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Genetic Polymorphisms at TNF-Alpha Receptors Associated some Autoimmune Diseases and Response of Anti-TNF Biologics: Review

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Abstract

Some genetic factors are not only involved in some autoimmune diseases but also interfere with their treatment, Such as Crohn's disease (CD), Rheumatoid Arthritis (RA), Psoriasis (PS) and ankylosing spondylitis (AS). Tumor Necrosis Factor (TNF) is a most important pro-inflammatory cytokine, which has been recognized as a main factor that participates in the pathogenesis and development of autoimmune disorders. Therefore, TNF could be a prospective target for treating these disorders, and many anti-TNF were developed to treat these disorders. Although the high efficacy of many anti-TNF biologic medications, the Patients' clinical responses to the autoimmune treatment showed significant heterogeneity. The TNF receptors classified into two TNF receptors, namely TNFR1 and TNFR2. These receptors belong to two distinct superfamilies: the TNF-superfamily of ligands (TNFSF) consisting of 19 ligands and the TNF receptor superfamily (TNFRSF) comprising 29 receptors. This review aims to provide an overview of the impact of genetic polymorphism on TNF alpha receptors on the response of patients with some auto immune diseases to anti-TNF biologics. Several single nucleotide polymorphisms (SNPs) recorded in the TNFRs gene on various immune system cells may affect the lower corresponding TNFRs gene expression. The present review summarized the studies that highlighted the role of heterogeneity in varying the response of the auto immune patients. Many researchers indicated SNPs' have an effect on the response of autoimmune patients to treatment with anti-TNF biologic medications, while other studies did not find a correlation. In conclusion, TNF is involved in several diseases such as CD, RA, PS and AS; there was a link between TNFRs polymorphism and non-responsiveness to anti-TNF-α medications.

Keywords: TNF-α, Single nucleotide polymorphism, Biological medications, TNFRs, Anti-TNF.

Introduction

Write The TNF, also known as TNF-alpha or TNFα, is a kind II-transmembrane protein in which the plasma membrane is particularly expressed. It acts as an endotoxin-like substance and has a secreted form, a powerful pro-inflammatory cytokine with diverse functions in different cell types [(1)]. The TNF-α belongs to the TNF/TNFR-superfamily proteins (TNF/TNFR), a group of α superfamily proteins. Researchers later discovered that TNF could be a prospective target for treating some inflammatory disorders like CD, RA and AS [(2-5)].

Macrophages/monocytes mainly induce the TNF, but various cell types also secrete it, like B and T lymphocytes, neutrophils, natural killer cells, mast cells, fibroblasts, and osteoclasts [(6)]. In human tissues, two types of TNF are produced: transmembrane protein (mTNF) and soluble TNF (sTNF). The first one (mTNF) has a molecular weight of 26 kDa with 230 amino acids, expression confined on the cell surface, and functions in transmitting and cell interactions when combined with TNFR2[(7)]. The cellular signaling sequence initiates from outer to inner signaling [(8)]. Conversely, sTNF, with 157 amino acids and a weight of 17 kDa, is a second form of TNF cleaved from mTNF by a special TNF-converting enzyme (TACE) to be released into the blood [(9)].All TNF proteins, including TNF-α, have a structural motif called (TNF-Homological Domain (THD)), with trimeric symmetry. The THD binds to its particular receptors (TNFRs), particularly in its receptor's cysteine-rich domains (CRDs) [(10)]. The heterogeneity of the TNFRs arises from variations of these CRDs, such as TNFR1 (CD120a) and TNFR2 (CD120b) [(11)]. Both sTNF and mTNF made a cellular event after binding to their receptors: TNFR1 is expressed along the major tissues, while the expression of TNFR2 is restricted in neurons, endothelial cells, and immune cells [(12,13)]. The sTNF and mTNF binding sites (of the TNFR1 and 2) are identical in structures, but they have an intracellular structure that can bind to several adaptor proteins [(14)]. Although the TNFRs signaling pathways activate nuclear factor kappa B (NF-κB), which

induces a cell survival response, TNFR1 is also responsible for cell death induction. At the same time, TNFR2 does not possess an intracellular death domain (DD) that allows interactions (Hetero and homo-binding) with another TNFR Associated Factor (TRAF) family [7,15].

