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Review Article

CD40 Gene Variants and Disease Susceptibility: A Comprehensive Review of Associations with Immune-Mediated Inflammatory Diseases, Cancer, and Infectious Diseases

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Abstract

CD40 is a type 1 transmembrane protein composed of 277 amino acids, and it belongs to the tumor necrosis factor receptor (TNFR) superfamily. It is expressed in a variety of cell types, including normal B cells, macrophages, dendritic cells, and endothelial cells, as a costimulatory molecule. This study aims to summarize the CD40 polymorphism effect and its susceptibility to immune-related disorders. The CD40 gene polymorphisms showed a significant association with different immune-related disorders and act as a risk factor for increased susceptibility to these diseases.

Keywords: CD40, Case control, Immune disease, Polymorphism.

المتغيرات الجينية CD40 والقابلية للإصابة بالأمراض: مراجعة شاملة للارتباطات مع الأمراض الالتهابية المناعية والسرطان والامراض المعدية

الخلاصة

CD40 هو بروتين غشائي من النوع 1 يتكون من 277 من الأحماض الأمينية ، وهو ينتمي إلى عائلة مستقبلات عامل نخر الورم (TNFR) الفائقة. يتم التعبير عنه في مجموعة متنوعة من أنواع الخلايا ، بما في ذلك الخلايا البائية الطبيعية ، والضامة ، والخلايا المتغصنة ، والخلايا البطانية ، كجزيء تكلفة. تهدف هذه الدراسة إلى تلخيص تأثير تعدد الأشكال CD40 وقابليته للإصابة بالاضطرابات المناعية. أظهرت تعدد أشكال جينات CD40 ارتباطا كبيرا بالاضطرابات المختلفة المتعلقة بالمناعة وتعمل كعامل خطر لزيادة التعرض لهذه الأمراض.

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INTRODUCTION

CD40 is a type 1 transmembrane protein composed of 277 amino acids, and it belongs to the tumor necrosis factor receptor (TNFR) superfamily [1]. CD40 is expressed in a variety of cell types, including normal B cells, macrophages, dendritic cells, and endothelial cells, as a costimulatory molecule [2]. CD40 ligand CD40L (CD154) is a type 2 transmembrane protein expressed often on activated T CD4+ cells. The interaction between CD40 and its ligand is important in the regulation of B cell proliferation, immunoglobulin class switching, germinal center formation, antibody production, and generation of memory B cells [3]. Several studies mentioned the importance of this interaction in autoimmune diseases; higher levels of CD40 (sCD40) have been noticed in patients with immune-related disorders compared with control subjects [4]. Considering the formation of autoantibodies (AB), it is a characteristic feature of many autoimmune diseases, so it has been indicated that the increased level of CD40 expression on B cells enhances autoimmune disease development and has been widely investigated in different health-related conditions [5-8]. This study aims to summarize the CD40 polymorphism effect and its susceptibility to different immune-related disorders and other. Table 1 summarizes the published studies on the role of CD40 in various pathologies.

Association of CD40 Gene Polymorphisms with Immune-mediated Inflammatory Diseases

Association with ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a disabling form of a systemic chronic inflammatory arthritis that may affect the axial skeleton through structural damage and inflammation, with or without extra-spinal manifestations, such as dactylitis, peripheral arthritis, uveitis, and enthesitis [9]. Ankylosing spondylitis treatment has ranged from relief of symptoms to pathogenetic treatment using disease-modifying anti-rheumatic drugs, such as tumor necrosis factor (TNF) alpha inhibitors. Most patients had variable treatment responses, so this required further studies [10]. Several genes have been marked as candidate genes related to arthritis or, more specifically, AS onset [8-13]. This may affect treatment response [14]. A cross-sectional study included 98 AS patients as the case group and 154 as a control group to study the association of CD40 gene polymorphisms with ankylosing spondylitis (AS) and showed that the relationship between the disease and genotypes was significant and the homozygous and *GG* genotypes can be a protective factor for AS development [15].

