



INVITED REVIEW

The dentomaxillary apparatus from molecular biology to variational anatomy—Underpinning interdisciplinary research

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ABSTRACT

Over the past decades, the research environment in anatomy has dramatically changed. Studies have become more interdisciplinary and complex, with many components required, from basic to clinical research. Within this framework, this special issue was designed to create a link between fundamental fields such as developmental and molecular biology, dental materials, anatomy, histology, and their applications in the clinical research of the dentomaxillary apparatus.

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1. Teeth and support structures

Our selected content about teeth and support structures spans research of many different aspects including those related to the success and long-term maintenance in endodontics. Indeed, the evaluation of the displacement resulting from the relocation of root canal orifices during the initial phase of rotary root canal treatment using the dental operating microscope revealed substantial reductions in crown fracture resistance (Rusu et al., 2018). On the other hand, to harness the importance of preserving teeth as long as possible, we have also included a clinical case report of a maxillary central incisor which emphasises the successful result of an apexification with calcium hydroxide monitored for 20 years (Fonzar et al., 2018). The most important finding of this study was the complete development of the root analyzed macroscopically, histologically,

and through scanning electron microscopy. Nowadays, the increasing complexity and diversity of the advances in endodontics have been the most striking developments in dentistry. The root canal morphology and pattern of different tooth categories has been extensively studied. Among them, maxillary third molars which might show high variability. A Polish study investigated the root canal morphology of these teeth using micro-computed tomography (Tomaszewska et al., 2018). The results showed that a typical maxillary third molar tooth has one or three roots, 1–4 root canals, as well as buccal/palatal root curvature. Lack of apical constriction and frequent deviation of the apical foramen from the radiographic apex should be considered before performing endodontic procedures on these teeth.

From endodontics and root canal variations, we go further into the field of dental mineralised and soft tissue research. The ever inconclusive evidence about the effects of bleaching agents on human enamel and dentin microstructure has increased the number of publications evaluating morphological and mineral changes

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after tooth whitening. Thus, in this special issue, we have included a remarkable *in vitro* study on human teeth using confocal laser scanning microscopy, comparing the application of 37.5% hydrogen peroxide and 35% carbamide peroxide, both with neutral pH (Llena et al., 2018). Interestingly, similar morphological changes were observed with both products. So, histological changes occurred and the amount of calcium and phosphate was reduced although without significant differences compared to the corresponding controls. Apart from the bleaching affairs, we also selected work in which differences between crystalline nanostructures from the enamel and dentin of human, bovine, porcine, and ovine species were assessed (Ortiz-Ruiz et al., 2018). Samples were analyzed using X-ray diffraction, Fourier Transform Infrared Spectroscopy, and Differential Scanning Calorimetry. Differences in the organic and inorganic content of human, bovine, porcine, and ovine enamels and dentins were found. Future studies should take these results into account when using animal substrates as substitutes for human material.

Periostin, a matricellular protein present in the human periodontal ligament and human dental pulp-derived cells lines, up-regulates *in vitro* the expression of some genes involved in dentin mineralisation. Its distribution has been mapped in adult tooth tissues by means of immunohistochemistry (Menéndez-Díaz et al., 2018). The study has demonstrated the localization of periostin in the extracellular matrix of the periodontal ligament and the subodontoblastic zone of the dental pulp in adult human teeth. Although periostin regulates the expression of DMP-1 and P2rx7, involved in dentin mineralisation, these were not colocalized with periostin, except in the mineralization zone of the periodontal ligament. The results might be a good starting point for future studies on pathological conditions.

There are still unanswered questions in relation to the functions of odontoblasts, the peripheral dental pulp cells responsible for dentin formation. Accumulating data strongly suggest that they can also function as sensory cells that mediate the early steps of mechanical, thermic, and chemical dental sensitivity. This issue is addressed by a comprehensive review (Solé-Magdalena et al., 2018). The molecular basis is mainly represented by the expression of different families of ion channels involved in various modalities of sensitivity, and the release of putative neurotransmitters in response to odontoblast stimulation which are able to act on pulp sensory nerve fibres. The paper updates the current knowledge on the expression of the transient-potential receptor ion channels and acid-sensing ion channels in odontoblasts, trigeminal sensory neurons, and pulp cells. Odontoblasts' innervation and their relationship with the nerve fibres is also revisited. Novel therapeutic approaches to dentin sensitivity and dental pain may target the activity of different ion channels, leading to the disruption of signal transduction.