Materials and Methods

Data collection and examination

A systematic and exhaustive search has been conducted using the keywords "genetic polymorphism", "TNF-", " TNF- receptors", and "Biological medication" in the PubMed, Google Scholar, and Research portal databases. Subsequently, all the papers have been carefully investigated and presented in the text. All studies that satisfy the inclusion criteria and have been published between 2010 and March 2023 will be included.

Results and Discussion

Signaling Pathway of TNFR

According to Sessler *et al*. (2013) [16], TNFR1 signaling pathways can activate both Mitogen-activated protein kinases (MAPKs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and induce a cell death response. In contrast, TNFR2 cannot stimulate cell death because it lacks a DD, but it can trigger both MAPK and NF-κB activation through TRAF recruitment [16,17].

Both sTNF-α and mTNF-α activate TNFR1, which has DD that interconnects with the "TNFR1 associated death domain (TRADD) adaptor protein [18-19]. After that, the TNFR1 spurs various signaling complexes (I, IIa, IIb, and IIc), responsible for several cellular responses [20,21].

Complex I signaling can induce cell survival, proliferation, immune defense, and inflammation against pathogens. The plasma membrane TNFR1 activates TRADD, which in turn made react with a vast component such as Cellular Inhibitor of Apoptosis Protein 1/2 (cIAP1/2) and Receptor-interacting protein kinase 1 (RIPK1) [22]. The linear ubiquitin chain assembly complex (LUBAC) and TRAF2/5 [23].Complexes II (IIa, IIb, and IIc); are cytoplasmic aggregates, complex IIa and IIb comprise pro-Caspase-8, TRADD, TRAF2, RIPK1, cIAP1/2, and the FAS-associating death domain (FADD). The complex build-up (especially IIa and IIb) activated the caspase-8 compound and caused apoptosis. The complex IIc (sometimes called necrosome) forms after RIPK1 and RIPK3 interact and activate MLKL, inducing necroptosis and inflammation [23-24].

Anti-tumor necrosis factor agents: concept and applications

The uses of anti-TNF agents have significantly improved for autoimmune and chronic inflammatory illness treatment. Various receptor-based medications or antibodies, including Etanercept, Infliximab, and Adalimumab, are available and approved for treating different disorders such as RA, Psoriatic Arthritis (PA), AS, CD, juvenile idiopathic arthritis, and Ulcerative colitis. These biological drugs work through prevent the sTNF and mTNF from bind to their receptors (competitive antagonists) and consequently inhibiting the signaling pathways [25-28].

TNF inhibitors are major successful protein-based medications clinically effective in lowering inflammation in several autoimmune disorders. Overall, the Fc region is a key component of antibody-based therapies like anti-TNF treatments, influencing how these therapies interact with the immune system and exert their effects on the targeted cytokine or protein. Infliximab (Remicade): Infliximab is a monoclonal antibody. The Fc region of infliximab interacts with immune cells and mediates immune responses. Adalimumab (Humira): Adalimumab is another monoclonal antibody used for similar autoimmune conditions. Its Fc region is also derived from human IgG1. Adalimumab's Fc region is designed to have a high binding affinity for the neonatal Fc receptor (FcRn), which can extend the antibody's half-life in the body. Etanercept is a fusion protein used to treat conditions like rheumatoid arthritis and psoriasis. It consists of the extracellular domain of the TNF receptor fused to the Fc region of human IgG1. The Fc region in etanercept contributes to its mechanism of action by binding to circulating TNF and preventing it from interacting with cell surface TNF receptors [29].

Treatment with anti-TNF therapy may also result in several side effects, such as immunogenicity, malignancies, infections, demyelinating disease, and heart failure [30]. Additionally, using biological medications to treat moderate to severe autoimmune cases patients may marginally increase the chance of acquiring hematological malignancies [31], and IBD patients may experience dermatological manifestations [32]. The large-scale genomic study revealed important gene correlations with sensitivity (response) and the adverse effects of TNF inhibitors [33].

