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The Current Knowledge of Genetic Susceptibility Influencing Dental Implant Outcomes

Fabiano Alvim-Pereira¹, Claudia Cristina Alvim-Pereira²
and Paula Cristina Trevilatto³

¹*Federal University of Sergipe (UFS), Lagarto-SE,*

²*Federal University of Pernambuco (UFPE), Recife-PE,*

³*Pontifical Catholic University of Paraná (PUCPR), Curitiba-PR,
Brazil*

1. Introduction

Oral diseases are still a major global health burden, in spite of big efforts in research and dental services, where disbursement on treatment may exceed that for other diseases, including major illnesses such as cancer, heart disease, stroke, and dementia (Williams, 2011). In this context, tooth loss is a topic of public health concern, since it is the final result of the first and second most prevalent diseases in dentistry: caries and periodontitis (Pihlstrom et al., 2005; Pitts et al., 2011). Although the prevalence of edentulism has decreased over the last decades, there will be a relevant proportion of edentulous individuals worldwide (Polzer et al., 2010a).

Tooth loss is a problem complex to be solved all over the world which affects children, adults and elderly. Complete edentulism prior 65 years old was associated with all-cause mortality, an evidence supporting the notion that poor oral health is an important public health issue across the lifespan (Brown, 2009). Although edentulism is not a life threatening condition, tooth loss impairs several orofacial structures, such as bony tissues, nerves, receptors and muscles. Consequently, most orofacial functions are diminished in edentate subjects (Polzer et al., 2010a). Regarding partially edentulous people, tooth loss is found in 5-20% of most adult populations all over the world (Petersen et al., 2005). Quality life levels were reported to be direct related to the number of remaining teeth (Polzer et al., 2010a). Thus, edentulism was found to be a global problem, with estimates for an increasing demand for oral rehabilitation in the future (Felton, 2009). In this context, oral health restoration should aim to restore function and esthetics. Dentistry has the challenge of improving the access and quality of oral rehabilitation (Tilman, 1985), although oral health care is still being conducted without a solid research evidence base (Pang et al., 2011).

2. Oral rehabilitation

A wide variety of treatments is available to replace tooth loss. Osseointegrated dental implant is the gold standard treatment modality to replace missing teeth in terms of

function and aesthetics (Davarpanah et al., 2002; Fugazzotto, 2005). It is estimated that over 10 million implants are installed all over the world annually (Hospitalar, 2007).

The term osseointegration was coined by Branemark to define a structural and functional contact between titanium surface and bone (Albrektsson et al., 1981; Branemark et al., 1969). Since 1982 in the Toronto Conference in Clinical Dentistry, when the guidelines for Implantology were proposed, they remain mainly unaltered. The main protocol change was regarding different times for loading (immediate and early load), which seem to be positive if patients present high degree of primary implant stability (high value of insertion torque) (Esposito et al., 2009). Other treatment differences regarding modification of implant macro and microstructure have limited evidence of clinical improvement supported by longitudinal studies (Esposito et al., 2007).

Dental implants are considered a very predictable rehabilitation procedure in dentistry, with a success rate above 90% showed in longitudinal studies (Adell et al., 1990). In spite of the high success rate, the absolute number of dental implant failure becomes significant and causes economic and social impact for patients and dental professionals. Dental implant failure has been extensively studied during the last years (Esposito et al., 1998a; b). The comprehension of the implant failure process may provide novel insights into the mechanisms underlying osseointegration (Mengatto et al., 2011).

3. The challenges of implantology

Dental implant failure could include surgical complications, patient aesthetic concerning or implant functional disability. A significant reduction in the bone-implant contact may jeopardize the osseointegration process and lead to implant loss. Implant loss is considered a complex, multifactorial trait, investigated by several clinical follow-up and retrospective studies (Esposito et al., 2004; Fugazzotto, 2005; Graziani et al., 2004).

The process is divided into early and late events: early failure occurs before implant load, and late failure takes place after the implant has received occlusal load (Esposito et al., 1999). Early failures have been related to smoking (Ganeles and Wismeijer, 2004), aging (Moy et al., 2005), systemic diseases (Quirynen and Teughels, 2003; Weyant and Burt, 1993), bone quantity and quality (Degidi and Piattelli, 2005; Rosenberg et al., 2004; Stanford, 2003), surgical trauma (Gruica et al., 2004), and contamination during surgical procedure (Kuttenberger et al., 2005; van Steenberghe et al., 1990). Late failures have been related to peri-implantitis (Rosenberg et al., 2004), and occlusal overload (Misch et al., 2004).

Although many studies have provided an important contribution to the understanding of the implant failure process, in some situations, clinical factors alone do not explain why some present implant loss (Deas et al., 2002; Montes et al., 2007). The goal that should be achieved by modern implantology research is developing tools able to predict the patient biological response to treatment before implant surgery intervention.