Human gingival cells are now highlighted. Gingival overgrowth (GO) is a recognized side-effect after the use of Cyclosporine-A (CsA) as an immunosuppressant. Current treatment options for drug-induced GO include non-surgical interventions, surgical interventions, or a combination of both. An *in vitro* study questioned whether UV photo-treatment can activate apoptosis in drug-induced GO, thereby potentially reversing the adverse effects seen in the condition (Ritchhart and Joy, 2018). Using TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labelling) and cell proliferation assays, the authors showed that UV treatment was effective in initiating controlled cell death in CsA-treated human gingival fibroblast cells *via* apoptosis, as compared to both positive control and negative control groups. These findings are encouraging further evaluations of UV mediated apoptosis as a mechanism to control certain forms of GO. Optical coherence tomography (OCT) as a tool for assessment of periodontal inflammation in the gingival tissues has been tested by Şurlin et al. (2018). This *in vitro* study

tested gingival samples collected from different groups of patients and concluded that OCT could be used by clinicians as a functional tool for the assessment of the inflammatory gingival status during disease evolution, and also for treatment efficiency evaluation. In addition, the authors demonstrated that chronic hepatitis C could be regarded as periodontal disease comorbidity in terms of OCT-identified tissue changes.

However, the gingival tissue may not be regarded only as a potential source of samples used for diagnosis and treatment approaches to different forms of periodontal disease. The ability of normal gingival stem cells to self-renew to differentiate into various tissue, together with their easy accessibility and abundance, renders them a promising alternative source of mesenchymal stem cells (MSCs) for regenerative medicine. Indeed, in the study by Soancă et al. (2018), the authors isolated MSCs from inflamed and normal gingiva to fully characterise them and observe their behaviour in relation to commercial resin composite materials and one experimental material. After demonstrating that both cell lines were relatively similar in terms of the expression pattern of surface markers, gene expression, multipotent differentiation capacity, and interaction with biomaterials, the authors concluded that inflamed gingiva-derived MSCs retained their stem cell properties and could be used as a valuable cell line for testing dental biomaterials.

2. Cranial structures and masticatory muscles

The dentomaxillary apparatus is a functional system composed of several structures, such as bones, teeth, and soft tissues, orchestrated by the temporomandibular joint and masticatory muscles. These assemblies act in coordination to perform various functional assignments. Nowadays, functional restoration of the numerous components of the dentomaxillary apparatus is a major focus of research from different perspectives.

In an effort to know how the temporomandibular joint movement parameters impact dental morphology, Oancea et al. (2018) examined the influence of three important articular parameters on dental morphology and crown volume in prosthodontic restorations. The study was performed on maxillary models prepared for single zirconia crowns, simulating different situations and analyzing the influence of one specific articular parameter variation on dental morphology, while keeping the other two parameters constant. The sagittal condylar inclination mostly influenced the dynamic tooth morphology; canine and molar morphology were strongly influenced by the Bennett angle and immediate side shift. The determinants of mandibular movements should therefore be accurately measured and transferred to the articulator in the process of crown design.

The skeletal characteristics of each individual may also affect the normal functioning of the dentomaxillary apparatus, and the question of whether the styloid process is altered in patients with temporomandibular disorders was addressed using panoramic radiographs taken in closed/opened mouth positions, associated with clinical examinations (Krohn et al., 2018). A high prevalence of elongated styloid processes was detected in patients with temporomandibular disorders. The authors concluded that elongated styloid processes and temporomandibular disorders coexist due to muscular disturbances associated with both conditions. In addition, the accuracy of some obtained X-ray measurements was confirmed by cone beam computed tomography (CBCT). CBCT investigation may also be useful to identify anatomical variations of the dentomaxillary apparatus. Such was the case of a lingular type of mylohyoid bridge associated with the presence of a retromolar canal on the same side (Rusu et al., 2017). For this particular case, practical clinical implications, such as anaesthesia, additional spreading routes for infections and tumors, are discussed. Likewise,

other modern forms of 3D-visualisation of the maxillary sinus have allowed the determination of the sinus shape and sinus floor morphology related to age in human cadavers with different dental status (Lovasova et al., 2018). The detailed information provided by this paper encourages a 3D investigation of the maxillary sinus whenever possible, in order to increase safety during dental treatment and surgical procedures in the orofacial region.