Association between The TNFRs Polymorphism and Non-Responsiveness to Anti-TNF-α Medications

The molecular role of their interaction

To begin with, the distinctive biochemical characteristics and ligand-binding locations of the three TNF antagonists can be partly blamed for the varied effectiveness of biological therapy. Etanercept and Adalimumab are TNF-receptor Etanercept -fusion proteins that bind to TNF and members of the lymphotoxin (LT) family; Adalimumab and Infliximab are monoclonal antibodies that selectively attach to TNF [34,35]. These dissimilarities could account for the diverse responses to different biological therapies. Additionally, TNF- receptor superfamily member 1A (TNFRSF1A) and receptor superfamily member 1B2 (TNFRSF1B2) exhibit restricted cellular expression distribution with signaling mechanisms. TNFRSF1A is exceedingly expressed, while TNFRSF1B2 is predominantly expressed in endothelial and hematopoietic cells [36]. Studies on TNFR1 and TNFR2 have shown that TNFR1 signaling induces inflammation, while TNFR2 signaling promotes immunoregulation [37].

Studies have revealed that some RA patients do not respond to TNF-α treatments or exhibit diverse responses [38, 39]. Gibellini *et al*. (2008)[29] found that patients who get anti-TNF therapy react differently to the medication. According to clinical statistics, a significant portion of IBD patients (10%–30%) do not initially react to anti-TNF medication and more than half of those who do lose their initial response over time [40,41]. Linares-Pineda *et al*. (2018) [42] hypothesized that other factors, such as hereditary conditions, induce anti-TNF therapy, a secondary component of pharmaceutical pharmacokinetics.

A meta-analysis discovered no correlation between TNFRSF1A rs767455 genotypes and resistance to anti-TNF medication using a fixed-effects model [39,43]. Nevertheless, neither the A nor G alleles of TNFRSF1A rs767455 predicted a stronger response to TNF antagonists than the G allele, and no correlation was found between any of the other TNFRSF1A rs767455 genotypes.

The Chen *et al* (2015) [34] study discovered connections between the TNFRSF1B SNP (rs1061622) and non-responsiveness to TNF antagonist therapy in four genetic models, indicating that the same drug could produce varying treatment outcomes in different diseases, significant associations were found in the population that has G loci and treatment outcomes, except for CD.

The primary reason for this heterogeneity among diseases is the diverse function that TNF- plays in the pathogenesis of several illnesses. TNF and TNFSF members, alpha and beta LT bind to their receptors (TNFR1&2) but have a particular role in immune function [44]. To start signal transduction, TNFRSF clusters its corresponding cell surface receptors, which can be membrane-anchored or soluble trimers. As a result of proteolytic cleavage of membrane TNFR, soluble TNFR affects the bioavailability of biological anti-TNF [45].

In addition, the meta-analysis identified other genes (TNFRSF1B) SNPs; significant heterogeneity was found in both allelic models, leading to random-effects models [46, 47]. The heterozygote model of rs1061624 demonstrated a significant correlation between not responding to anti-TNF-α treatment to autoimmune diseases [28,48].

However, it is remarkable to note that the failure of the fusion protein with TNFR1 (p55/60) in clinical studies, when etanercept was efficient in the treatment of the spondylarthritis patient, may be interpreted by G allele of TNFRSF1A carriers were related to nonresponse to anti-TNF medication [49].

The SNPs may affect the expression level of TNFR; Sennikov *et al*. (2014) [50] conducted a study that explored the impact of several SNPs in different loci on the expression of TNFR in various cells. The study revealed that the CC genotype of TNFRI at position 1207G/C (rs4149569) was linked to lower membrane-bound expression of TNFRI on intact CD14+ monocytes than the GC genotype. Also identified variations in TNFRII SNP 1709A/T TNFRII (rs652625) frequency among TNFRII expressed in both CD3 and CD19 cells in healthy persons. Moreover, compared to the CT genotype, the CC genotype of SNP C (3609) T for TNFRII (rs590368) was related to a reduced proportion of TNFRII expressed in CD14 cells.

Association of TNFRs Polymorphisms with Rheumatoid Arthritis

Several polymorphisms in TNF-TNFR superfamily genes were revealed within the promoter region that affect the gene expression levels and cause differences in receptor expression [51]. Sennikov *et al*. (2015) [52] reported an increment in membrane TNFRI in CD3 of T lymphocytes CD19+ of B cells subpopulations in individuals possessing GT+CC combination in promoter positions −3609 and −1709 exhibited, at the same time, the expression level of TNFRII was reduced in both CD14 of monocytes and CD3 of T lymphocytes.

Individuals homozygous for the T allele for G (609) T SNP of the promoter region in the TNFRI gene exhibited low blood levels of type I sTNFRs, according to studies by Sennikov *et al*. (2015) [52] and Gough and Myles (2020) [53], soluble receptors have been found to inhibit the biological effects of TNFα. Therefore, lower concentrations of soluble receptors result in lesser membrane-bound receptors competitors.