4. Physiopathology of dental implant loss

Inflammation surrounding implant placement area is a crucial physiopathological process that permits the elimination of local tissue damage and substitution for a viable tissue; process termed regeneration. An augmentation of this inflammatory process is directly related to the quantity of tissue that may be substituted (Thomas and Puleo, 2011).

A complete stabilization between implant pins and surrounding bone is required to achieve a successful implant osseointegration. Primary stability is a mechanical feature achieved during surgical implant placement, which helps stabilization at early phases, leading to a desirable outcome (Szmukler-Moncler et al., 1998). When the process is developing in the post-surgery timeline, implant stability in relation to surrounding bone tends to decline, with the lowest implant stability quotient values being reached at 3 weeks (Han et al., 2010). After the bone regeneration process, stability reaches the maximum value when the osseointegration is achieved.

The two of the main factors for achieving predictable success of osseointegrated oral implants are lack of stability and micromovements (Albrektsson et al., 1981; Turkyilmaz et al., 2009). An abnormal exacerbated inflammatory process may lead to an abnormal decline in implant stability. Micromovements of implants in this crucial phase may result in the formation of a conjunctive tissue between implant and surrounding bone, process known as implant encapsulation (Lioubavina-Hack et al., 2006). Encapsulated dental implants do not become integrated to the bone, not reaching sufficient stability, and sometimes causing patient local pain. Those implants cannot be used as support for a tooth prosthesis and need to be removed, representing the major cause of implant failure.

4.1 Interleukin (IL)-1 as a key inflammatory cytokine

Implant surface biological aggregates interact with the cell membrane-bound proteins or receptors, eventually initiating cell attachment to the implant surface (Kasemo and Gold, 1999). Studies have shown that the coating material of the implants, considered innocuous, can stimulate cells to produce immunogenic inflammatory mediators in vitro (Harada et al., 1996; Perala et al., 1992).

Interleukin-1 (IL-1) is considered a pro-inflammatory mediator with central importance in the initiation and maintenance of acute inflammatory responses (Hoffman and Brydges, 2011). Its name as an interleukin, which means “between leukocytes”, is misleading because IL-1 is synthesized not only by leukocytes but by other cell lineages as well. Besides acting as a mediator of local inflammation, IL-1 can produce systemic effects (Dinarello, 2007). IL-1 is the term for two polypeptides: IL-1 α and IL-1 β that possess a wide spectrum of inflammatory, metabolic, physiologic, hematopoietic, and immunologic properties (Pelegrin, 2008). IL-1 β has been particularly studied as a critical determinant of tissue destruction due to its proinflammatory and bone resorptive properties and increased levels of IL-1 β in gingival crevicular fluid were correlated with the severity of periodontal disease (Bloemen et al., 2011; Goutoudi et al., 2004; Hellmig et al., 2005; Stashenko et al., 1991). Although both forms of IL-1 are distinct gene products, they recognize the same cell surface receptors and share the various biologic activities. The IL-1 natural occurring inhibitor, the interleukin 1 receptor antagonist (IL-1ra), acts by binding the IL-1 receptors (IL-1R) inhibiting biological responses (Lennard, 1995). Produced and secreted by almost all cells expressing IL-1, IL-1ra functions as a competitive receptor antagonist, binding to IL-1 receptors, but not activating target cells (Molto and Olive, 2010). Today, IL-1 family is recognized to include 11 total members (Smith, 2011), which play particular roles in immune-inflammatory aspects of the host response. IL-1 is thus a “cytokine” and this term is used to connote that the sources and actions of IL-1 and related polypeptides include several different cell types. Moreover, IL-1 belongs to a group of cytokines with overlapping biologic properties such as tumor necrosis factor (TNF). IL-1 and TNF share the ability to

stimulate T and B lymphocytes, augment cell proliferation, and initiate or suppress gene expression for several proteins (Laurincova, 2000). IL-1 α , IL-1 β , and TNF- α were observed to signal fibroblasts to produce matrix metalloproteinases (MMPs) that induce connective tissue degradation (Kornman, 2006; Takashiba et al., 2003). Circulating levels of IL-1 are elevated in a variety of clinical situations and, together with elevated levels of TNF, correlate with the severity of some diseases, suggesting that these cytokines participate in the host response to or development of illnesses.

