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Research Article

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) IN CHRONIC PERIODONTITIS

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ABSTRACT

Periodontitis is an inflammatory disease affecting the supporting tissues of teeth with multifactorial etiology. Chronic periodontitis is the most prevalent form of periodontitis. While microbial factors are believed to initiate other environmental factors and modulate periodontal disease progression. Strong data supports that genetic polymorphisms play a role in the predisposition and progression of periodontal diseases. Different allelic variants can result in variations in tissue structure, antibody responses and inflammatory mediators. Genetic variations may also act as protective or risk factors for certain conditions, including periodontitis. Polymorphisms in the Interleukins (IL), Tumour necrosis factor (TNF) alpha, Human Vitamin D receptor (VDR), Matrix metalloproteinase-1, Toll-like receptor (TLR) and Cyclo-oxygenase-2 (COX-2) are found to have an influence on chronic periodontitis.

INTRODUCTION

Periodontitis is an inflammatory disease affecting the supporting tissues of teeth. Chronic periodontitis is the most prevalent form of periodontitis. "Chronic periodontitis is defined as an infectious disease resulting in inflammation within supporting tissues of teeth, progressive attachment and bone loss". A number of different factors influence the etiopathology of chronic periodontitis.[1]Genetic factors includes variation in genetics, single nucleotide polymorphisms (SNPs) and genetic copy number variation. SNP is a variation in the single nucleotide that occurs at specific position in the genome. Genetic copy number variations (CNVS) in sections of genome are repeated. CNVs are a type of structural variant involving alterations in the number of copies of specific regions of DNA, which can either be deleted or duplicated.[2] Genetic variation in the human genome takes many forms, ranging from large microscopically-visible chromosome anomalies to single nucleotide changes. Deletions, insertions, duplications, and complex multi-site variants collectively termed CNVs or copy number polymorphisms (CNPs), are found in all humans and other mammals examined.[3] CNVs, especially gene duplication and ex on shuffling, can be a predominant mechanism driving gene and genome evolution.[4]

Cytokine gene polymorphism refers to difference in expression of cytokine of great interest in periodontal research. IL-1 SNP IL-1α -889 in promoter or IL-1β +3954 gene associated with severe periodontitis. Other cytokine like IL-2 SNPs, IL-4 SNPs were associated with aggressive periodontitis. IL-6 SNPs were associated with protection against periodontitis in IL-10,IL-4,IL-6,IL-8,IL-18,TNF-α etc., gene polymorphism were studied and found to have an effect on periodontitis. Receptor gene polymorphism occurs in FCγ receptor of IgG are also associated with chronic periodontitis. Toll like receptor (TLR) gene polymorphism especially in TLR4 gene polymorphism acts as a risk factor for the development of chronic periodontitis. CD14 gene polymorphism, RANKL polymorphism, Vitamin D receptor gene polymorphism have etiological role in chronic periodontitis.

Role of Genetics in Chronic Periodontitis

Chronic periodontitis is suggested to have a genetic component. However the level to which the genetic component has been under study. Genes related to host immunity and inflammatory response such as cytokines, cell surface receptors, chemokines, enzymes and antigen recognition are under research for association with chronic periodontitis. Polymorphisms in the interleukins, Fc gamma receptor, tumour necrosis factor alpha, human vitamin D receptor, matrix metalloproteinase-1, toll-like receptor, cyclo-oxygenase-2 and C-reactive protein genes are found to have an influence on chronic periodontitis.[1] Genetic variations may have a protective

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effect or risk factors for certain conditions including periodontitis. In particular, genetic differences in immune-cell development and antigen presentation may contribute to the susceptibility to autoimmune and infectious diseases.

Genetic Polymorphisms

This includes: (i) single nucleotide polymorphisms [SNPs], (ii) small insertions and deletions (INDELs) ranging from 1 to 10,000 base pair in length and (iii) larger forms of structural variation. In this review, we focus on progress that has been made with detecting small INDELs in human genomes. Despite the fact that small INDELs are highly abundant in humans and cause a great deal of variation in human genes, they have received far less attention than SNPs and larger forms of structural variation. Small INDELs have been particularly challenging to detect, validate and genotype, and customized tools have been necessary to study this class of variation.[6]

Detection of Single Nucleotide Polymorphisms

Majority of the SNPs came from three sources. The first set arises from analysing overlapping large-insert clone sequences from the human genome project. When the overlapping bacterial artificial chromosome (BAC) clones came from different libraries, the overlapping sequences (most of them 20-30 kb in length) are from different individuals and many SNPs are found. Because the donors of the BAC libraries are diploid, even when the overlapping clones are from the same library, the two BACs are derived from different parental lineage 50% of the time and SNPs will be found. Certainly, some 8,00,000 SNPs were found in the overlapping sequences by the end of year 2000. The second set came from with the data derived from the sequencing of clones from "reduced representation libraries". By reducing the complexity of the genome through cloning of size selected restriction fragments from a pooled DNA sample, the same loci were sequenced multiple times when a large number of clones from each library were sequenced.