Furthermore, according to Sainz *et al*. (2010) [54], the encoding G allele of the interferon consensus sequence-binding protein (ICSBP) binding site, also called interferon regulatory factor 8 (IRF8), is associated with reduced expression of TNFα receptors. This ligand made TNFRI-mediated activation and consequently began the NF-κB signaling pathway.

Genetic Polymorphisms in TNFR in Rheumatoid Arthritis

Various studies have reported that genetic polymorphisms in TNFR could impact the effectiveness of anti-TNF biologic effects in patients with disorders (inflammatory syndromes) such as CD, PS, and RA [34,38,39]. The TNF-α receptor plays a crucial role in the inflammatory response, and any alterations in its structure or expression can lead to different drug responses. Anti-TNF biological drugs can either include TNF-receptor fusion protein (e.g., certolizumab and etanercept), which bind to the cell surface receptor of TNF and prevent its action, or rely on TNF-binding monoclonal antibodies [55-57].

Some studies have yielded conflicting results regarding the potential relationship between the response of anti-TNF blockers and the polymorphisms in TNFRs (TNFR1 and TNFR2) [58]. There is a correlation between TNFR SNPs and the responsiveness of RA patients to anti-TNF drugs. However, this relationship is controversial since some studies have shown that the presence of polymorphism sites on TNFRs receptors is correlated with improvement in treated individuals, while others have reported poor responses.

According to Kalliolias and Ivashkiv (2016) [59], the efficacy of infliximab treatment in 58 RA patients can be influenced by the variant 676 T > G (TNFR2), the individuals with the TNFR1 36 A/A genotype had a superior European Alliance of Associations for Rheumatology (EULAR) response after 3 months of therapy compared to those with the G allele in a trial on 280 RA patients treated with TNF inhibitors. Those with the TNFR1 36 A/A genotype demonstrated less disease activity after six months than those with the G/G genotype. Swierkot *et al*. (2015) [60] observed that individuals with the TNFR1 36 A/A genotype had a superior EULAR response after 3 months of therapy compared to those with the G allele in a trial on 280 RA patients treated with TNF inhibitors. Those with the TNFR1 36 A/A genotype demonstrated less disease activity after six months than those with the G/G genotype. In contrast, a significant association was observed between the A/A genotype in the TNFR1 SNP and a poor response to anti-TNF treatment (worse Disease Activity Score (DAS)-based EULAR response) compared to the A/G or G/G genotypes.

Furthermore, Chen *et al*. (2015) [43] reported that RA patients with the T allele TNFR2 (rs1061622) responded to anti-TNF medication less than those with the G allele. Additionally, TNFR2, rs161622 G/G, 3397C/C, and rs1061631 A/A genotypes were associated with a higher chance of worse reactions to anti-TNF medications [61]. The p-values for these correlations were specifically 0.014, 0.0085, and 0.028.

Several researchers have looked at the interaction between SNPs in the receptor and TNF genes and how it affects the effectiveness of treatment for RA patients. In one research, 58 RA patients on infliximab had their six SNPs; G (308) A, G(238)A, G(489)A, and C(857)T in the TNF gene, A(36)G in TNFR1, T(676)G in TNFR2, examined [62]. According to the study, the interaction of the genes T(676)G (TNFR2) and C(857)T (TNF) may affect the therapeutic efficiency of infliximab. In a related investigation, five SNPs in the TNF and TNF-receptor encoding genes were examined in 280 RA patients using TNF inhibitors. The findings revealed that individuals with the TNFR2 T/T genotype had better EULAR responses after therapy than those with the G/G [63].

A higher response to therapy was also linked to polymorphic sites on TNF- receptors, indicating the value of pre-evaluation for prescribing the best medication based on a patient's genetic profile. In conclusion, therapies are affected by the G allele in those who carry the 308 TNF polymorphism independent of the anti-TNF administered) [59].

