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RESEARCH ARTICLE

ROLE OF INTERLEUKIN-1 POLYMORPHISM IN PERIODONTAL DISEASE

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ABSTRACT

Periodontitis is defined as an disease of supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, gingival recession or both. The etiology of periodontitis is gram negative anaerobes but multifactorial factors may play a role in etiopathogenesis of periodontal destruction. Among various risk factors, genetic factors play a major role. In regulating the different signalling protein involved in periodontal tissue homeostatis. The most important protein molecules involved in periodontal tissue homeostasis are cytokines. Cytokines are small molecular protein, signalling molecules involved in regulation of various cell membranes. So among cytokines the proinflammatory cytokines like IL-alpha, IL-beta, TNF-alpha plays a major role in periodontal destruction. So the genes regulating the synthesis and secretion of these cytokines might determine the progression of the periodontal disease.

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INTRODUCTION

A variety in the DNA arrangement that happens in a population with a recurrence of 1 % or higher is named a polymorphism 1. The higher frequency in the populace proposes that a polymorphism is actually happening, with either an unbiased or advantageous impact. Polymorphisms can likewise be of at least one nucleotide changes, much the same as transformations. A polymorphic variation of a quality may prompt to the irregular expression or to the or to the generation of a strange type of the quality; this may bring about or be related with disease 2.

Types of Polymorphism

- Single nucleotide polymorphism
- Variable number of tandem repeats
- Restriction fragment length polymorphism

Single nucleotide polymorphism: SNPs are DNA sequence variations that result from alteration of a single nucleotide.Some SNPs are population-specific. SNPs in these genes do not result in the amino-acid substitution but can alter the gene function or/and alter gene expression 3. More than 10 million single-nucleotide polymorphisms (SNPs) have been identified in the human genome 4. A single genetic variation may play only a limited or moderate role in common diseases, but it can have important interactions with other genetic variations or environmental factors 5.Most of the genetic research in oral disease has focused on genetic polymorphisms that play a role in immune response, tissue destructive process, or metabolic mechanism. In some situations, genetic polymorphisms may cause a change in protein or its expression, possibly resulting in the alterations in innate and adaptive immunity and may thus be deterministic in disease progression. On other hand, genetic polymorphisms shall act like a protector or a destructive factor for a disease 6.It is thought that SNP analysis will facilitate in identifying multiple genes associated with periodontitis as a genetic markers. By acting as genomic markers, SNPs can aid in clarifying the risk factors for complex diseases 3. The SNPs in TRAF1 gene was associated with the aggressive periodontitis (AgP) and the MMP9 gene was associated with the chronic periodontitis (CP). Suzuki et al. investigated the associations between 637 SNPs in 244 genes related to systemic diseases and severe periodontitis on large scale. They reported that the SNPs in the GNRH1, PIK3R1, DPP4, FGL2 and CALCR genes are genomic markers for severe periodontitis 7.Some study did not find the association between the polymorphism of proinflammatory genes and periodontitis in different races for example, in South Indian populations IL beta gene polymorphism associated to be found in many races like

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Caussians and Africans but these polymorphism were not associated to be found in these articles 8.

Variable number of tandem repeats: VNTR stands for variable number of tandem repeats .A variable tandem repeat is a short sequence of DNA that is repeated in a head-to-tail fashion at a specific chromosomal locus. Tandem repeats are interspersed throughout human genome. Some sequences are found only at one site single locus in the human genome. For many tandem repeats, the number of repeated units vary between individuals. Such loci are termed variable number tandem repeats . One VNTR in humans is 17 bp sequence of DNA repeated between 70 & 450 times in the genome. The total number of base pairs at this locus could vary from 1190 to 7650 9.For example VNTR polymorphism were found to be associated with IL-1 alpha 10,11.

Restriction fragment length polymorphism: Restriction fragment length polymorphism referred as RFLP, is a technique that exploits variations in the homologous DNA sequences. It refers to a difference between the samples of homologous DNA molecules from differing locations of restriction enzyme sites, and related laboratory technique by which these segments are illustrated. In RFLP analysis, DNA sample is broken into pieces and (digested) by restriction enzymes and resulting restriction fragments are separated according to their lengths by gel electrophoresis. Although now widely obsolete due to rise of inexpensive DNA sequencing technologies, RFLP analysis was first DNA profiling technique inexpensive enough to see the widespread application. RFLP analysis was an important tool in the genome mapping, localisation of genes for genetic disorders, determination of risk for disease, and the paternity testing. If researchers were trying to initially determine chromosomal location of a particular disease gene, they would analyse the DNA of members of a family affected by the disease, and look for RFLP alleles that show a similar pattern of inheritance as that of the disease.Once a disease gene was localized, the RFLP analysis of other families could reveal who was at risk for the disease, or who was likely to be a carrier of the mutant gene12.