Table 1: Association of CD40 Gene Polymorphisms with different immune related disorders

Author and Date	Study type	CD40 Genetic polymorphisms	Ethnicity	Immune related disorder	Outcome
Zepa *et al*., (2018) [15]	Cross-sectional study included 98 AS patients and 154 as controls	rs4810485	Latvia	Ankylosing spondylitis	The relationship between the disease and genotypes was of moderate significance
Shukla *et al*., (2024) [20]	Case-control study included 50 GD patients and 50 as controls	A C/T Polymorphism at the 5'	India	Graves' Disease	CD40 gene was a new susceptibility gene for GD within certain families
Hafez *et al*., (2018) [25]	Case-control study including 150 JIA patients and 194 as controls	CD40 C allele	Egypt	Juvenile idiopathic arthritis (JIA)	Patients with severe and moderate disease activity had a higher frequency of the CD40 C allele.
Tapia-Llanos *et al*., (2019) [28]	Case-control study included 293 SLE patients as the case group and 294 as a control group	rs1883832 rs4810485	Mexico	Chronic kidney disease in systemic lupus erythematosus	CD40 gene polymorphisms increase the risk of SLE
Patra *et al*., (2023) [33]	Case-control study included 41 KD patients as the case group and 41 as a control group	rs153045	India	Kawasaki disease	significantly associated with KD
Thude *et al*., (2014) [39]	Retrospective study included 209 patients who underwent orthotopic liver transplantation	rs1883832 rs4810485	Germany	Liver transplant rejection	No role of CD40 SNPs in the susceptibility to liver transplant rejection
Bagheri *et al*., (2014) [43]	Retrospective study included 240 patients who underwent kidney transplant	rs1883832	Iran	Kidney transplant rejection	no correlation between CD40 polymorphism and kidney transplant rejection
Ellithy *et al*., (2022) [46]	Case-control study included 50 ITP patients as the case group and 50 as a control group	rs4810485 rs1883832	Egypt	ITP	No statistically significant differences between the two groups, while combined gene polymorphism genotyping showed a significant difference between the two groups
Joshi *et al*., (2024) [57]	Case-control study included 203 T2DM, 49 T1DM patients, and 80 healthy individuals	rs1883832	Germany	DM	SNP of CD40 gene enhances the susceptibility of human vascular endothelial cells to pro-inflammatory dedifferentiation and EndMT in DM
Shuang *et al*., (2011) [66]	Case-control study included 591 sporadic breast cancer patients as and 600 as controls	rs1883832 rs4810485 rs1800686 rs3765459	China	Breast Cancer	CD40 gene polymorphisms contribute to sporadic breast cancer risk and have a significant association with clinic-pathological features
Zhu *et al*., (2023) [73]	Case-control study included 421 CSCC patients and 594 as controls	rs4810485	China	Cervical squamous cell carcinoma	polymorphisms were associated with parity of the patients with CSCC
Tian *et al*., (2019) [79]	Cross-sectional study included 1513 uninfected subjects, 496 spontaneous viral clearance subjects and 768 persistent HCV-infected subjects.	rs1883832 rs1535045	China	HCV infection	Significantly associated with an increased risk of HCV infection
Liu *et al*., (2018) [88]	Cohort study included 261 sepsis patients as the case group and 322 as a control group	rs1883832	China	Sepsis	CD40 SNPs acts as a risk factor for increased susceptibility to sepsis

Association with Graves' disease

Graves' disease (GD) is an organ-specific autoimmune disorder [1]. Its etiology remains unknown; it is thought to be as a result of an interaction between genetic and environmental factors [16,17]. Interaction of CD40 with CD154 induces release of cytokines from the activated helper T cell that promotes differentiation of T cells into TH2 cells [9]. This change of immune response results in thyroid autoimmunity driving in the direction of GD

and could affect the production of stimulating thyrotropin receptor antibodies (TSHRAbs) in B cells from patients with Graves' disease. Thyroidal CD40 high expression results in higher production of thyroid-specific autoantibodies; many studies showed more severe autoimmune GD [18,19]. From other aspects, a case-control study included 50 GD patients as the case group and 50 as a control group to study the association of CD40 gene polymorphisms with Graves' disease (GD) and mentioned that there was no significant difference in allele or genotype frequency of the CD40 SNP between GD and control subjects [20].

Association with juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is one of the common diseases with the risk of disability in children [21]. Its exact cause is still unknown and thought to be because of viral infection, which may trigger the disease onset in susceptible children. Many genomic regions are thought to be contributors to JIA risk. JIA is characterized by high levels of pro-inflammatory cytokines that increase by enhancing CD40 expression; these cytokines, including tumor necrosis factor-a (TNF-a) and interleukins, have a major role in the pathogenesis of this disease [22-24]. A case-control study that included 150 JIA patients as the case group and 194 as a control group showed that the frequency of the CD40 C allele was significantly increased in patients with moderate to severe disease activity [25].