Genetic Polymorphisms in TNFRSF1A / 1B and Crohn's Disease

Qasem *et al*. (2019) [64] conducted a study that revealed that patients with CD had a significantly higher relative expression of TNFα than healthy individuals. TNFRSF1A and TNFRSF1B expression levels were considerably lower in CD patients. The response to anti-TNF therapy in CD patients was shown to be correlated with genetic variants in TNFRSF1A and TNFRSF1B. The relative gene expression level of TNFRSF1A in CD patients with the TNFRSF1A: GG genotype for rs767455 was significantly lower than that of CD

patients with the AA genotype and that of TNFRSF1B in CD patients with the TNFRSF1B:rs3397 CT or TT genotype was significantly lower than that of CD patients with the CC genotype.

Cao *et al*. (2018) [65] reported that the TNFRSF1A, GG, and AG genotypes rs767455 were significantly more frequent in non-responders to anti-TNFα than in drug responders with the AA genotype. Similarly, Medrano *et al*. (2014) [66] and Chen *et al*. (2015) [43] found out that the TNFRSF1B genotypes (TT and CT) for rs3397 were significantly more frequent in CD patients compared to patients who do not react to anti-TNF (classed as treatment responder), where there, the CC genotypes were more prevalent.

Genetic Polymorphisms in TNFRSF1A/1B and Psoriasis

Iannone *et al*. (2019) [67] reported a variety of biopharmaceuticals approved for treating mild to severe PS. These medications are categorized into two types based on their curative targets: Anti-TNF inhibitors; including etanercept, adalimumab, certolizumab, and infliximab, and cytokine inhibitors; like secukinumab, brodalumab, ustekinumab, ixekizumab, tildrakizumab, guselkumab, bimekizumab, mirikizumab, and the recently approved risankizumab.

Anti-TNFs were the first biologics approved for treating PS, and a network meta-analysis conducted by Armstrong *et al*. (2020) [68] found that INF is the more effective (80% of patients reaching psoriasis area and severity index (PASI) 75 at week 10, followed by adalimumab and certolizumab).

Armstrong *et al*. (2020) [68] claim that TNFRSF1B is a receptor that controls this protein's activity (TNF protein) and drives most of the metabolic effects of TNF. As etanercept is the soluble p75 subunit of the TNFR, changes in the TNFRSF1B gene may affect the TNF-mediated immune response, particularly in etanercept, which suppresses the activity of this receptor.

The effect of the TNFRSF1B rs1061622 (T>G) SNP on the responsiveness to anti-TNF medications has been examined in two trials and a meta-analysis; [39,43,69] Compared to the GG and GT genotypes in an 80-patient trial in Greece, the TNFRSF1B TT genotype of (rs1061622) showed a higher response to etanercept therapy (PASI 75 at 6 months).

This result was proven in a trial of 90 patients, where patients with G allele (rs1061622) for TNFRSF1B were associated with a worse response to anti-TNF medications and cytokine inhibitors (ustekinumab) treatment (6 months, PASI=50) in comparison with patients with the mutant allele (allele T), especially in those on anti-TNF treatment [39]. A meta-analysis of seven trials with 929 patients with autoimmune diseases, including CD, found that the T allele (rs1061622) for TNFRSF1B was with a greater response to anti-TNF medications, and a subset of 170 individuals with moderate to severe psoriasis validated this connection [43,70].

Genetic Polymorphisms in TNFRSF1A/1B and Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a diverse chronic systemic inflammatory disease primarily affecting the axial skeleton (spine) and causing inflammation in the sacroiliac joints [71,72]. It frequently manifests as pain in the buttocks, nighttime back pain, and morning stiffness [73]. In addition to sacroiliitis symptoms, individuals with AS may experience non-skeletal issues, such as uveitis, pulmonary fibrosis, as well as neurological, cardiac, and renal complications [74-76]. The TNF is a main mediator of immune responses that precipitate in the pathogenesis of AS [77,78].

A polymorphism in the promoter region of the TNFR1 gene that results at position -383 relative to the translation start site (-383) was described. The findings from this exploratory study indicate that the AA genotype of the -383 TNFR1 polymorphism is linked to an increased risk of ankylosing spondylitis (AS) in Mexican Mestizo patients because TNF- exerts its pro-inflammatory effects through its binding to two different cell surface receptors: TNFR1 and TNFR2 [79]. The genetic SNPs may perform a conformational alteration in the molecule of TNFR1, leading to modifications in the signaling induced by TNF- through mediating abnormal signaling [80]. Additionally, another study showed that the G allele (GG genotype) in loci 676 could have a protective role, but the 676-T allele represents a risk factor for SA [81]. While another study did not find an association between TNFR1 polymorphism and AS in the Russian Caucasian population, and the polymorphism tested does not appear to be useful for assessing predisposition to this disease or for its diagnosis or prognosis [82].