There is a dramatic increase in IL-1 production by a variety of cells in response to infection, microbial toxins, inflammatory agents, products of activated lymphocytes, complement, and clotting components. At the site of inflammation, IL-1 acts on macrophages, further increasing the production of IL-1 and inducing the synthesis of IL-6. In endothelial cells, increases the expression of surface molecules that mediate leukocyte adhesion (Abbas et al., 1998). This cytokine also acts on fibroblasts, stimulating their proliferation and transcription of collagen type I, III and IV. Thus, the development of fibrosis appears to be partly mediated by IL-1 (Dinarello, 1988). Indeed, production of IL-1 in tissues is thought to contribute to local effects such as fibrosis and tissue matrix breakdown, besides the influx of inflammatory cells (Stevens et al., 2009). IL-1 has also significant effects on bone, increasing constitutive receptor activator of NF-kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratios (Stein et al., 2011). In vivo experiments indicated that IL-1 cytokine plays potent activity in bone resorption (Polzer et al., 2010b). Osteoclasts possess surface receptors for IL-1, which, when activated, stimulate the production of prostaglandins and IL-1 itself, modulating gene expression of several other cytokines. Thus, it is suggested that IL-1 participates in the pathogenesis of diseases involving bone tissue (Masada et al., 1990; Tatakis, 1993).

Many studies have investigated tissues surrounding unsuccessful dental implants in order to clarify the implant failure mechanisms (Aboyoussef et al., 1998; Ruhling et al., 1999). The bone-implant interface area is first occupied by red blood and inflammatory cells, degenerating cellular elements, then is gradually replaced with spindle-shaped or flattened cells, with initiation of host bone surface osteolysis (Futami et al., 2000). An abnormal immune-inflammatory response involving different cell types such as macrophages, polymorphonuclear neutrophils, T and B lymphocytes, endothelial cells, fibroblasts, keratinocytes, osteoclasts, and osteoblasts can impair periodontal and peri-implant tissues (Seymour et al., 1989). If activated, these cells can synthesize and release cytokines such as IL-1, which mediates both inflammatory and bone resorption processes (Gainet et al., 1998). Searching for diagnostic markers to monitoring implant health status, levels of interleukins have been measured in diseased implant sites (Boynuegri et al., 2011). Higher levels of IL-1 β were found in diseased implant sites when compared with healthy ones (Aboyoussef et al., 1998), suggesting that such inflammatory mediator is associated with implant failure (Salcetti et al., 1997). Higher levels of TNF- α also showed association with unfavorable clinical outcomes at 2 and 14 days after implant placement, being proposed that TNF- α gene expression may predict clinical complications (Slotte et al., 2010). The association between implant surface modification and inflammation molecular markers has been investigated and suggested as an additional indicator of implant clinical outcome (Monjo et al., 2008).

4.2 Extracellular matrix (ECM) on the osseointegration process

Osseointegration has been considered not the result of an advantageous tissue response but rather the lack of a negative tissue response (Mavrogenis et al., 2009). Some research has

been progressed in order to better understand the implant-bone tissue interface and the kinds of matrix produced on an implant surface (Wierzechos et al., 2008), although those events have only been characterized at a morphological level, using several histological approaches (Linder et al., 1983; McKibbin, 1978; Schenk and Perren, 1977; Winet and Albrektsson, 1988). Extracellular matrix (ECM) appears to vary morphologically between different material surfaces, suggesting that the extracellular response can be affected by the implant surface. However, ECM investigations, valuable in determining the vascular and morphological changes occurring in the healing site, suffer from the inability to biochemically evaluate the cellular response around a fixture (Winet and Albrektsson, 1988). Only more recently, studies aiming to characterize ECM at a molecular level start dissecting the structural components during implant osseointegration process and a cartilage ECM gene was found to be expressed (Mengatto et al., 2011). Patient individual response to implant treatment, in terms of the interfacial response of cells in contact with the implant surface, seems to impact clinical outcomes (Huang et al., 2004).

4.2.1 Matrix metalloproteinases (MMPs) and other mediators involved in ECM remodeling

Matrix metalloproteinases (MMPs) represent the major class of enzymes responsible for ECM metabolism (Kerrigan et al., 2000). They are metal-dependent proteolytic enzymes that contribute to the degradation and removal of collagen from damaged tissue. MMPs are secreted by inflammatory cells in response to stimuli such as lipopolysaccharide and cytokines (Birkedal-Hansen, 1993). Specific enzymes of this family can function beneficially during tissue remodeling and during formation of the ECM (Fanchon et al., 2004). However, MMPs may increase the adverse effects of cardiovascular disease (Kukacka et al., 2005), cancer metastasis (Nemeth et al., 2002), caries process (Sulkala et al., 2001) and periodontal disease (Liu et al., 2006) by destruction of collagen and other proteins of the ECM.

Previous studies have also shown that MMPs (e.g. collagenases, gelatinases) are present in peri-implant sulcular fluid (Apse et al., 1989; Ingman et al., 1994; Ma et al., 2000; Teronen et al., 1997) and may play a pathologic role in peri-implant bone loss (Golub et al., 1997).

