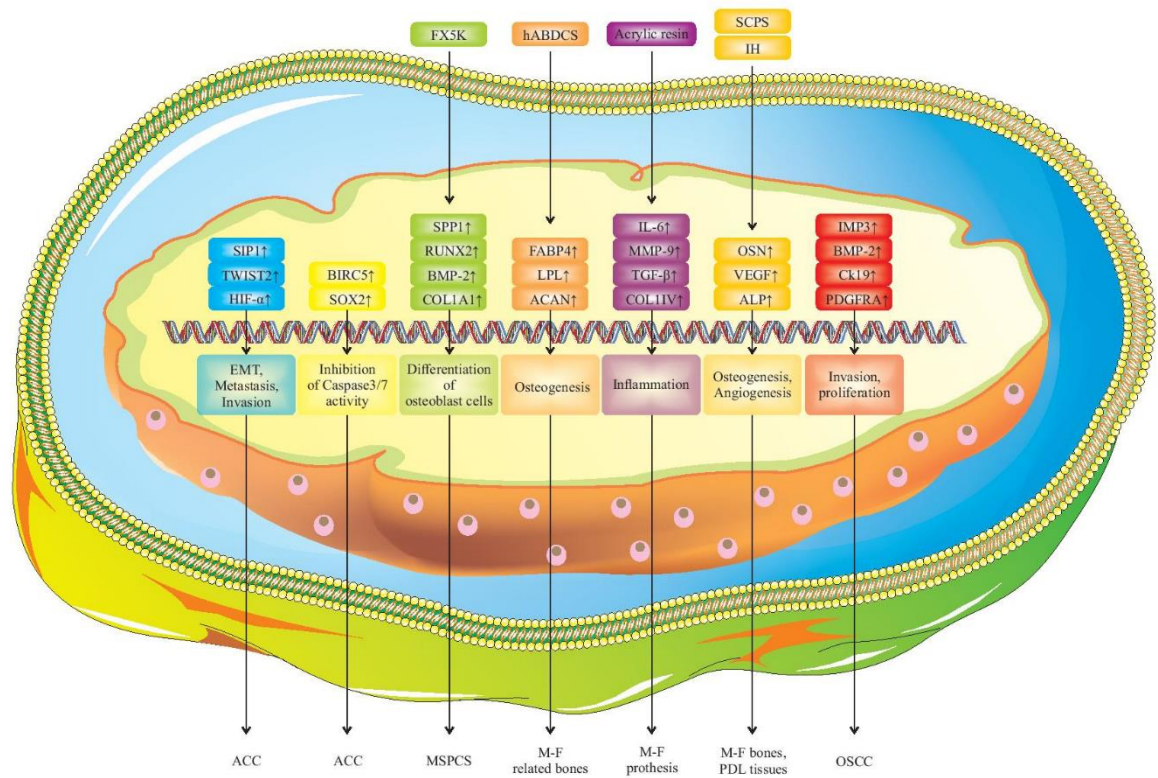
[113] Casarin RC, Casati MZ, Pimentel SP, Cirano FR, Algayer M, Pires PR, et al. Resveratrol improves bone repair by modulation of bone morphogenetic proteins and osteopontin gene expression in rats. Int J Oral Maxillofac Surg 2014;43:900-6.

[114] Murgia D, Mauceri R, Campisi G, De Caro V. Advance on resveratrol application in bone regeneration: progress and perspectives for use in oral and maxillofacial surgery. Biomolecules 2019;9:94.