Conclusion

This study examined the role of genetic polymorphism in TNFR receptors in the pathogenesis of various autoimmune disorders, including RA, CD, PS, and SA. The promoter region of TNFR superfamily genes revealed numerous variants (genetic biomarkers). These SNPs influence the anti-TNF drug responsiveness of RA, CD, PS, and SA patients. The results suggest that certain alleles in certain loci are associated with a poor response or a better response to therapy with anti-TNF biological medications. These variations are explained by the effect of polymorphism on the binding of anti-TNF to receptors and by increasing the mRNA expression of TNFR.

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Conflicts of Interest

There is no conflict of interest.

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Ethics Statements

The review article does not need ethical approval from the ethics committee. Only approval from the scientific committee in the Department of Clinical Pharmacy.

Author Contribution

The study conception and design, analysis and interpretation: First author. Draft manuscript preparation: Second author.

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أرتباط تعدد الأشكال الجينية في مستقبلات عامل نخر الورم - الفا ببعض أمراض المناعة الذاتية واستجابة الأدوية البيولوجية المضادة لـعامل نخر الورم: مقال مراجعة

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الخلاصة

بعض العوامل الوراثية لا تشارك في بعض أمراض المناعة الذاتية فحسب ، بل تتداخل أيضًا مع علاجها ، مثل مرض كرون , التهاب المفاصل الروماتويدي, الصدفية و التهاب الفقار المقسط. أن عامل نخر الورم الفا هو أهم السيتوكينات المحفزة للالتهابات ، والذي تم التعرف عليه كعامل رئيسي يساهم في التسبب في اضطرابات المناعة الذاتية وتطورها. لذلك ، يمكن أن يكون عامل نخر الورم هدفًا محتملًا لعلاج هذه الاضطرابات ، وعلى هذا الاساس تم تطوير العديد من مضادات عامل نخر الورم لعلاج هذه الاضطرابات. على الرغم من الفعالية العالية للعديد من الأدوية البيولوجية المضادة لعامل نخر الورم ، فإن استجابات المرضى السريرية لعلاج المناعة الذاتية أظهرت تباينًا كبيرًا. يتم تصنيف مستقبلات عامل نخر الورم الفا إلى اثنين من مستقبلات عامل نخر الورم الفا ، وهما TNFR1 و .TNFR2 تنتمي هذه المستقبلات إلى عائلتين متميزتين: عائلة عامل نخر الورم التي تتكون من ١٩ رابطًا وعائلة مستقبلات عامل نخر الورم الفائقة التي تشتمل على ٢٩ مستقبلًا. تهدف هذه المراجعة إلى تقديم نظرة

عامة عن تأثير تعدد الأشكال الجيني على مستقبلات عامل نخر الورم ألفا على استجابة المرضى الذين يعانون من أمراض المناعة الذاتية للبيولوجيا المضادة لعامل نخر الورم. قد تؤثر العديد من تعدد الأشكال للنيوكليوتيدات المفردة المسجلة في جين مستقبلات عامل نخر الورم على خلايا الجهاز المناعي المختلفة على التعبير الجيني السفلي المقابل لـ مستقبلات عامل نخر الورم . لخصت المراجعة الحالية الدراسات التي سلطت الضوء على دور عدم التجانس الجيني في تغيير استجابة مرضى المناعة الذاتية. حيث أشار العديد من الباحثين إلى أن التغايرات لها تأثير على استجابة مرضى المناعة الذاتية للعلاج بالأدوية البيولوجية المضادة لعامل نخر الورم ، بينما لم تجد دراسات أخرى ارتباطًا. في الختام ، ان عامل نخر الورم له دوراساس في العديد من الأمراض مثل مرض كرون, التهاب المفاصل الروماتويدي, الصدفية و التهاب الفقار المقسط ؛ وأثبتت الدراسات ان هناك ارتباط بين تعدد الأشكال ل مستقبلات عامل نخر الورم وعدم الاستجابة للأدوية المضادة لـ عامل نخر الورم ألفا.

الكلمات المفتاحية: عامل نخر الورم ألفا، تعدد أشكال النوكليوتيدات المفردة ، الأدوية البيولوجية ، مستقبلات عامل نخر الورم، مضادات عامل نخر الورم.