Matrix metalloproteinase-1 (MMP-1), also known as collagenase-1, is a key mediator of the degradation of collagen, which is abundant in connective tissue and bone matrix (Yamada et al., 2002). MMP-1 degrades types I, II, III, and IX collagen, which are the most abundant protein components of extracellular matrices (de Souza et al., 2003; Dunleavey et al., 2000). An enhanced secretion of MMP-1 was verified in peri-implantitis fibroblasts compared to healthy and periodontitis sites (Bordin et al., 2009). Gelatinase B (MMP-9) is particularly active against gelatins, denaturing type I collagen, and type IV collagen, a major component of the basement membrane. It also acts proteolytically against proteoglycan core protein and elastin, which are resistant to degradation by some other MMPs (Birkedal-Hansen, 1993). MMP-9 is produced by inflammatory cells as well as by stimulated connective tissue cells (Foda and Zucker, 2001) and has been identified in many human cancers both in neoplastic tissues and in the surrounding stromal and inflammatory cells (Crawford and Matrisian, 1994). Related to dental implants, zymography studies showed increased activities of MMP-9 in cells exposed to titanium particles between 48 to 72 hours (Choi et al., 2005). Transforming growth factor-beta 1 (TGF- β 1) is a member of a large family of growth factors and cytokines, which are synthesized by a wide range of cells and therefore are distributed

in many different tissues (Massague, 1990). There are at least three homologous TGF- β isoforms in humans: TGF- β 1, TGF- β 2, and TGF- β 3. TGF- β 1 is the best characterized TGF- β isoform, and its primary sequence is highly conserved throughout evolution (Syrris et al., 1998). It is synthesized as precursor latent forms, and the active form consists of two identical disulfide linked polypeptide chains (Derynck et al., 1985; Syrris et al., 1998). TGF- β possesses some major activities: it inhibits proliferation of most cells, but can stimulate the growth of some mesenchymal cells; exert immunosuppressive effects and reduction of inflammation; is involved in extracellular matrix deposition, and promotion of wound healing (Lawrence, 1996; Santos et al., 2004a). In the health organism TGF- β is involved in wound repair processes and in starting inflammatory reactions and then in their resolution. The latter effects of the TGF- β derive in part from their chemotactic attraction of inflammatory cells and of fibroblasts (Lawrence, 1996). In periodontal diseases, TGF- β concentration was directly associated with plaque index and probing pocket depth. Moreover, decreases in gingival crevicular fluid concentration levels after surgical treatment of periodontitis sites was also found (Sattari et al., 2011). Cytokines such as TGF- β and MMPs can affect the attachment and synthetic activities of osteoblasts and cause the reduction of bone matrix and mineral deposition (Kwon et al., 2000; Kwon et al., 2001).

4.3 Bone metabolism on implant healing

The properties of bone are directly related to the features of the mineralized ECM adjacent to implants in two ways. First, the implant geometry and the insertion approach (surgery technique) determine the principal bone-implant relation. Second, the properties of bone homeostasis and turnover have a major impact on the load-related characteristics of the microenvironment adjacent to implants (Joos et al., 2006). The cortical part of bone provides the mechanical and protective functions, whereas cancellous bone is also involved in metabolic functions (e.g. calcium homeostasis). Both aspects (structural and metabolic) are closely related to the features of the mineralized extracellular matrix at implant surfaces. Trabecular bone fills the initial gap and arranges in a three-dimensional network at day 14 (Franchi et al., 2005). The *de novo* formation of primary bone spongiosa offers not only a biological fixation to ensure secondary implant stability (Ferguson et al., 2006) but also a biological scaffold for cell attachment and bone deposition (Franchi et al., 2005). After 28 days, delineated bone marrow space and thickened bone trabeculae with parallel-fibered and lamellar bone can be found within the interfacial area. After 8 to 12 weeks, the interfacial area appears histologically to be completely replaced by mature lamellar bone in direct contact with titanium (Berglundh et al., 2003).

Osseointegration has been defined as the direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant (Branemark et al., 1969). Since Branemark's initial observations, the concept of osseointegration has been defined at multiple levels such as clinically (Adell et al., 1981), anatomically (Branemark et al., 1977), histologically, and ultrastructurally (Linder et al., 1983). When an implant is placed, the space between the fixture and bony crypt will heal with new bone by reparative osteogenesis resulting in clinical fixation of the implant. The bone turnover is also evidenced by bone changes during the first 6-year period *in vivo*, resulting in an increased thickness (up to 200 nm), which contain increased levels of organic and inorganic (Ca, P, S) material. This may suggest the potential for a surface reactivity not

usually associated with titanium and supports the concept of a dynamic definition of osseointegration (Stanford and Keller, 1991).

