Impact of the -308 TNF promoter polymorphism on the transcriptional regulation of the TNF gene: relevance to disease

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Abstract: A biallelic G (TNF1 allele) to A (TNF2 allele) polymorphism 308 nucleotides upstream from the transcription initiation site in the tumor necrosis factor (TNF) promoter is associated with elevated TNF levels and disease susceptibilities observed in human subjects. The TNF2 allele is strongly associated with the high-TNF-producing autoimmune MHC haplotype HLA-A1, B8, DR3, with elevated serum TNF levels and a more severe outcome in infectious diseases, such as cerebral malaria. A number of groups have set out to determine whether the -308 polymorphism could affect transcription factor binding and hence influence TNF transcription and expression levels. Although some studies have failed to show any functional difference between the two allelic forms, others have shown that the -308 polymorphism effected transcription factor binding to the region encompassing -308, with the region in the TNF2 allele showing altered binding characteristics. The -308 polymorphism also has been found by some groups to be functionally significant in reporter gene assays in Raji B cells, Jurkat T cells, and U937 pre-monocytic cells. Up to fivefold differences can be measured between TNF1 and TNF2 allelic constructs when the TNF 3′UTR is present, indicating a role in the expression of the polymorphism. Although controversial, the majority of the data support a direct role for the TNF2 -308 allele in the elevated TNF levels observed in TNF2 homozygotes and HLA-A1, B8, DR3 individuals. Elevated TNF levels due to the -308 polymorphism may alter the immune response such that it confers susceptibility to certain autoimmune and infectious diseases. *J. Leukoc. Biol.* 66: 562–566; 1999.

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INTRODUCTION

Transcriptional regulation of the tumor necrosis factor (TNF) gene is essential to avoid the deleterious effects of inappropriate or excessive synthesis of TNF. As such, genetic variations located within the TNF promoter could potentially affect TNF transcription and expression, and hence play a contributing role in certain diseases associated with elevated TNF expression. Several polymorphisms have been identified in the TNF gene promoter that may be responsible for the variations in TNF levels observed between individuals of different HLA haplotypes [1–4].

Wilson et al. [1] identified a biallelic G to A transition polymorphism located at position -308 in the TNF promoter, which defined the TNF1 (-308G) and TNF2 (-308A) alleles. The less common TNF2 allele is strongly associated with the MHC haplotype HLA-A1, B8, DR3 [5], which is, in turn, associated with high TNF production [6–9] and autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM) [8] and systemic lupus erythematosus (SLE) [10]. Furthermore, TNF2 homozygous individuals have higher circulating TNF levels than TNF1 homozygotes [11]. In addition, carriage of the TNF2 allele is associated with a worse outcome in infectious diseases such as cerebral malaria [12] and leishmaniasis [13], characterized by high levels of TNF [14, 15]. These observations are suggestive of a role for the TNF -308 polymorphism in altering TNF expression levels and possibly acting as a genetic susceptibility factor in certain MHC-associated autoimmune and infectious diseases.

Single-nucleotide polymorphisms located within other gene promoters have been demonstrated to affect transcription factor binding and hence gene expression [16–18]. The -308 polymorphism could potentially effect the cell-type and stimulus specific regulation of TNF synthesis at the transcriptional level. A genetic propensity to produce elevated TNF levels, due to the presence of the -308A polymorphism, may alter the course of an immune response such that an individual has an increased risk of disease.

A number of groups have carried out investigations into the functional significance of the TNF -308 polymorphism to determine, first, whether this promoter polymorphism effects transcription by altering transcription factor binding to the TNF gene promoter, and second, the mechanisms involved, knowledge of which could be utilized to possibly negate the effects of the -308A polymorphism on TNF expression. Finally, recent studies into the cell-type and stimulus-specific expression of the -308 polymorphism have been carried out to determine

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conditions under which the polymorphism is most functionally significant because this may help identify where in the disease process differential TNF expression may have the greatest effect and hence the role that the -308 polymorphism plays in diseases associated with the TNF2 allele.

EFFECT OF THE -308 POLYMORPHISM ON TRANSCRIPTION FACTOR BINDING

TNF synthesis is tightly regulated at the level of gene transcription. The -308 TNF promoter polymorphism is located in a region of the TNF promoter not originally characterized as a transcription factor binding element important in TNF gene transcription. After the identification of the -308 polymorphism, it was important to determine whether the region contributed to the transcriptional activity of the TNF gene and it was subsequently shown that the -308 element was indeed able to bind nuclear proteins and modulate transcription [19].

