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The use of omics profiling to improve outcomes of bone regeneration and osseointegration. How far are we from personalized medicine in dentistry?

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ABSTRACT

Increased life expectancy and broader restorative dental treatment alternatives for missing teeth have resulted in an increasing request of bone regeneration/augmentation procedures not only in healthy patients, but also in elderly and medically compromised ones. This is also combined with a growing demand for short implant loading protocols and for optimal aesthetic results. In order to meet these new dental needs, personalized treatment strategies tailored on each individual's characteristics and healing profile are warranted.

Omics technologies are emerging as powerful tools to uncover molecules and signalling pathways involved in bone formation and osseointegration and to investigate differences in the molecular mechanisms between health and systemic diseases that could be targeted by future therapies.

This review critically appraises the available knowledge on the application of omics technologies in the field of bone regeneration and osseointegration and explores their potential use for personalized medicine in the dento-maxillo-facial field.

Significance: The use of omics in personalising dental maxillo-facial treatments emerges as a desirable diagnostic and treatment strategy. Omics represent, in fact, powerful tools not only to shade light on the cascade of events taking place during bone formation/osseointegration, but also to identify specific signalling pathways and molecules that can be targeted by future therapies with the aim to enhance clinical outcomes in patients with compromised healing conditions.

1. Introduction

One of the most challenging goals in the field of oral reconstruction is the rehabilitation of partial and total edentulism in a functional and aesthetic way. Irrespective if the oral reconstruction is due to a trauma, ablative tumour resection, infection, or to a genetic/congenital deformity, the success of the treatment is based on the predictable and long-lasting regeneration of the lost/damaged tissue.

The oral cavity presents unique characteristics compared to other anatomical sites, as it is an open system connecting the body with the environment and it hosts the most varied and vast flora [1].

During the last half century, dental implants have completely revolutionised our approach to dental rehabilitations. After the pioneering works of Branemark in the late fifties, the concept of osseointegration has emerged, which can be described as the “direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant” ensuring a long-term clinical stability of the implants [2–4]. At histological level, it resembles a functional ankylosis, with no intervention of fibrous or connective tissue between the bone and the implant surface [5]. Several patient-related factors seem to influence both the bone formation/regeneration process and the osseointegration of dental implants in the jawbones, such as smoking, poor level of oral hygiene, infective processes, systemic diseases (e.g. osteoporosis, diabetes mellitus) and medications affecting bone metabolism [6–11].

It has been extensively demonstrated that surface properties of dental implants (mainly topography, porosity, wettability, surface charge and chemistry) directly influence the binding capacity of fibrin and the adhesion, proliferation and differentiation of cells, thus affecting the process of osseointegration [12,13]. In addition, the use of bone substitutes and barriers is able to guide and influence the bone formation process [14].

Advances in molecular biology are progressively improving our understanding of complex biological processes such as bone formation and osseointegration. A research conducted in Medline via Ovid using the Mesh terms “Bone and Bones”, “Bone regeneration”, “Biomedical

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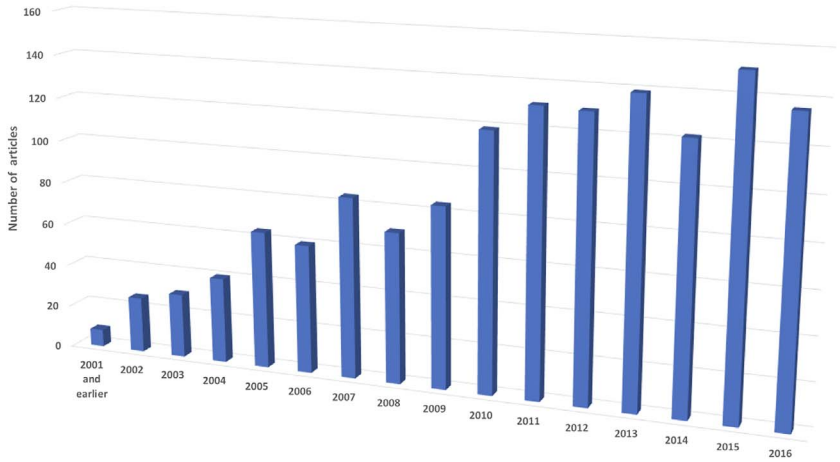

Fig. 1. Number of articles found in PubMed when the Mesh terms "Bone and Bones", "Bone regeneration", "Biomedical and Dental Materials" were combined with the term "Computational Biology" in Medline via Ovid. The search returned 1431 results. Until end of September 2017, 37 additional papers were found.

and Dental Materials" combined with the term "Computational Biology" showed how the number of articles in this this field has progressively increased, with more than a hundred papers published every year during the past 7 years (Fig. 1).