Association with systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with unknown etiology characterized by increased production of autoantibodies directed to the cytoplasm and nuclear components that can prompt an inflammatory process affecting multiple tissues and organs [26,27]. The CD40 could have a role in regulating B cell activation and production of autoantibody that is induced by T cell interaction or may act as a control system to decrease damage in a target tissue by promoting T regulatory cells. A case-control study included 293 SLE patients as the case group and 294 as a control group focused on the association of CD40 gene polymorphisms with systemic lupus erythematosus (SLE) indicated that CD40 gene polymorphisms increase the risk of SLE [28].

Association with Kawasaki disease

Kawasaki disease (KD) is a medium-vessel vasculitis that mostly affects young children [29,30]. The interaction of CD40–CD154 (CD40 ligand) is believed to play an essential role in acute coronary syndrome [31]. By enhancing the proliferation of B cells and release of pro-inflammatory cytokines such as TNFα, IL6, and IL10 [18]. CD40–CD0l signaling in non-hematopoietic cells plays an important role in inflammation [19]. However, still its role in the evolution of KD is unclear [32]. A case-control study included 41 KD patients as the case group and 41 as a control group trying to find the association of CD40 gene polymorphisms with KD and proved it is significantly associated with KD [33].

Association with liver transplant rejection

Liver transplantation is a life-saving therapy for patients experiencing complications from those with stage T2 hepatocellular carcinoma and cirrhosis [34]. The CD8+ T cell-derived CD40 signals are an essential factor in the attenuation of Treg responses and control alloimmune responses. CD40/CD154 interaction also has an important role in allograft rejection. Previous studies showed that blocking the CD40/CD154 interaction by CD154 mAbs can prevent kidney and heart allograft rejection in several nonhuman transplant models [35–38]. Another retrospective study included 209 patients who underwent orthotropic liver transplantation trying to link CD40 gene polymorphisms and liver transplant rejection, but there was no role of CD40 SNPs in the susceptibility to liver transplant rejection [39].

Association with kidney transplant rejection

Kidney transplant rejection is a continuous and gradual process, its activity depending on heterogeneous immunologic responses to this genetic mismatch, the efficacy of the immunosuppression medications prescribed to the patients, and donor-recipient genetic disparity [40,41]. Cytokines are an essential factor in deciding the outcome of transplantation. The Th1 cytokine profile is usually associated with allograft rejection, and the Th2 has a role in the acquisition of tolerance and stable graft survival in transplantation models [42]. Since recipient ability in the production of co-stimulatory molecules and cytokines could be affected by gene polymorphisms, a retrospective study included 240 patients who underwent kidney transplants to try to prove the association of CD40 gene polymorphisms with kidney transplant rejection; unfortunately, no correlation was found between CD40 polymorphism and kidney transplant rejection [43].

Association with thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune disease of unknown cause. Both environmental and genetic factors are thought to play a critical role in disease development [44]. CD40L plays an important role in the pathogenesis of ITP by producing autoantibodies against platelet surface antigens. CD40L expression is increased in ITP patients and stimulates the activation of autoreactive B lymphocytes; thus, CD40L overexpression causes

abnormal activation of reactive B lymphocytes. So, blocking the CD40/CD154 signal could be considered an immunomodulatory strategy for T-cell-mediated diseases and effective for ITP management by suppression of autoreactive B and T lymphocytes to platelet antigens [45]. A case-control study included 50 ITP patients as the case group and 50 as a control group. It studied the association of CD40 gene polymorphisms with thrombocytopenic purpura (ITP) and found no statistically significant differences between these two groups, but combined gene polymorphism genotyping presents a statistically significant difference between them [46]. The CD40 gene in previous studies has been widely investigated in different diseases, including osteoporosis, multiple sclerosis, Crohn's disease, ischemic stroke, and post-stroke epilepsy [47-49].

Association with endothelial dysfunction in a pro-diabetic microenvironment

Type 1 diabetes (T1D), a chronic, autoimmune condition often diagnosed in childhood or adolescence, is characterized by high blood glucose levels that, with extended periods, can trigger an inflammatory response that affects other health complications, such as cardiovascular disease (CVD) [50]. Interleukin (IL)-6, tumor necrosis factor (TNF)-α, vascular cell adhesion molecule (VCAM)-1, or E-selectin as pro-inflammatory markers are observed in the plasma of diabetic patients [51]. CD40 acts as an inflammation inducer that promotes insulin resistance and vascular complications in diabetic patients [52], and CD40 overexpression exaggerated TGF-β signaling that is involved in the progression of diabetes [53]. Which is also a known mediator of EndMT [54]. Different studies showed that genetic factors are associated with a risk of developing DM [55,56]. A recent study that included 203 type 2 diabetes (T2D) patients, forty-nine type 1 diabetes (T1D) patients, and eighty healthy individuals provides evidence that the SNP of the CD40 gene enhances the susceptibility of human vascular endothelial cells to pro-inflammatory dedifferentiation and EndMT in diabetes [57].