The hypothesis of a relationship between the gonial angle values and the gender and age of young Caucasian Mediterranean subjects was tested by means of a prospective study using panoramic radiographs (Larrazabal-Moron and Sanchis-Gimeno, 2018). According to their findings, the values of gonial angles vary depending on gender in different age categories. A significant negative correlation was found between age and gonial angle values. Knowledge of these pattern differences may serve for age and gender determination in anthropology.

Within the frame of mandibular pathology, two different therapeutic approaches for treating mandibular condylar fractures were reviewed and compared in terms of intra- and postoperative complications: conservative (CTR) and surgical treatment (ORIF, Open Reduction and Internal Fixation) (García-Guerrero et al., 2018). CTR was found to be associated with complications deriving from delayed mobilisation leading to functional limitations, whereas the main complication associated with ORIF treatment was facial nerve damage. Clinical recommendations are made towards ORIF in condylar displacements, while CTR associated with rehabilitation therapies seems to be the treatment of choice for intra-capsular fractures in patients under 12 years of age.

Alterations of craniofacial structures were investigated by means of macroscopic and histological assessments, in an experimental study on mouse fetuses from dams fed a folic acid (FA) deficient diet (Maldonado et al., 2018). Pharyngeal arches-derived structures were affected, and the main malformations observed corroborate the vulnerability of cranial neural crest cells to FA deficiency. The results could signal new advances in the elucidation of the influence of folate and FA on craniofacial development.

Expression patterns of the mRNA transcripts of the myosin heavy chain (MyHC) isoforms in different parts of the temporal muscle were analyzed in *Pan troglodytes* primates (Ciurana et al., 2017). Significant differences were found in the expression patterns of the MyHC-IIIM isoform in the sphenomandibular portion when compared with the anterior superficial temporalis, and anterior deep temporalis, respectively. The differential expression patterns may be related to the functional differences that have been observed in electromyographic studies in other species of primates. The masseter muscle was the preferred topic of another paper hypothesising that a molecular response involving changes in expression of muscle atrophy and bone resorption markers precedes detectable changes in the muscle and subchondral bone of the mandibular head in adult mice after masseter muscle paralysis induced by a single injection of botulinum toxin type A (BoNTA) (Balanta-Melo et al., 2018). Changes in mRNA levels of molecular markers were addressed by qPCR. The findings showed that masseter muscle atrophy and subchondral bone loss were preceded by molecular responses occurring during the first week after BoNTA intervention.

3. Biomolecules in oral diseases

Biomolecules are currently tested and used not only for disease diagnostics, but also for treatment. The diagnostic potential of salivary markers with relevance for systemic lupus erythematosus (SLE) associated inflammation has been explored (Stanescu et al., 2018). The results suggest that salivary IL-6 determination can be a reliable alternative to serum levels of IL-6; saliva can rep-

resent a potential diagnostic fluid when monitoring SLE-related inflammation. Local application of autologous growth factor and proteins for oral lichen planus (OLP) treatment have been tested in patients with refractory erosive OLP (Piñas et al., 2018). Plasma rich in growth factors proved to be effective in the management of such kind of lesions refractory to corticosteroid therapy. These promising results may boost further research studies focused on using biomolecules in OLP treatment.

4. Concluding remarks

The research questions addressed in this special issue are relevant to different research areas, from molecular biology to clinical practice in dental medicine. All types of studies, from *in vitro* to clinical, were performed involving collaborations between researchers from various fields, such as anatomy, embryology, biochemistry, radiology, periodontology, and oral and maxillofacial surgery. Researchers from Spain, Romania, Germany, Chile, the United States of America, Italy, Poland, Slovak Republic, Czech Republic, United Kingdom, Ireland, Japan, Brazil and Colombia have contributed with valuable work to this special issue. Our hope is that all papers published in this issue will have a widespread impact, raising the interest in oral and craniofacial research and opening new research questions for further investigations.

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