Nature of association studies with periodontitis: Genes contributing to common, complex diseases such as periodontitis have proven more difficult to isolate. When multiple, perhaps many, genes act with environmental factors to contribute to a disease liability, it's difficult to formulate the disease models. In absence of specific genetic models, the etiology of complex diseases is often conceptualized as due to multiple factors, several genetic loci interacting with each other to produce an underlying susceptibility, which in turn interacts with additional environmental factors to produce an actual disease state. For complex traits, such as bipolar disorder , diabetes, obesity, and oral–facial clefting, traditional parametric linkage analysis has produced either negative results orplethora of weak, positive results not easily replicated. Theoretical research suggests the several reasons for ambiguity of the linkage results in these cases. First, if a disease gene is necessary or sufficient to cause a disease, but rather is an`modifier gene' that elevates a non zero baseline risk, conventional parametric linkage analysis may not detect the gene 13-18. Second, if relative contribution of a gene to a disease phenotype is small, the disease susceptibility allele raises the risk by a factor of <2, linkage analysis using affected sibling pairs will not be powerful enough to detect the gene, given realistic sample sizes 19. Thus, linkage analyses may not be a useful strategy to detect modifier genes or genes that exert the small effects precisely those genes which may be operating in chronic periodontitis and many other complex disorders. Consequently, attention has shifted away from model dependent parametric linkage analysis to model free, nonparametric association analysis as alternative means of locating the disease susceptibility genes, especially since association studies can sometimes detect weaker effects than can linkage analysis 20. Two types of association analysis are commonly employed in genetic studies: population based and family-based 21. The population-based approach utilises a standard case control design, in which the marker allele frequencies are compared between cases (affected individuals) and controls (either unaffected individuals or individuals randomly chosen from population). When a positive association is found, several interpretations are possible. They are

- The associated allele itself is the disease-predisposing allele;
- The associated allele is in the linkage disequilibrium with actual disease-predisposing locus;
- The association is due to population stratification;
- The association is a sampling, or statistical, artifact.

The first two interpretations represents the alternative hypotheses of interest in a gene mapping context. In the first case, the marker itself is the disease-susceptibility locus. This outcome is rationale behind candidate gene studies, in which alleles of genes being tested have some a priori expectation of being directly involved in the disease process. Evidence of a positive association can be followed up by investigations to establish the functional role. In the second case, the associated allelic polymorphism itself does not play a functional role in causing disease, but rather polymorphism is in close physical proximity to the gene that does contribute to susceptibility. A classic example is the human leukocyte antigen (HLA) system, in which various HLA haplotypes are associated with number of diseases, includes insulin dependent diabetes mellitus, rheumatoid arthritis, and ankylosing spondylitis 22. There is currently considerable attention being directed towards clinical use of the disease-associated genetic polymorphisms for genetic testing. However, most initial reports of these polymorphisms have not been replicated 23. reinforcing the need to develop acceptable criteria to determine the clinical validity of such reports 24. Fortunately, new approaches hold promise to identify the significant disease associations that may be important for understanding susceptibility for complex diseases. There is currently great interest in comprehensively characterizing human SNPs to facilitate evaluation of their role in common diseases.

Interleukin-1alpha Polymorphism: Shirodaria et al have taken the research by attempting an assessment of the functional effect of the 'composite genotype' in terms of the quantity of interleukin-1α protein in gingival crevice fluid of severe chronic periodontitis patients 25 .These researchers found that allele 2 at position −889 of the interleukin-1α gene (one of the alleles linked with susceptibility to periodontitis by Kornman et al was associated with a fourfold increase in interleukin-1α as determined by enzyme linked immunoassay 26. This technique does not demonstrate activity but merely protein presence or absence and would not differentiate protein bound to receptors or inhibitors. Furthermore, it's feasible that

inhibitors of proinflammatory cytokines may concomitantly be produced to dampen this effect. The authors noted the reduced levels of interleukin-1α protein in severe smokers regardless of genotype but this may be related to the reduced gingival crevice fluid noted in smokers 27. This is a useful study given that it addresses the in vivo effects of polymorphism on interleukin-1 protein quantities, However, differences in local gingival crevice fluid production among patients, sites, smokers, and across gender add considerable variance to such a study, and these factors should be considered in the interpretation of the data.

Interleukin-1beta Polymorphism: Studies on the 'composite genotype' reported by Kornman et al and aggressive periodontitis have had similarly mixed results. For example, the studies by Diehl et al actually found that allele 1 rather than allele 2 of the interleukin-1β +3953 exhibited polymorphism 28,29. Furthermore, Parkhill et al investigated the frequency of polymorphisms in the genes encoding interleukin-1β in Caucasians with aggressive periodontitis compared to controls 30. The frequency of interleukin-1β genotypes homozygous for allele 1 of the interleukin-1β + 3953 SNP was found to be significantly increased in the aggressive periodontitis patients (P = 0.025). Upon stratification for smoking status, a noteworthy distinction was found in the interleukin-1β genotype appropriation between forceful periodontitis smokers and control smokers (F-correct test, P = 0.02), however not between forceful periodontitis nonsmokers and control nonsmokers. The interleukin-1β 1/1 genotype happened at a higher recurrence in forceful periodontitis smokers (chances proportion = 4.9) than in control smokers. These discoveries of Parkhill et al as opposed to those of Hodge et al found that an interleukin-1β genotype in blend with smoking is related with forceful periodontitis31.

Polymorphism in interleukin-1 receptor antagonist: Early onset periodontitis (EOP), currently proposed, which is a replacement of the term aggressive periodontitis (Armitage et al. 1999), represents an inflammatory disease with pathogenic features, such as onset in juvenile or early adult years and aggressive clinical course characterized by localized or generalized loss of alveolar bone (Ranney 1992). In one of the study only the most common alleles, corresponding to 4 and 2 repeats respectively, had been identified. These alleles are designated 1 and 2, respectively (Tarlow et al. 1993). There was no significant difference in the IL-1RA genotype distributions between EOP patients and controls (p=0.110) .There was a significant difference in allele frequency (p=0.028). The OR for allele 1 versus allele 2 in EOP was 1.9, 95%CI=1.4,2.5. There is difference in the frequencies of theIL- 1 RA genotype and allele distribution between EOP smokers and control group.

Conclusion

Thus the polymorphism of various signaling molecules of inflammatory pathway might play a significant role in periodontal disease.Further studies of large sample size and cross checking multiple polymorphism in different races is required to establish the genetic role in periodontal disease.

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