Patients have a mean time to repair an implant surgery in terms of bone, and create new mineralized tissue around implants. The meantime repair does not have to apply to all patients because they present different bone turnover rate (Chang et al., 2010; Courbebaisse and Souberbielle, 2011). This issue is not clinically measured and may have an impact on implant osseointegration. Quality and quantity differences in proteins that are classically involved in bone metabolism may modulate bone remodeling (Alvim-Pereira et al., 2008b). Guidelines taking into account bone tissue repair and turnover rate are desirable to ensure a successful osseointegration. These characteristics are nowadays based only clinically, considering medical and dental history. In this way, it cannot be established a clear cutline across patients that are suitable or have an increased risk for dental implant therapy in terms of host response. Therefore, it has been proposed that progression of osseointegration may be accelerated by growth factors and modification of implant surface, and functional integration of peri-implant structure may be feasible to predict the implant function during osseointegration (Chang et al., 2010). Although it is important to study extrinsic factors which could impair or accelerate osseointegration, there is still a lack of understanding over inter-individual differences on host physiologic response.

4.3.1 Bone metabolism proteins

Bone is one of the classical target tissues for vitamin D action. Vitamin D regulates calcium homeostasis by influencing intestinal calcium absorption, renal calcium reabsorption, and bone calcium metabolism (Binkley, 2006). Vitamin D is ingested or cutaneously produced upon exposure to ultraviolet B radiation in an inactive form. To be activated, vitamin D is transported in the blood bound to a vitamin D-binding protein, hydroxylated in the liver and the resulting metabolite is further hydroxylated mainly at the kidney, resulting in the active form called 1,25-dihydroxyvitamin D₃ (Panda et al., 2004). In target tissues, 1,25-(OH)₂D₃ is believed to exert most of its actions by binding to the vitamin D receptor (VDR), a member of the nuclear steroid hormone receptor superfamily, and by regulating the transcription of vitamin D target genes (Haussler et al., 1998). VDR also plays a complex role in the control of bone homeostasis and recruits co-regulators, which may have activating or repressing effects. In VDR knockout growing mice, the primary defect of calcium metabolism is at the intestine; loss of VDR causes calcium malabsorption and rickets that can be prevented by a high-calcium diet. Additionally, VDR knockout mice reveal that VDR plays a role in suppression of bone formation (Fleet, 2006). Functionally, in experimental model, vitamin D analogs dramatically increase bone mass, size and strength in rodents (Slatopolsky et al., 2003). Observations suggest that bone integration around implants may be critically impaired by vitamin D deficiency (Mengatto et al., 2011).

Bone morphogenetic protein (BMP) family, as a member of the TGF- β superfamily, has a variety of functions in the development and reparation of bone tissue (Rider and Mulloy, 2010). The hallmark of the BMPs is their ability to induce bone formation *in vivo* by promoting osteoblast differentiation (Rider and Mulloy, 2010). BMP-2 has been shown to stimulate bone ingrowth, gap healing, and implant fixation in several animal studies (Cochran et al., 1999; Sumner et al., 2004). BMP-2 recombinant protein application showed a good potential in terms of regeneration and decreased morbidity as compared with bone

autografts (Tonetti and Hammerle, 2008), also suggesting an important role on bone regulation in oral repair sites.

Calcitonin is a peptide hormone that rapidly, transiently, and reversibly inhibits osteoclast-mediated bone resorption and also modulates calcium ion excretion by the kidney (Pondel, 2000). The physiological effects of calcitonin are specifically mediated by high affinity calcitonin receptors (CTRs), which belong to the class B subfamily of seven-transmembrane domain G protein-coupled receptors. The effect of calcitonin drugs during the period of bone maturation around titanium implants was investigated in animal model, and a positive time effect was verified improving bone mass (Januario et al., 2001). Moreover, it was shown that implant surface modifications might alter the expression of calcitonin receptor gene in osteoclasts (Monjo et al., 2008).

The system RANK/RANKL/OPG has been described as a central regulator of bone metabolism. RANKL was shown to bind its receptor, RANK, on osteoclast lineage cells to induce osteoclastogenesis. The molecule blocked by the soluble receptor OPG was identified as the key mediator of osteoclastogenesis in both a membrane-bound form expressed on preosteoblastic/stromal cells as well as a soluble form. The RANK/RANKL/OPG regulatory axis is also involved in inflammatory bone destruction induced by pro-inflammatory cytokines such as prostaglandin E_2 (PGE_2), IL-1 β , IL-6, and TNF- α (Boyle et al., 2003). In addition, a number of other mediators of bone metabolism, such as TGF- β (Takai et al., 1998), parathormone (PTH) (Lee and Lorenzo, 1999), 1,25-dihydroxyvitamin D3 (Kitazawa et al., 1999), glucocorticoids (Hofbauer et al., 1999), and estrogen (Hofbauer et al., 1999; Saika et al., 2001) exert their effects on osteoclastogenesis by regulating osteoblastic/stromal cell production of OPG and RANKL. RANKL and OPG concentrations were significantly higher at the crevicular fluid sampling sites of patients presenting peri-implantitis, suggesting an increased risk of alveolar bone loss around dental implants (Arikan et al., 2011).

