

TNF – α Polymorphism In Periodontitis: A Review

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Abstract: A gene is the molecular unit of heredity of a living organism. A gene is said to be polymorphic if multiple allele occupies that gene's locus within a given population. Tumor necrosis factor (TNF) is a pro-inflammatory adipokine involved in systemic inflammation and arouse acute phase reaction. Large amounts of TNF- α are released in response to lipopolysaccharides, other bacterial products, and Interleukin-1 (IL-1). TNF- α maps to chromosome 6p21.3, spans to about 3 kilobases and contains 4 exons. Single nucleotide polymorphisms (SNP) in the gene encoding TNF α are largely studied. Transcription activity and levels of TNF- α is dependent on the single nucleotide polymorphisms at the various intron and exon positions. This article sheds light on the many conditions associated with TNF- α polymorphism in relation to periodontitis and other systemic diseases in brief. [Jose K NJIRM 2015; 6(6):79-82]

Key Words: TNF- α , polymorphism, allele, genotype

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Introduction: Cytokines are a large group of secreted proteins with varied structures and functions, which regulate and harmonize many activities of the cells of innate and adaptive immunity. Adipokines are cell signaling proteins secreted by the adipose tissue. Pro-inflammatory cytokine is a cytokine which promotes systemic inflammation. Tumor necrosis factor(TNF) is a pro-inflammatory adipokine. Other pro-inflammatory cytokines are IL-1, IL-6,IL-8, IFN- γ . A gene is the molecular unit of heredity of a living organism. A gene is said to be polymorphic if multiple allele occupies that gene's locus within a given population.

TNF- α

Tumor necrosis factor alpha also previously 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, although it can be produced by many other cell type such as CD4+ lymphocytes, natural killer cells(NK cells), neutrophils, mast cells, eosinophils, and neurons.¹

TNF- α is primarily produced as a 212-amino acid-long type II transmembrane protein structured as stable homotrimers.^{2,3} From this membrane-integrated type of the soluble homotrimeric cytokine (sTNF) is released through proteolytic cleavage by the metalloprotease TNF alpha converting enzyme (TACE, also called ADAM17).⁴ The secreted and the membrane bound forms are biologically active, although the precise functions of each is controversial. However, both forms do have overlapping and distinctive biological activities.⁵

Large amounts of TNF- α are released in response to lipopolysaccharides, other bacterial products, and Interleukin-1 (IL-1). In the skin, mast cells appear to be the principal source of pre-formed TNF- α , which can be released upon inflammatory stimulus (e.g., LPS).⁶

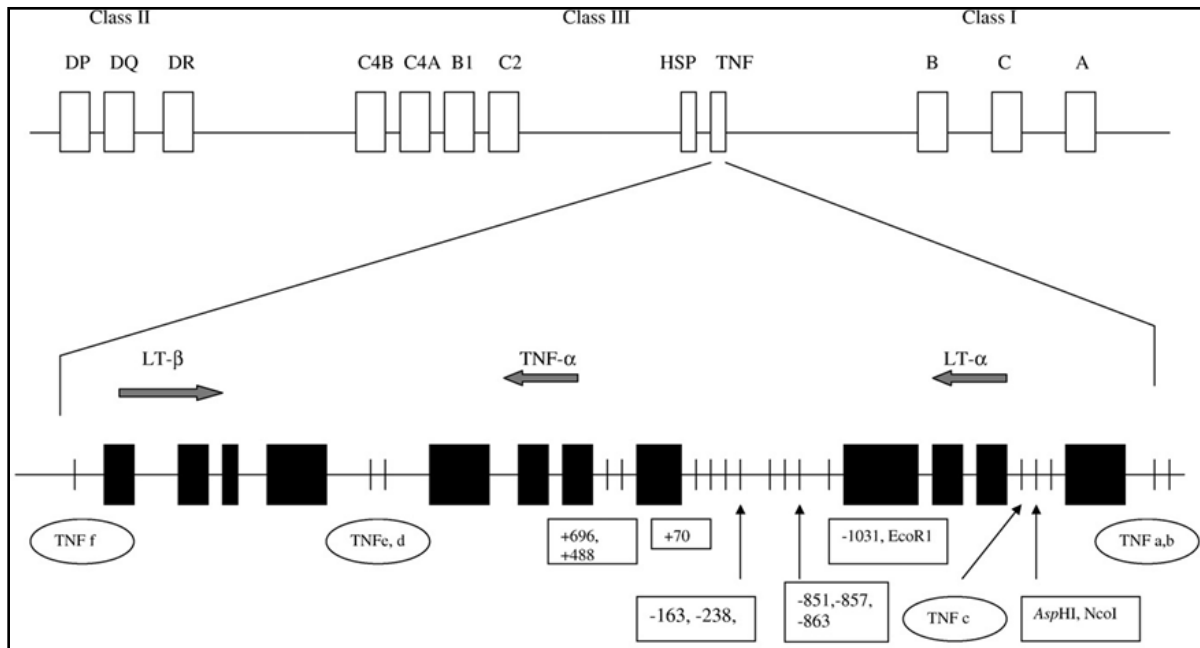
TNF Receptors & Cell Signaling: TNF- α is recognized by the TNF receptor family, a constituent of the cytokine receptor family. Upon contact with their specific ligand, TNF receptors also form trimers, their tips fitting into the grooves produced between TNF monomers. This binding causes a conformational change to occur in the receptor, leading to the dissociation of the inhibitory protein from the intracellular death domain. This dissociation helps in the adaptor protein TRADD (TNF Receptor Associated Death Domain) to bind to the death domain, serving as a platform for subsequent protein binding. Following the TRADD binding, activation of nuclear factor-*kappa* beta (NF- κ β) takes place leading to the activation of MAP Kinase (MAPK) pathways that which finally results in the induction of cell signaling.