Also for the singleton clones and their sequences were applicable for SNP discovery because they could be balance to the reference human genome sequence and 9,00,000 SNPs were settled to the public database by the end of 2000. The third set came from the whole genome shotgun sequencing project by a private enterprise and the data were kept from the public. Larger set of SNPs is accessible only to "subscribers" of the private database. In addition to these large-scale projects, smaller efforts using a variety of approaches also contributed to the global SNP discovery project and with the reference human genome sequence now close to completion, global SNP discovery is most efficient when one takes a shotgun sequencing approach and compares the sequencing data obtained against the reference sequence. This approach is applicable to any organism as long as the reference sequence of that organism is available.[7]Newer technologies hybridisation, chemical cleavage of mismatch, denaturation gradient of gel electrophoresis, ribonuclease cleavage of mismatched DNA, single stranded conformational polymorphism, cleavage fragment length polymorphism analysis, mismatch repair deletion, endonuclease activity, denaturation high performance liquid chromatography, UNG mediated sequencing, sequence by hybridisation are all newer technologies of DNA sequencing.

Interleukin Polymorphisms

Interleukin-1 is a potent pro-inflammatory agent that is released by macrophages, platelets and endothelial cells. The gene encodes chromosome 2q13–21. An unveiled interaction exists between the IL-1 genetic polymorphism and environmental factors such as smoking. Smokers bearing the genotype-positive IL-1 allele combination may be at an increased risk of developing periodontitis.[3]

Interleukin-2 is a cytokine produced by CD4+ cells and has a direct effect on the activation, growth and differentiation of T and B lymphocytes and natural killer cells. The gene encoding IL-2 is located on chromosome 4q26-q27.[5] Due to its biological effects, IL-2 has been proposed to be a useful marker of pathologic inflammatory activity in systemic diseases and periodontal conditions. The assessment of in vitro IL-2-producing capacity of peripheral blood mononuclear cells and lymphocytes from patients with different forms of periodontitis showed no correlation between IL-2 production and disease types. Individuals with the TT genotype seem to be 2.5-times less likely to develop severe periodontitis than individuals who are heterozygous or GG homozygous.[2]

Interleukin-4 is a cytokine generally involved in humoral immunity and important in down-regulating macrophage function. On the immune reactions of the host, the role of T cells in the pathogenesis of periodontitis has been investigated as they play a key role in the regulation of immune responses. IL-4 is a potent down regulator of macrophage function that inhibits the secretion of proinflammatory cytokines after stimulation with lipopolysaccharides of periodontopathogenic bacteria.[8]

Interleukin-6 is a pro-inflammatory cytokine that is also an important regulator of the immune response and has been associated with periodontal disease. Human IL-6 is made up of 212 amino acids, including a 28-amino-acid signal peptide, and its gene encoded on the chromosome 7p21. Although the core protein is 20 kDa, glycosylation accounts for the size of 21 –26 kDa of natural IL-6.[9]

Interleukin-8 was proposed in 1987 as a novel type of neutrophil-activating cytokine. The gene encoding IL-8 is located on chromosome 4q12-q13. IL-8 is generated as a precursor of 99 amino acids and is secreted after cleavage of a signal sequence of 20 residues. The predominant variant consists of 72 amino acids and has a molecular weight of 8,383.[10]

Interleukin-10 is a Type II cytokine and the 'founding' member of a family of cytokines which includes IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29. All of these cytokines have similar intron–exon genomic organization, bind to receptors with similar structures and in some cases shared components, and all activate Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling pathways. The human IL-10 gene spans about 4.7 kb on chromosome 1q21–32.[11]

Interleukin-12 family of cytokines which includes IL-12 (IL-12p35/IL-12p40), IL-23 (IL-23p19/IL-12p40), IL-27 (IL-27p28/Ebi3) and IL-35 (IL-12p35/Ebi3) and has arises as regulators of host immunity. A polymorphism in the 3'-

untranslated region of IL-12B (+16974) was evaluated and found to be associated with chronic periodontitis.[12]