5. A research focus on the host genetic susceptibility

The knowledge that implant loss i) is not totally explained by clinical conditions and ii) tends to cluster in subsets of individuals (Montes et al., 2007; Weyant and Burt, 1993) may indicate that specific host response characteristics, that disturb the osseointegration process, are influenced by genetic factors (Alvim-Pereira et al., 2008a).

Gene polymorphisms are a mechanism by which individuals may exhibit variations in DNA sequence. These variations may impact specific protein production and/or function (Hu et al., 2005) that in turn could alter host response modulating disease susceptibility or implant treatment outcome. Most polymorphisms are single nucleotide exchanges (SNPs) that occur in a high frequency in the human genome (Venter et al., 2001). Functional polymorphisms may account for variation in the production or function of proteins (Hu et al., 2005; Pociot et al., 1992). Those resultant slight changes in the immunoinflammatory response modulation might influence implant loss (Lachmann et al., 2007; Laine et al., 2006).

The focus of studies investigating genetic susceptibility to dental implant failure has been limited to candidate gene, population-based association analysis (Alvim-Pereira et al., 2008a). In this approach the physiology and involved metabolic pathways of healing and osseointegration process are the basis to search for candidate genes underlying host susceptibility to implant failure. But, a number of biologic mechanisms is involved in the osseointegration complex process, some of which have not yet been identified (Mengatto et

al. 2011; Montes et al., 2007). Although some similarities between osseointegration and tooth extraction socket were seen, different pathways of transcription and growth factors, extracellular matrix molecules, and chemokines were proposed (Lin et al., 2010). A recent study with rats showed a possible network of genes that associated with success and failure of implant osseointegration (Mengatto et al., 2011).

In the PUBMED library available literature, a total of twenty-three original papers analyzing genetic polymorphisms in candidate genes in humans related to implant outcomes were found. The main data and results of each study are summarized in Table 1.

5.1 Genetic polymorphisms and dental implant failure

The most commonly studied polymorphisms in genetics of implant failure are functional variations in the interleukin-1 (IL-1) gene cluster in several populations. Because of IL-1 proinflammatory and bone resorbing properties, a role has been suggested for this cytokine in controlling genetic risk of implant failure. The association of *IL1A* gene (which codes for IL-1 α) polymorphisms with dental implant outcome was investigated in several studies (Campos et al., 2005c; Feloutzis et al., 2003; Gruica et al., 2004; Jansson et al., 2005; Lachmann et al., 2007; Laine et al., 2006; Lin et al., 2007; Rogers et al., 2002; Shimpuku et al., 2003b; Wilson and Nunn, 1999). Since *IL1B* gene (which codes for IL-1 β) was seen to be up-regulated at early stages of healing and then down-regulated at later stages (Lin et al., 2010), polymorphisms in *IL1B* gene were also investigated for association with implant failure susceptibility (Campos et al., 2005b; Dirschnabel et al., 2011; Feloutzis et al., 2003; Gruica et al., 2004; Jansson et al., 2005; Lachmann et al., 2007; Laine et al., 2006; Lin et al., 2007; Melo et al., 2011; Montes et al., 2009; Rogers et al., 2002; Shimpuku et al., 2003b; Wilson and Nunn, 1999). Moreover, *IL1RN* gene (which codes for IL-1 α) was also searched for association to implant failure (Campos et al., 2005c; Laine et al., 2006; Montes et al., 2009). Even though *IL1* gene cluster is the most frequent analyzed inflammatory candidate genes, the results are divergent, yet not conclusive and generally not replicated (see table 1 for review). However, genotype 2/2 of *IL1RN* polymorphism was significantly more frequent in patients who presented multiple losses. Some other functional polymorphisms in inflammatory candidate genes were also analyzed: *IL2* (Campos et al., 2005a), *IL6* (Campos et al., 2005a; Melo et al., 2011), and *TNFA* (Campos et al., 2004; Cury et al., 2007; Cury et al., 2009) (Table 1).

Also, genes involved in the regulation of ECM such as *TGFB1* (Santos et al., 2004a), *MMP1* (Leite et al., 2008; Santos et al., 2004b) and *MMP9* (Santos et al., 2004b) have been investigated (Table 1).

It has been suggested that polymorphisms in the *VDR* gene significantly alter expression and/or function of VDR, which may interfere in mineral bone density (Shishkin et al., 2010). So far, only one paper has investigated the association of *VDR* gene polymorphisms with dental implant loss with no association evidenced between a functional polymorphism and implant loss (Alvim-Pereira et al., 2008b) (Table 1).