The many and often-conflicting effects mediated by the above pathways indicate the existence of extensive cross-talk. Activated caspases cleave several components of the NF- κ β pathway, including catalytic regulatory subunits of the inhibitor of NF- κ β kinase (IKK) complex, Receptor Interacting Protein (RIP), and the subunits of NF- κ β itself. Other factors, such as the cell type, simultaneous stimulation of other cytokines, or the quantity of reactive oxygen species (ROS) can shift the balance in favor of one pathway or another. Such complex signaling ensures that, whenever TNF- α is released, various cells with immensely varied

functions and conditions can all respond appropriately to inflammation.^{7,8}

TNF - α Polymorphism: The cloning of the human TNF gene (*TNFA*) was accomplished in 1985.⁹ It maps to chromosome 6p21.3, spans to about 3 kilobases and

contains 4 exons. The last exon codes for over 80% of the secreted protein.¹⁰ Single nucleotide polymorphisms (SNP) in the gene encoding TNF α are largely studied in the promoter region at positions 1031, 863, 857, 376, 308, 238 and also in the coding region of the first intron at position +489.



Adopted from *Biochimica et Biophysica Acta* 1792 (2009) 163–172: Tumor necrosis factor alpha –308 gene locus promoter polymorphism: An analysis of association with health and disease^[11]

Common Sites where polymorphism is seen are :-1031 (T→C), -863 (C→A), -857 (C→A), -851 (C→T), -419 (G→C), -376 (G→A), -308 (G→A), -238 (G→A), -162 (G→A), and -49 (G→A).

The 5' flanking region is a region of DNA that is adjacent to the 5' end of the gene. It has been found that in Japanese patients with early onset periodontitis there is no significant association between polymorphisms in the 5'-flanking region of the TNF- α gene and susceptibility to early onset periodontitis.¹² It has been shown that carriers of the TNF- α 308 A allele appeared to have superior transcription activity and produced higher levels of TNF- α as compared to carriers of G allele at the site.^{13,14}

However contradictory studies show that there is no indication that carriage of an TNF- α A allele at positions 376, 308, 238 and 489 are associated with increased susceptibility to periodontitis.¹⁵ Studies also show that no differences in distribution of TNF alleles of the -238, -308, or +252 gene polymorphisms were

observed between patients and controls or between patients with different disease severity. However, the level of TNF- α production by oral polymorphonuclear neutrophils correlated with the TNF- α ⁻³⁰⁸ genotype in patients with adult periodontitis and increased production was associated with patients with the A allele.¹⁶

When cytokine production was examined in patients according to disease severity, an association between the A allele and increased production was observed only in patients with advanced disease. Allele C of IL-1 β +3954 and allele A of TNF- α -308 appears to be risk factors for Chronic periodontitis individuals.¹⁷ Several case-control studies in both Caucasians and non-Caucasians have investigated genetic polymorphisms in the TNF- α gene as supposed risk factors for periodontitis. The level of TNF-alpha production by oral Polymorphonuclear neutrophil correlated with the TNF-alpha 308 genotype in patients with adult periodontitis, with increased production found in patients with the T1,2 genotype .When cytokine

production was examined in patients according to disease severity, an association between the T1,2 genotype and increased production was observed only in patients with advanced disease). However further studies are required to determine if the TNF genotype is a risk factor for severity of disease in adult periodontitis.¹⁶

Few studies have also shown no significant differences in the frequency of the alleles and the genotypes G/G, G/A, and A/A among groups.¹⁸

Tnf-A 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.¹⁹ The TNF-308A was shown to be associated with SLE.²⁰

In RA, among patients with 238 A allele, the severe form of RA was more frequent^{21,22}, 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.²³

Biopsies from rejecting kidney or heart transplants show the presence of an inflammatory infiltrate of cells capable of producing TNF. Kidney, heart and liver transplant recipients have revealed an association between TNF α -308 polymorphisms and acute rejection. Death of heart transplant recipients as a consequence of irreversible acute rejection of their graft is exclusively confined to those of the TNF α -308A genotype.

TNF inhibition: TNF promotes the inflammatory response, which, in turn, causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis, hidradenitis suppurativa and refractory asthma. These disorders are sometimes treated by using a TNF inhibitor. This inhibition can be achieved with a monoclonal antibody such as infliximab (Remicade), adalimumab (Humira) or certolizumab pegol (Cimzia), or with a circulating receptor fusion protein such as etanercept (Enbrel).

Conclusion: TNF- α has been shown to be an important pro-inflammatory cytokine in disease and health. The

TNF polymorphisms are found in a region of great polymorphic variation and they are in linkage disequilibrium with the HLA genes and with each other. Because of differences in the distribution of HLA alleles wide variations in associations between TNF polymorphisms are seen. Given the biological regulation of TNF- α and its role in the inflammatory process, it is surprising that the genetic influences on cytokine production have much influence on disease processes, progress and their outcome. The associations between TNF- α genotype and disease are not complete as suggested by different conflicting studies SNP's in certain promoter regions in the TNF- α gene have been able to demonstrate a aggravated inflammatory response. Therefore it is of paramount importance that genetic studies related to TNF- α polymorphisms need to further conducted and evaluated to fully understand the mechanics behind the polymorphisms and gene expressions.

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