Three groups have reported that the -308 TNF polymorphism may differentially affect binding transcription factors from different cell types [20–22]. To determine whether the -308 polymorphism was able to bind transcription factors and to affect their binding, Kroeger et al. [20] used a 39-bp region of the TNF promoter encompassing the -308 G/A polymorphism from nucleotides -323 to -285, relative to the transcription start site, to assay for its ability to bind nuclear factors present in T (Jurkat) and monocytic cell lines (U937) known to express TNF. Using the electrophoretic mobility shift assay (EMSA), multiple nuclear factors displayed binding activity for the 39-bp sequence representing the TNF1 allele (-308G) to form four major complexes (B, C, D, and DI), suggesting that this region may play a role in TNF transcription. More importantly, the G to A change resulted in differential binding of nuclear factors, with the -323 to -285 sequence from the TNF2 (-308A) allele preferentially binding an additional protein to form a fifth complex, E [20]. In addition, the binding of complex E to TNF2 appeared to have an effect on the differential binding activities of common complexes B, C, D, DI, and DII binding to both TNF1 and TNF2 [20]. In support, Wu and McClain [21] reported that the -308 polymorphism affected transcription factor binding to the -347 to -269 region of the TNF1 and TNF2 promoters.

Wilson et al. [22] also demonstrated that the region surrounding the -308 site bound nuclear proteins by DNase I footprinting. However, they were unable to show that -308 itself was involved in influencing transcription factor binding in EMSA with the use of the -345 and -226 region as a probe. One major complex was apparent but no differences were seen when comparing the two alleles. These different observations may be due to the effects of additional proteins binding to the larger DNA fragment (119 bp) used in EMSAs by Wilson and co-workers and occluding any differences in EMSA profiles.

In summary, it is now thought that the G to A nucleotide change at -308 alters a transcription factor binding site, affecting the binding activities of other proteins binding to the -323 to -285 composite element, resulting in the formation of an altered composite transcriptional element.

EFFECT OF THE -308 POLYMORPHISM ON TRANSCRIPTION

Transcriptional control plays a major role in regulating TNF gene expression [23, 24]. Economou et al. [25] have established by deletion analysis that the TNF promoter region between -479 and -295 contains sequences that modulate transcription of a TNF/luciferase reporter gene. In addition, Fong et al. [26] demonstrated that the region between -351 and -280 makes a modest contribution to phorbol myristate acetate (PMA)-induced transcription. Therefore, before the discovery of the -308 polymorphism, the region encompassing -308 was thought to play a role in TNF transcription.

Single-nucleotide promoter polymorphisms associated with certain diseases and expression phenotypes have been identified in many other gene promoters [17, 27, 28] and in some cases have been shown to affect gene transcription and expression [16, 18, 29]. Determining whether a particular polymorphism is directly responsible for a phenotype and disease association is difficult when the polymorphism is within the MHC region, due to strong linkage disequilibrium between alleles across the MHC [22, 30]. Therefore, associations between MHC haplotypes and TNF phenotypes may not be due to the polymorphisms within the TNF gene itself, but rather to variation in a linked gene that directly or indirectly regulates expression of TNF. Thus, it is important to show a direct functional effect for the -308 polymorphism. Utilizing promoter-reporter gene constructs enables the consequence of the -308 polymorphism to be determined independently of other linked genes. To investigate whether the -308 polymorphism could influence TNF gene transcription and expression, a number of studies have been undertaken to determine whether the transcriptional activity of the two allelic forms of the TNF promoter are different in reporter gene assays.

Various groups have performed reporter gene studies using -308 allelic TNF promoter constructs. Stuber et al. [31] found no significant difference in the transcriptional activity of the TNF1 and TNF2 allele promoters in PMA-stimulated Jurkat cells and a lipopolysaccharide (LPS)-induced macrophage line. Kroeger et al. [20] also found that activity of TNF1 and TNF2 allelic constructs was indistinguishable in Jurkat and U937 cells when the 3′UTR of TNF was not present. In contrast, three studies [21, 22, 32] have demonstrated that TNF2 promoter constructs have increased transcriptional activity compared to TNF1, in the absence of the 3′UTR in unstimulated cell lines including U937.