Figure Legend 1:

Upregulation of SIP1 (Smad interacting protein 1) , TWIST2 (Twist Family BHLH Transcription Factor 2), HIF-α (Hypoxia-inducible factors-alpha), BIRC5 (baculoviral inhibitor of apoptosis repeat-containing 5), SOX2 (SRY-related HMG-box) in ACC (Adenoid Cystic Carcinoma)cells, can affect and increase the EMT, metastasis and invasion and inhibi Caspase 3/7 activity, FX5K (flexcell) induces differentiation of osteoblast cells in MSPCs (Mesenchymal stromal, progenitor cells) by upregulation of some related genes, hABDCs (human alveolar bone-derived cells) via increased expression of FABP4 (Fatty Acid Binding Protein 4), LPL1 (Lipoprotein lipase 1), ACAN (Aggrecan), elevated osteogenesis in M-F related bones, Acrylic resin in M-F prosthesis upregulated some genes and subsequently inflammation, OSN, VEGF (vascular endothelial growth factor) and ALP (Alkaline phosphatase) is expressed by SCPS (Silica-calcium phosphate nanocomposite) and IH (Intermittent hypoxia) and then increased osteogenesis in M-F bones, dysregulation of IMP3, BMP-2, Ck19 and PDGFRA cause invasion and proliferation of OSCC (Oral squamous cell carcinoma).

Table 1. Variations in mRNAs related to maxillofacial defects or tissues

Direction of changes	mRNAs name	effect	Disease or target	Ref.
upregulation	SIP1, TWIST2	Increase EMT	ACC	[12].
upregulation	HIF-1α	Increase metastasis and invasion	ACC	[12].
upregulation	BIRC5	Inhibits the activity of caspase-3 and Caspase-7	ACC	[17].
upregulation	SOX2	Anti-apoptotic of cancer cells	ACC	[17].
upregulation	RUNX2, Col1A1, BMP-2, SPP1	Induced by FX5K, - osteoblast cells differentiation	Human intraoral MSPCs	[28]

upregulation	FABP4, LPL, ACAN	Induced by hABDCs, increase adipocyte and osteogenic	-	[35].
Not a significant difference	SPARC	Induced by hABDCs, increase- adipocyte and osteogenic	-	[35].
upregulation	IL-6	Induced by acrylic resin and increase the inflammatory process	M-F prosthesis group	[42]
Not a significant difference	MMP-9, Col1 IV, TGF-β	Induced by acrylic resin	M-F prosthesis group	[42]
upregulation	PDGFRA, BMP-2, IMP3, Laminin-5	Increase- invasive, motility, spreading of tumor cell	OSCC	[58, 63, 80]
upregulation	CK19	Increases invasive of carcinoma tissue in all mucosal layer	OSCC	[81]
upregulation	Smo	Differentiation and proliferation in the normal development of M-f	Mouse M-F development	[97]
upregulation	HIF-α, VEGF, ALP, BMP-2	Induced by IH, increase- osteogenesis and angiogenesis	PDL tissue	[107]
upregulation	Col-I, OSN, osteocalcin	Induced by SCPC, increase osteoblast in M-F bones	M-F bones	[111]

EMT: Epithelial – to – Mesenchymal Transition, SIP1: Smad interacting protein 1, TWIST2: Twist family BHLH transcription factor2, ACC: adenoid cystic carcinoma, HIF-1α: Hypoxia-inducible factors-alpha, BIRC5: baculoviral inhibitor of apoptosis repeat-containing 5, RUNX2: runtrelated transcription factor 2, Col1A1: type I collagen, BMP-2: bone morphogenetic protein 2, SPP1: osteopontin, MSPCs: mesenchymal stromal and progenitor cells, FABP4: fatty acid binding protein4, LPL: lipoprotein lipase, ACAN: aggrecan, hABDCs: human alveolar bone-derived cells, SPARC: secreted protein acidic cysteine-rich osteonectin, IL-6: interleukin 6, M-F: maxillofacial, MMP-9: matrix metalloproteinase-9, CK19: cytokeratin 19, OSCC: Oral squamous cell carcinoma, VEGF: Vascular endothelial growth factor, ALP: alkaline phosphatase, OSN: osteonectin, SCPC: Silica-calcium phosphate nanocomposite