Bone morphogenetic protein 4 (*BMP4*) gene expression was reported to be slowly increased during osseointegration and the bone healing process (Lin et al., 2010), and a gene polymorphism in this gene was associated with marginal bone loss around dental implants (Shimpuku et al., 2003a) (Table 1). Another polymorphism in the *CTR* gene was also associated with marginal bone loss in the jaw, but not in the maxilla (Nosaka et al., 2002) (Table 1). Polymorphisms in *CTR* gene were also associated with bone metabolism regulation in postmenopausal women (Masi et al., 1998; Nakamura et al., 2001) and severe periodontitis (Suzuki et al., 2004).

Authors	Year	Polymorphisms	Case (n) / Control (n)	Mean age (years)	Smoking Yes / No	Population	Results
Wilson and Nunn	1999	<i>IL1A</i> (-889) and <i>IL1B</i> (+3953)	17 / 38	57	27 / 35	?	Not associated with implant failure
Nosaka et al.	2002	<i>CTR</i> (+1377)	15 / 20	54.8	15 / 20	Asian Japanese	Associated with marginal bone loss in mandible, but not in maxilla
Rogers et al.	2002	<i>IL1A</i> (-889) and <i>IL1B</i> (+3953)	19 / 31	66	?	Australian Caucasian	Not associated with implant failure
Shimpuku et al.	2003	<i>IL1A</i> (-889) and <i>IL1B</i> (-511, +3954)	17 / 22	55.1	14 / 25	Asian Japanese	Associated with marginal bone loss
Shimpuku et al.	2003	<i>BMP4</i> (+538)	21 / 36	52.6	24 / 38	Asian Japanese	Associated with marginal bone loss
Feloutzis et al.	2003	<i>IL1A</i> (+4845) and <i>IL1B</i> (+3954)	?	59.5	41 / 39	European Caucasian	Smoking + <i>IL1</i> positive genotype associated with marginal bone loss
Campos et al.	2004	<i>TNFA</i> (-308)	38 / 38	47.2	0 / 66	Brazilian	Not associated with early implant failure
Santos et al.	2004	<i>TGFB1</i> (-509, -800)	28 / 40	46	0 / 68	Brazilian	Not associated with early implant failure
Santos et al.	2004	<i>MMP1</i> (-1607) and <i>MMP9</i> (-1562)	20 / 26	45.9	0 / 46	Brazilian	<i>MMP1</i> : associated, and <i>MMP9</i> : not associated with implant failure
Gruica et al.	2004	<i>IL1A</i> (+4845) and <i>IL1B</i> (+3954)	34 / 176	25 to 90	53 / 127	European Caucasian	Smoking + <i>IL1</i> positive genotype associated with late infection
Campos et al.	2005	<i>IL1A</i> (-889), <i>IL1B</i> (-511, +3953), and <i>IL1RN</i> (intron 2 - 86 bp repeats)	28 / 34	47.5	0 / 62	Brazilian	Not associated with early implant failure
Campos et al.	2005	<i>IL2</i> (-330) and <i>IL6</i> (-174)	34 / 40	46.3	0 / 74	Brazilian	Not associated with early implant failure
Jansson et al.	2005	<i>IL1A</i> (-889) and <i>IL1B</i> (+3954)	6 / 16	54	10 / 12	European Caucasian	Smoking + <i>IL1</i> positive genotype associated with implant loss
Laine et al.	2006	<i>IL1A</i> (-889), <i>IL1B</i> (-511, +3953), and <i>IL1RN</i> (intron 2 - 86 bp repeats)	71 / 49	67.2	84 / 36	European Caucasian	<i>IL1RN</i> associated with peri-implantitis
Lin et al.	2007	<i>IL1A</i> (-889), <i>IL1B</i> (-511, +3953)	29 / 30	42.8	32 / 27	Asian Chinese	<i>IL1B</i> associated with marginal bone loss
Cury et al.	2007	<i>TNFA</i> (-308)	36	46	0 / 36	Brazilian	Not associated with marginal bone loss
Lachmann et al.	2007	<i>IL1A</i> (-889), <i>IL1B</i> (+3953)	11 / 18	66	?	European Caucasian	Not associated with levels of peri-implant crevicular fluid nor with cytokine concentration
Alvim-Pereira et al.	2008	<i>VDR</i> (exon 9, <i>Taq I</i>)	80 / 137	51.7	43 / 174	Brazilian	Not associated with implant failure
Leite et al.	2008	<i>MMP1</i> (-1607 and -519)	44 / 60	?	0 / 104	Brazilian	<i>MMP1</i> associated with early implant failure
Montes et al.	2009	<i>IL1B</i> (+3954) and <i>IL1RN</i> (intron 2)	90 / 176	51.5	58 / 208	Brazilian	<i>IL1RN</i> associated with multiple implant loss
Cury et al.	2009	<i>TNFA</i> (-308)	49 / 41	?	?	Brazilian	Not associated with peri-implantitis
Dirschabel et al.	2011	<i>IL1B</i> (-511)	92 / 185	53.6	61 / 216	Brazilian	Not associated with implant loss
Melo et al.	2011	<i>IL1B</i> (+3954), <i>IL1B</i> (-511), and <i>IL6</i> (-174)	31 / 16	?	?	Brazilian	Not associated with peri-implantitis

Table 1. Studies investigating the association between genetic polymorphisms and dental implant failure.