The consequence of the -308 polymorphism has also been assessed in the context of the TNF 3′UTR. Brinkman et al. [33] found no significant difference in the transcriptional activity, in Jurkat or Raji cells, of the TNF1 and TNF2 promoter regions when the TNF 3′UTR and the downstream NKκB site was present. In contrast, Kroeger et al. [20] showed that in their experiments differential expression occurred only when the 3′UTR (which did not include the downstream NKκB site) was present (**Fig. 1**). The TNF2/UTR reporter gene construct had two- to threefold greater expression than the TNF1/UTR construct in PMA-stimulated Jurkat and U937 cells but not in unstimulated cells [20]. Interactions between additional tran-

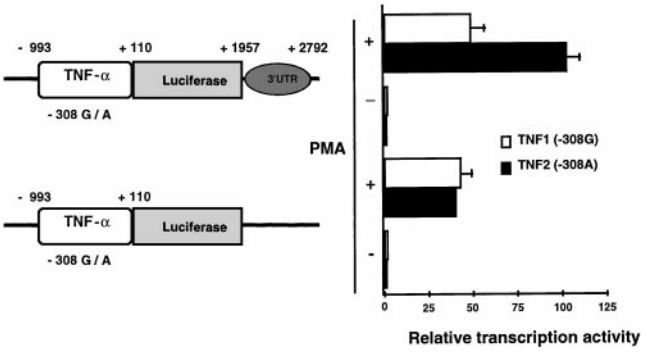


Fig. 1. The -308 polymorphism influences transcription of the TNF promoter in U937 cells. (A) TNF1 (-308G) and TNF2 (-308A) promoter/luciferase reporter gene constructs with or without the TNF 3′UTR were transfected into U937 cells. Cells were either incubated untreated or PMA (20 ng/mL) stimulated for 24 h and assayed for luciferase activity. Bars represent the mean (± SEM) of three independent transfections.

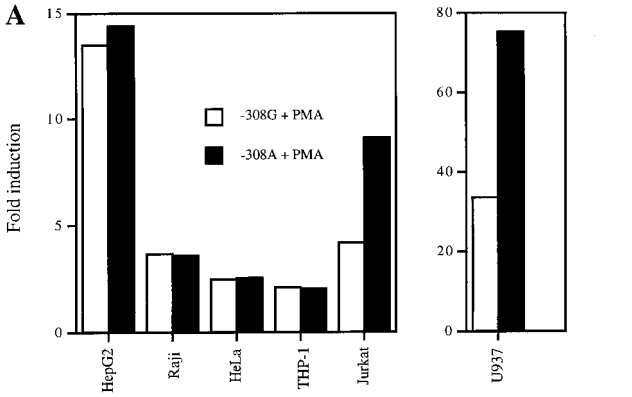
scription factors binding outside the -323 to -285 region of the TNF promoter and the -308 element are thought to influence the function of the -308 polymorphism, such that its expression is only observed in stimulated cells and only in the context of the TNF2 promoter and 3′UTR. We propose that the TNF 3′UTR interacts with the -308 element at a transcriptional level, to influence TNF promoter-driven reporter gene expression *in vitro* and presumably TNF gene expression *in vivo*.

It is unclear why data from the different groups are contradictory, but a number of issues need to be considered. One difference may be in the behavior or identity of the cell lines used by the different groups. Differences in the extent of TNF upstream promoter and 3′UTR sequences present may have a major influence on expression. Because the TNF promoter is complex and the context within which the transcription elements operate has been shown to influence results of reporter gene studies of the TNF gene [34], it is probable that reporter construct differences may lead to quite different responses in terms of expression of the -308 polymorphism. Another source of variation may result from the use of different reporter genes (chloramphenicol acetyl transferase or luciferase) that may contain cryptic regulatory elements that serve to enhance or mask full expression of the -308 polymorphism. Overall the data suggest that under certain circumstances the -308 polymorphism, by affecting transcription factor binding, can influence TNF gene transcription.

CELL-TYPE AND STIMULUS-SPECIFIC EXPRESSION OF THE -308 POLYMORPHISM

Several investigators have shown that different *cis*-acting elements and *trans*-activating proteins are involved in the cell-type and stimulus-specific regulation of TNF transcription [24, 34–38]. Given the controversy surrounding the data concerning the functionality of the -308 polymorphism, and considering the possible explanations for the differing results, we recently investigated the effects of different cellular environments and different stimulation conditions on expression of the -308 polymorphism. Using the TNF/luciferase/3′UTR constructs (see Fig. 1), we investigated the cell-type specific expression of the -308 polymorphism and revealed that it was functional in Jurkat T cells and U937 pre-monocytic cells and not in HeLa (epithelial), HepG2 (hepatoma), Raji (B cell), or THP-1 (pro-monocytic) cells [39]. In PMA-stimulated Raji, HeLa, HeG2, and THP-1 cells, there was no significant difference in the expression of the TNF1 and TNF2 promoter/3′UTR reporter constructs (**Fig. 2A**), despite the presence of the -323 to -285 TNF promoter region binding activities in these cell lines [20]. The results suggested that, although the proteins involved in binding to the -308 region are ubiquitous, this, in itself, was not sufficient to get expression of the -308 phenotype. Additional cell-type specific transcription factors binding outside the -323 to -285 region, possibly in the TNF promoter or 3′UTR, may be required for the differential expression seen in Jurkat and U937 cells.