Interleukin-13 is a cytokine which is secreted by activated T-helper 2 (Th2) cells. IL-13 has a wide range of roles on the fibroblasts inducing the expression of periostin, integrins and proliferation. It also has diverse functionality on the non-immune cells by initiating the production of eotaxin and enhancing contractility in bronchial smooth muscle cells. IL-13 has a major role in systemic sclerosis, asthma and gastrointestinal Inflammatory Diseases.[13]

Interleukin-17 is a pro-inflammatory cytokine that has six known ligands (IL-17 A-F). IL-17 induces tissue inflammation, it has also been found to activate cells such as osteoclasts and has been suggested to be a possible candidate gene for rheumatoid arthritis, a chronic inflammatory condition that has similarities to chronic periodontitis. IL-17 and chronic periodontitis, there is more limited information on its association with aggressive periodontitis SNPs of IL-17 (IL-17A and IL-17F) have been analysed, in which a significantly higher frequency of the G allele and GG genotype of IL-17A was seen in aggressive periodontitis group and no significant difference was seen with IL-17 F. IL-17 A, both the A allele and AA genotype which might confer protection against periodontal disease. Analysis of IL-17 F found no differences among allelic frequency or genotype distribution for SNPs IL-17 F 7383A/G and 7488A/G.[14]

Interleukin-18 is a pro-inflammatory cytokine and a member of the IL-1 family that has the capacity to induce either Th1 or Th2 cells in response to gram-negative infections. It has only been examined in a small number of studies to date, looking at different loci. IL-18 − 838 C > A and − 368 G > C as well as SNPs of Toll-like receptor 4 there is no significant differences noted in any of the alleles or genotypes, evaluating multiple alleles including IL-18 (−607) the genotype or allele in patients with aggressive periodontitis. IL-18 (−607) was significantly associated in combination with other SNPs. Insufficient studies exist that correlate IL-18 polymorphisms with aggressive periodontitis. Existing studies show that there is no significant trend in association of IL-18 polymorphisms with aggressive periodontitis alone, but may show significant associations in combination with polymorphisms in other genes.[15]

Interleukin 23 is a member of the IL-12 cytokine family produced by dendritic cells and macrophage. Interlekin-23 is a pro-inflammatory cytokine produced by activated antigen presenting cells and is involved in stimulating IL-1β and tumour necrosis factor-α, as well as inducing the secretion of IL-17. Insufficient studies exist that correlate IL-23 polymorphisms with aggressive periodontitis. Existing studies show that there is no significant trend in association of IL-23 polymorphisms with aggressive periodontitis.[16]

MMP 1 and Chronic Periodonitis

MMPs are a family of structurally related but genetically distinct enzymes that degrade extracellular matrix and basement membrane components.[17]MMP gene cluster in chromosome 11. This group consists of 23 human enzymes which is broadly classified into collagenases, gelatinases, stromelysins, membrane-type MMPs and other MMPs, which is based on the substrate specificity and molecular structure. The individuals carrying -1607 2G allele tended to be more susceptible to severe Chronic periodontitis, elevated risk of chronic periodontitis and aggressive periodontitis was also found in 2G carriers. MMP-1 playing a crucial role in paradentiumdestruction was suggested to be an important risk factor of chronic periodontitis. It was previously demonstrated that 2G allele instead of 1G allele at MMP-1 -1607 created a new 5′-GGA-3′ core recognition sequence for members of the erythroblast transformation specific family as the binding site, causing increased transcriptional activity, systemically accelerate MMP-1 gene transcription and protein over-expression, expounding the molecular basis of a anabatic matrix degradation. In addition, some scholars demonstrated that MMP-1-1607 2G allele was associated with increased MMP-1 mRNA expression in vivo. Therefore, it was biologically plausible that individuals carrying MMP1-1607 2G allele were associated with over-expression of MMP-1, consequently contributing to more susceptibility to chronic periodontitis.[18]