This literary review aims to summarize and critically appraise the available evidence on the application of omics technologies (namely transcriptomics and proteomics) in the field of bone regeneration and osseointegration and at the same time to explore the potential of omics profiling to personalise the treatment of patients undergoing dental implant and bone regeneration treatments. In order to identify suitable articles for this review, both Medline via Ovid and Embase databases were searched with a combination of MeSH (or Emtree) terms and free text. Moreover, the bibliography of review papers identified as part of the process was screened to search for additional articles.

2. Omics characterization of bone tissue

The main omics platforms that have been applied to study bone tissue are transcriptomics, proteomics and epigenomics [15]. Metabolomics is still an almost unexplored technique for bone tissue samples, but it has been extensively applied on salivary, urinary and serum samples to discover potential markers for osteoporosis, osteoarthritis, ankylosing spondylitis, bone tumours and other pathological conditions [16–18].

Several pre-clinical studies investigated, either with reverse transcription (RT) polymerase chain reaction (PCR) or with microarray platforms, the genes expressed by bones of different anatomic locations [19], that underwent different loading protocols [20] and of healthy and medically compromised animals [21–23]. Conversely, owing to the technical challenges related to protein extraction from bone samples, only few proteomic investigations are available. Mass spectrometry was applied to characterize the proteome of rat bone metaphysis and diaphysis and to study the proteins involved in normal compared to fatigue loading [24,25]. Furthermore, the proteomes of bone samples of healthy and ovariectomized rodents were investigated with two-dimensional electrophoresis (2-DE) and mass spectrometry (MS) to identify proteins and signalling pathways influenced by oestrogen deficiency [26,27].

Since bone samples can be easily obtained from orthopaedic surgeries, a few clinical studies were also able to apply omics technologies to characterize human bone samples. In particular, microarray analyses were performed on bone samples collected at the iliac crest and lumbar spinal lamina during spinal decompression laminectomies or spinal fusions [28,29]. The marked differences in mechanical and functional load associated with these bones reflected in differences in gene expression. Transcriptome analyses suggested, in fact, an increased osteocyte (upregulation of *SOST*, *DMP1*, *MEPE*) and osteoblast-osteoclast activity (upregulation of *COL1A*, *SPARC*, *CTSK*, *ACP5*) in the spine, and that *ZIC1*, *GLI1*, and *GLI3* might act as a link between mechanosensing and Wnt signalling. Differences in gene expression between healthy, osteoarthritic and/or osteoporotic patients have also been investigated by several studies with microarray and RT quantitative PCR [30,31].

Only limited clinical studies have applied proteomics to human bone samples. Alves et al. [32] published a library of proteins expressed in 4 samples of healthy trabecular bone fragments obtained from patients undergoing hip replacement surgery, which were identified by combining gel electrophoresis with nano-liquid chromatography-tandem mass spectrometry (LC-MS/MS). Beside collagenous proteins, 1051 non-collagenous protein were detected, which were mainly involved in mineral metabolism, such as transporters or Ca-dependent phosholipid binding proteins, nucleosomes, histones and proteins with antioxidant activity.

When comparing the proteins expressed in the femur head and neck of patients with osteoarthritis, Chaput et al. [33] found that carbonic anhydrase I and phosphoglycerate kinase 1 were increased in the presence of osteopenia, while apolipotrotein A-1 was reduced.

The proteins associated with dental cementum and alveolar bone were also characterized by LC-MS/MS with the aim of identifying putative unique markers in each tissue [34]. Remarkably, COL14A1 was strictly associated with alveolar bone, while SERFINF1 and SOD3 were markers of dental cementum.

The improvement in protein extraction protocols for bone samples and the introduction of more advanced techniques, such as multiple reaction monitoring, isotope labelling and targeted proteomics will likely lead in the future to an increased number of studies applying proteomics to bone samples, both for the characterization of this complex tissue, but also as a strategic tool to shade light on the pathogenesis of bone related diseases. Standardised protocols for protein extraction that minimise thermal protein degradation and allow to obtain reproducible results also in high-density cortical bones have been recently published [34,35].

3. The regulation of bone regeneration

Although bone has an intrinsic regenerative ability, this can be overcome by the amount of bone loss or by the presence of concomitant diseases impairing bone metabolism. Appropriate treatment of dento-maxillo-facial defects therefore requires a profound understanding of the molecular mechanisms regulating bone formation and bone metabolism in order to facilitate their manipulation, when needed.

Omics technologies have been applied to different pre-clinical