We also were interested in whether the effect of the -308 polymorphism on TNF transcription in U937 cells was also different in response to different stimuli [39]. Our data (Fig. 2B) indicate that the differential transcriptional activities of the TNF1 and TNF2 promoters are greatest after treatment of U937 cells with combinations of PMA plus retinoic acid (4.5-fold difference). Treatment with TNF, on the other hand, showed no difference in activity between the TNF1 and TNF2 alleles. These results may suggest that the -308 polymorphism has its



B

Stimulus	-308G	-308A	Fold difference
PMA	33.47	75.06	2.24
PMA + retinoic acid	51.17	233.33	4.56
PMA + LPS	45.98	131.53	2.86
LPS	0.48	1.35	2.81
Retinoic acid	1.38	4.65	3.37
IFN-γ	1.03	1.08	1.05
TNF	4.52	4.41	0.98

Fig. 2. Cell-type and stimulus-specific expression of the TNF -308 polymorphism. (A) Raji, HeLa, HepG2, THP-1, Jurkat, and U937 cell lines were transfected with the TNF1 (-308G) or TNF2 (-308A) forms of the TNF promoter/luciferase/3′UTR reporter gene constructs, incubated uninduced or induced with PMA (20 ng/mL) for 24 h and assayed for luciferase activity. For each cell type, the results are the fold induction after PMA activation. The representative set of data from one experiment is shown. (B) The TNF1 and TNF2 constructs were transfected into the cell lines as indicated and left unstimulated or stimulated with either PMA (20 ng/mL), PMA plus retinoic acid (500 nM), PMA plus LPS (1 μg/mL), LPS, retinoic acid, interferon-γ (100 units/mL), or recombinant human TNF (5 ng/mL) for 24 h.

greatest effect on TNF expression in mature macrophages because there appears to be a correlation between degree of differentiation of our U937 cells and differential activity [39]. These results have a bearing on the conflicting results outlined above. It may be that different cell lines under different culture environments may provide one explanation for the different results. It appears that, at least under some conditions, the -308 polymorphism will affect expression of TNF.

SUMMARY AND CONCLUSIONS

A number of studies have now demonstrated that the -308 polymorphism affects transcription factor binding and enhances transcription from the TNF2 promoter in lymphocytic and monocytic cell lines after stimulation with various inducers of TNF synthesis. In addition, the TNF 3′UTR was found under some conditions to be important for the function of the -308 polymorphism in TNF2 transcription and represents a novel role for the TNF 3′UTR in transcriptional regulation of the TNF gene.

Recent data indicate that the -308 polymorphism has the most significant effect on TNF transcription in macrophages [39]. TNF is predominantly produced by cells of the monocytic-macrophage lineage, thus a fivefold increase in TNF transcription could lead to a dramatic change in circulating TNF levels. Diseases associated with high TNF levels, such as IDDM and malaria, involve a critical role for macrophages and monocytes in the disease process. For instance, it has been demonstrated that elevated macrophage-derived TNF levels precede and accompany the onset of IDDM and, along with dendritic cells, are the first and major producers of TNF in pancreatic islets [40, 41]. It is possible that overproduction of TNF by these myeloid cells may play a role in the initiation and/or development of diabetes. Thus, inappropriate and excessive production of TNF due to the -308A polymorphism may play a role in the development of TNF2-associated autoimmune diseases, such as diabetes. The -308A polymorphism may act as a genetic susceptibility factor driving high TNF expression, which could subsequently skew the immune response toward a more deleterious outcome.

In summary, the association between the -308A TNF promoter polymorphism and susceptibility to various diseases [8, 12, 13, 42] is suggestive for the polymorphism being functionally relevant *in vivo*. The results concerning the transcriptional changes due to the -308 TNF promoter polymorphism provide a possible explanation for the associations observed between TNF2 homozygotes or individuals carrying the autoimmune haplotype HLA-A1, B8, DR3, and elevated TNF levels. In addition, it is suggestive that the -308 polymorphism may contribute to associations between certain HLA haplotypes and disease.

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