GPR126 and Periodontitis

GPR126 SNP rs536714306 showed a putative difference with respect between aggressive periodontitis cases and the Japanese control database HGVD (Human genetic variation database). ELISA of cAMP concentrations indicated that the GPR126-induced cAMP/PKA signaling pathway was impaired in cells transfected with mutant GPR126 carrying rs536714306 compared with those carrying wild-type GPR126. Moreover, while GPR126 induced the cytodifferentiation of HPDL (human periodontal ligament cells) through the up-regulation of BMP-2, ID2 and ID4 expression, rs536714306 had no effect on the cytodifferentiation of HPDL. Thus, GPR126 appears to be important in maintaining the homeostasis of periodontal tissue. The topical application of recombinant cytokines is one of the most effective regenerative procedures for enhancing osteoblastic differentiation. To date, however, the device using platelet-derived growth factor is the only commercially available product for periodontal regenerative therapy. Because GPR126-induced elevation of cAMP enhanced the osteoblastic differentiation of PDL cells in our study, elevation of thecAMP/PKA signaling pathway may be a potentially important target to develop a novel periodontal regenerative therapy.[19]

Cox- 2 and Periodontitis

Cyclooxygenase (COX) plays a very important role in the progress of inflammation and carcinogenesis. It has at least two subtypes: COX-1 and COX-2. COX-1 is constitutively expressed in most cell types, while COX-2 is an induced isoform, which is highly expressed in pathological conditions. Elevation of the COX-2 expression is reported in periodontitis and COX-2 mediated PGs synthesis is associated with the bone resorption in periodontal disease, which can be reduced by the selective COX-2 inhibitor. Furthermore, it produced initial evidence for a possible association between COX-2 genotype rs (6681231) and local IL-6 expression. Despite the publication of several genetic association studies in the field of periodontitis, including recent genome-wide association studies, there is considerable uncertainty as to which genetic variants predispose to periodontitis.

IL-6 gene promoter and COX-2 polymorphisms are some of a few promising genetic variants studied in association with periodontitis in different populations. However, studies for independent validation of these findings and functional studies showing the effect of these genetic variants in inducing periodontal pathology are still lacking, investigating the possible effect of COX-2 and IL-6 haplotypes on local expression of COX-2 and IL-6 in the gingiva. Interestingly there exhibited a similar average of IL-6 positive cells in the gingival biopsies, while COX-2 expression was significantly associated with periodontal disease severity. The association between COX-2 periodontal expression and periodontal pathology confirms and highlighting the role of this enzyme in periodontal destruction. However, it is not clear whether increased production of COX-2 may predispose to periodontitis or if on the other hand, COX-2 increased expression is just a result of chronic exposure to periodontopathogenic bacteria. The rare G allele, which was enriched in chronic periodontitis patients, was found to be associated with aggressive periodontitis. This SNP was not associated with COX-2 expression, but showed an association with IL-6 cellular infiltrate in the connective tissue, the −765 C polymorphism of the COX-2 gene is associated with a decreased risk for periodontitis, especially in aggressive periodontitis.[20]

Calprotectin and Gingiva

Calprotectin levels were significantly higher in the GCF of periodontitis patients. Thus local calprotectin levels have the potential to be used as a diagnostic marker of periodontitis. However, the biological function of calprotectin in PDLCs and the mechanism by which calprotectin contributes to the pathogenesis of periodontitis remains unclear.[21]

Effects of α TGF-β Receptor Inhibitor on PDL Cells

Role of endogenous TGF-β on the proliferation of MPDL22 (Murine periodontal ligament cells). Exogenous fibroblast growth factor-2 stimulated MPDL22 cell proliferation in a dose-dependent manner. A potential regulation mechanism by TGF-β in the BMP-2 signal-dependent early commitment of MPDL22 cells into osteoblastic cells during this period. Moreover, SB431542 treatment partially suppressed the expressions of Smurf1, Smad6 and Smad7 during the late ossification period (days 9–12). The dual functions of SB431542 in BMP-2 induced calcified nodule formation at different maturation stages. Smad7 inhibits both BMP and TGF-β/activinsignaling, whereas Smad6 preferentially inhibits BMP signalling.

The inhibition of endogenous TGF-β signalling resulted in blocking the negative feedback signalling cascades for the TGF-β/BMP-2 signalling pathway. Therefore, SB431542 consideration may participate in both osteoblastic differentiation and maturation of mineralized tissue formation in MPDL22 cells. TGF-β induced collagen synthesis in MPDL22 cells during the ossification process and SB431542 treatment diminished the production of collagen I at the transcription and protein levels. Consistent with this result, the addition of SB431542 during the late ossification period decreased BMP-2-stimulated calcified nodule formation. However, the inhibition of collagen synthesis by SB431542 did not affect the enhancement of BMP-2-induced MPDL22 ossification.[22]