Role in Malignant Diseases

Association with breast cancer

Breast cancer is the most common cause of cancer death among women. Recent research has mentioned that changes in some immune regulatory genes cause interindividual differences in breast cancer susceptibility [58]. CD40 is an important part of the immune system's fight against tumors because it boosts cytotoxic lymphocyte (CTL) responses and the development of helper T cells into Th1 cells [59]. Other studies showed that CD40 agonists can be effective against human malignancies [60,61]. Another study has shown that CD40 may lead to tumor growth and metastasis [61]. Since CD40 signaling in endothelial cells can result in less apoptosis and enhanced proliferation, which may stimulate tumor growth through angiogenesis [62–64]. Besides, chemokines, such as VEGF and IL-10, induced by the CD40-CD153 complex interaction on various cell types are all suggested to have an essential role in malignant cell metastasis [65]. A case-control study that included 591 sporadic breast cancer patients as the case group and 600 as a control group showed that CD40 gene polymorphisms contribute to sporadic breast cancer risk and have a significant association with clinical pathological features. So, these genotypes could be a good marker to predict the prognosis of breast cancer and the response to treatment [66].

Association with cervical squamous cell carcinoma

Persistent human papillomavirus infection is one of the major risk factors for the development of cervical cancer and squamous intraepithelial lesions (SIL) [67,68]. A study observed that the expression of CD40 on persistent human papillomavirus-infected lesions and advanced CSCC is significantly higher than that of normal cervical tissues [69]. Other studies showed that the expression of CD40 is correlated with HPV positivity and vascular endothelial growth factor expression [70]. The CD40 activation can upregulate vascular endothelial growth factor expression, IL-6, and other factors by activating MAPK, PI3K/Akt, and other signal transduction pathways that promote tumor angiogenesis by endothelial cell apoptosis inhibition and enhance the growth of vascular endothelial cells to develop cervical cancer [71,64,72]. A case-control study included 421 CSCC patients as the case group and 594 as a control group to study the association of CD40 gene polymorphisms with cervical squamous cell carcinoma (CSCC) and indicated that these polymorphisms were associated with parity of the patients with CSCC [73].

Role in Infectious Diseases

Association with hepatitis C infection

Hepatitis C virus (HCV) infection is highly correlated with hepatic and extrahepatic diseases such as hepatocellular carcinoma, cirrhosis, and hepatic failure [74]. Still, an HCV vaccine is not available for the prevention of HCV infection [75]. CD40 is highly expressed on tissues of the liver and has an essential role in hepatocyte survival [76]. It can inhibit HCV replication and prompt viral clearance by activating innate immune mechanisms [77]. CD40 might have important effects by enhancing hepatocyte survival and decreasing death in HCV-associated chronic liver diseases [76,78]. In a cross-sectional study that

included 1513 uninfected subjects, 496 spontaneous viral clearance subjects, and 768 persistent HCV-infected subjects, the association of CD40 gene polymorphisms with HCV was significantly associated with increased risk of HCV infection [79].

Association with sepsis

Systemic inflammatory response syndrome is a serious condition that results from local or systemic infection [80–82]. Patients in different stages of sepsis will exhibit different immune statuses, which chiefly depend on the balance between pro-inflammatory and anti-inflammatory cytokines. The interferon (IFN), tumor necrosis factor (TNF), and immunoglobulin families of type II cytokines all play a crucial role in sepsis. Since CD40 belongs to the TNF family of type II cytokines, it can be used to identify a new method for the development of new strategies for the treatment or prevention of sepsis [83,84]. Several studies proved that genetic factors could increase susceptibility to infection [85,86]. Previous studies approved abnormal elevation of sCD40L was observed in sepsis patients [87], while others indicated that CD40 SNPs act as a risk factor for increased susceptibility to sepsis [88].

Conclusion

CD40 gene polymorphisms showed a significant association with malignant, infectious, and immune-mediated inflammatory disease progression and can act as a risk factor for increased susceptibility to these diseases, since genotypes could also be a good marker to predict the prognosis and response to treatment of these diseases. Further studies are required to predict and establish a new strategy to prevent or treat these conditions.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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