5.2 Future insights in dental implants genetic research

Although candidate gene, association analysis has proved to be a promising tool for the dissection of the nature of the genetic component controlling dental implant failure, the design is limited by the fact that just a small segment of the genome is analyzed. Moreover, the sample sizes are often small; therefore, findings must be replicated in larger populations (Alvim-Pereira et al., 2008a). As a consequence, genetic susceptibility to osseointegrated implant failure remains widely unknown.

Despite these promising advances, the exact number, identity and role of regulatory factors that lead to a successful implant osseointegration and its maintenance are still largely unknown, which limits genetic analysis approaches based on functional candidate genes. The challenge then is to map all the involved genes (Bosse et al., 2004), a considerably difficult task given that the human genome is composed of at least 30,000 genes (Baltimore, 2001), reaching 4.1 million of SNPs catalogued in public databases markers.

Genomewide association scans (GWAS) are a fully automated technology that allows genotyping hundreds of thousands of SNPs in a single experiment (Thomas et al., 2005). This extremely high throughput SNP genotyping technology is making possible the development of association-based case-control design covering the entire genome (Hirschhorn and Daly, 2005). However, some limitations do exist. Those analyzes are still very expensive and need cutting-edge genotyping technology (Detera-Wadleigh and McMahon, 2004) and tremendous amount of raw data demands adequate statistical methods of analysis (Devlin et al., 2001). False-positive results are likely to increase (Marchini et al., 2004), in this context, replication in independent populations becomes mandatory (Neale and Sham, 2004). On the other way around, the great amount of failure in identifying significant associations of complex traits and diseases with common variants across the genome may indicate that those complex phenotypes may possibly be determined by rare gene variants. In this context, the whole genome sequencing of a few individuals, whose phenotype is very well characterized and extreme, may be cheaper and offer more valuable results.

Another development in the genetic field is called next-generation sequencing (NGS) technology, which includes genome sequencing and resequencing, transcriptional profiling (RNA-Seq) and high-throughput survey of DNA-protein interactions (ChIP-Seq) (de Magalhaes et al., 2010). The advantages may change the landscape of genetics by a reasonable cost and high throughput (Mardis, 2008). In spite of giving rise to new challenges, in particular in processing, analyzing and interpreting data, this type of application may clarify and increase knowledge over physiologic pathways of bone remodeling and osseointegration.

6. Conclusion

Despite the difficulties, the motivation to continue applying traditional and new approaches for genetic analysis to the effort towards a better understanding of dental implant physiology and failure mechanisms is clear. For example, genetic studies may shed new light not only upon the physiopathology of dental implant failure, but also upon broader, related processes, such as bone healing. In addition, a direct result of such studies may be the definition of potential targets for effective screening, prevention and maintenance of dental implants.

7. References

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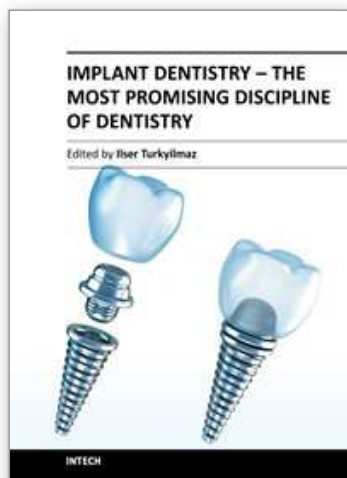
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Since Dr. Branemark presented the osseointegration concept with dental implants, implant dentistry has changed and improved dramatically. The use of dental implants has skyrocketed in the past thirty years. As the benefits of therapy became apparent, implant treatment earned a widespread acceptance. The need for dental implants has resulted in a rapid expansion of the market worldwide. To date, general dentists and a variety of specialists offer implants as a solution to partial and complete edentulism. Implant dentistry continues to advance with the development of new surgical and prosthodontic techniques. The purpose of *Implant Dentistry - The Most Promising Discipline of Dentistry* is to present a contemporary resource for dentists who want to replace missing teeth with dental implants. It is a text that integrates common threads among basic science, clinical experience and future concepts. This book consists of twenty-one chapters divided into four sections.

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Phone: +86-21-62489820
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