TNF Alpha and Periodontitis

Tumour necrosis factor alpha was known as (TNF, cachexin or cachectin) is involved in systemic inflammation and is a member of a group of cytokines that arouse the acute phase reaction. It is produced primarily by activated macrophages and also it can be produced by many other cell types such as natural killer cells, neutrophils, eosinophils, CD4+ lymphocytes, mast cells and neurons.[23]

TNF- α Polymorphism in Autoimmune and Systemic Diseases

TNF- α polymorphism has been studied in various autoimmune and systemic diseases like psoriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA). Susceptibility to psoriasis is increased in heterozygous TNF-α allele as against homozygous gene expression. The TNF-308A was shown to be associated with SLE. In RA, among patients with 238Aallele, the severe form of RA was more frequent and RA patients with the 489GA genotype had a 3.9 times decreased chance of having erosive disease than patients with the 489 GG genotype.

TNF inhibition*:* TNF stimulates the inflammatory response which causes many of the clinical problems associated with autoimmune disorders such as inflammatory bowel disease, ankylosing spondylitis, rheumatoid arthritis, psoriasis, refractory asthma and hidradenitis suppurativa. These disorders are sometimes treated by using a TNF inhibitor. This inhibition can be achieved with a monoclonal antibody such as infliximab, adalimumab or certolizumabpegol or with a circulating receptor fusion protein such as etanercept. The TNF polymorphisms are found in a region of polymorphic variation and they are associated in linkage disequilibrium with HLA genes and other. Because of differences in the distribution of HLA alleles wide variations in associations between TNF polymorphisms are seen. The associations between TNF-α genotype and disease are not complete as suggested by different conflicting studies SNPs in certain promoter regions in the TNF-α gene have been able to demonstrate an aggravated inflammatory response.[23]

TLR4 and Periodontitis

Toll-like receptors (TLRs) belong to the pattern recognition receptor (PRR) family, a key component of the innate immune system. TLRs detect invading pathogens and initiate an immediate immune response to them, followed by a long-lasting adaptive immune response. Activation of TLRs leads to the synthesis of pro-inflammatory cytokines and chemokines and the expression of co-stimulatory molecules. Polymorphic site in the TLR9 gene promoter region differentially expressed and TLR9 gene and protein expression increased in chronic periodontitis. TLR4 was a pattern-recognition receptor, which played an important part in innate immunity by realizing lipid based structures of bacteria and mediating intracellular signaling.[24]

Vitamin D Receptor Polymorphsims in Periodontitis

Vitamin D plays a role in the metabolism of calcium and phosphorus. The human vitamin D receptor (VDR) gene is localized in chromosome 12q12–q14, and exhibits functional polymorphisms associated with osteocalcin levels and bone mineral density. Vitamin D receptor polymorphisms may

therefore play a role in the destruction of alveolar bone.[2] Susceptibility to dysbiotic microbial communities with potential for destructive inflammation are based on host genetic factors that may predispose to or protect from disease. Hence, dysbiosis alone may not necessarily precipitate chronic periodontitis, but it could induce disease in the context of other risk variables such as host genotype, ageing, and/or behavioural habits such as smoking. Data suggest that accumulation of molecular, cellular, structural and functional noxious challenges to the integrity of periodontal tissues over time alongside with an individual genetic predisposition increases susceptibility to subgingival bacterial colonization and might result in increased risk of the elderly to chronic periodontitis.[25]

SUMMARY AND CONCLUSION

After the completion of the human genome project and with the technology of cutting-edge, researchers have analysed a larger number of proteins encoded by genes after studying genetic sequences. Genetics is the major determinant of the severity and progression of periodontitis. A number of aspects of the inflammatory and immune responses those suspected to play a role in the development of periodontitis had a clearly defined genetic basis. Comparison of genetic polymorphisms with periodontitis showed a significant use of genetic determinants in periodontitis. In the diagnosis and treatment of periodontitis use of information and technology should be based on clinical utility of genetic information rather than the basis of concepts. Sufficient number of cases and controls with the controls exhibiting clear association between polymorphisms and periodontitis. The choice of candidate genes must be identified and represented in the range of effect and the risk attributable to the genetic variation.[6] Nowadays genome wide association studies using Single nucleotide polymorphism or microsatellite polymorphism have become possible due to the development of single nucleotide polymorphism typing which is cost effective in nature. Single nucleotide polymorphism is a valuable tool for identifying disease alleles for periodontitis.[26]

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