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The association of CD28 polymorphism, rs3116496, with Cancer: A meta-analysis

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ABSTRACT

Objective: To determine the relationship between CD28 polymorphisms, rs3116496, and cancer.
Design: Meta-analysis.
Methods: PubMed, EMBASE, Web of Science, and Cochrane library databases were searched to identify studies reporting the association between CD28 polymorphism and cancer. Two authors selected identified studies, extracted, and analyzed the data independently.
Results: Individuals carrying a T allele (TT homozygotes and TT+TC heterozygotes) at rs3116496 had a lower incidence of cancer than carriers of a C allele. Subgroup analysis showed that this association held true for Asians, but not Europeans.
Conclusion: CD28 polymorphism, rs3116496, contributes to cancer susceptibility in the case of multiple cancers.

1. Introduction

Tumorigenesis can occur on successful avoidance of immunosurveillance, the immune mechanism that limits tumor occurrence and progression through the production of immunosuppressive cytokines, promotion of differentiation of immunosuppressive cells, and inhibition of immunostimulatory substances [1–6]. Although tumorigenesis can be influenced by multiple factors such as genetic and environmental variations, perturbation of a tightly controlled immune system can greatly increase cancer risk [7–9]. Cell-mediated immunity is a critical antitumor defense mechanism in which cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are major effectors. CTLs and NK cells use perforin, granzyme, FasL, and TNF-related apoptosis-inducing ligand to eradicate tumor cells [10–12]. Genetic variation in genes that govern T cell and NK cell function may contribute to increased susceptibility to cancer [13].

Immune responses are partly regulated by the immunoglobulin superfamily, including antigen receptors, antigen-presenting molecules, coreceptors, costimulatory molecules, and antigen receptor accessory molecules [14]. Costimulatory molecules play crucial roles in regulating T and B cell immune responses and homeostasis [15–19]. In particular, members of the cluster of differentiation (CD) family, including CD28, cytotoxic T-lymphocyte antigen 4, and inducible T-cell costimulator, are major costimulatory molecules [15–20]. CD28 is constitutively expressed on the majority of naïve T cells, while the others are expressed on activated T cells [21–25]. CD28 interacts with B7-1 and B7-2 on antigen-presenting cells (APCs) and induces T cell differentiation and proliferation [15,20,26–30]. In addition, CD28 has been shown to enhance glucose uptake, glycolysis, production of cytokines such as interleukin-2, and cell survival through induction of the antiapoptotic factor Bcl-XL [31–42]. Studies have shown that memory T cells require CD28 costimulation for maximal expansion and pathogen clearance, and decreased CD28 expression on peripheral blood T lymphocytes is observed in patients with neoplastic diseases. Thus, CD28-mediated costimulation is critical for T cell proliferation and survival and for the activation of effector functions, including cytolysis of cancer cells [31,43,44].

The human CD28 gene maps to chromosome 2q33 [45] and is composed of four exons encoding the leader, V-like, connecting, transmembrane, and intracytoplasmic regions. Previous studies have shown that polymorphisms in the CD28 gene are associated with autoimmune disorders. For instance, a single nucleotide polymorphism (SNP) in rs1980422 or rs3116496 has been linked to rheumatoid arthritis, and an rs3116496 SNP is associated with Bechet's disease [5,14,46]. Many studies have examined the association between *CD28* polymorphism and cancer incidence in various populations. Polymorphisms in rs1181388, rs1181390, rs3116487, rs3116494, rs3116496, rs3181097, rs3181098, rs3181110, rs3181101, rs3181107, rs3181113, rs3769684, rs3769686, rs4673259, rs10932017, rs12693993, and rs35593994 affect the incidence of breast cancer [15], non-small cell lung cancer [28], cervical cancer [23,47], malignant melanoma [48], colorectal cancer [49], B cell chronic lymphoblastic leukemia [50], and other cancer types. In particular, polymorphisms in rs3116496 have

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been widely studied for their connection to cancer, while polymorphisms in other positions are quite limited in numbers. Nevertheless, the results of the studies reporting the association of rs3116496 polymorphism with cancer have been variable, and the lack of statistical power in most studies has precluded reliable conclusions. Taking into consideration the limitations of a single study and the significant role played by CD28 in the antitumor response, a meta-analysis was performed in order to investigate whether CD28 rs3116496 polymorphisms contribute to cancer susceptibility.

2. Materials and methods

2.1. Literature search and selection of eligible studies

A literature search was conducted in the PubMed (US National Library of Medicine, National Institutes of Health), EMBASE, Web of Science, and Cochrane library databases using the following terms: ("polymorphism, genetic" or "genetic polymorphism" or "polymorphism" or "variant" or "mutation" or "single nucleotide polymorphism" or "SNP") and ("neoplasm" or "cancer" or "carcinoma" or "carcinogenesis" or "tumor") and ("antigen, CD28" or "CD28 antigen" or "CD28" or "cluster of differentiation 28"). All studies published until October 23, 2013, were eligible, and there was no language restriction. All studies that showed an association between the CD28 polymorphism and cancer were retrieved. Additional studies were also found by scanning references citing important studies and reviews. Studies included in the meta-analysis met the following criteria: (1) the association between CD28 genetic polymorphism and cancer was evaluated; (2) the odds ratio (OR) with 95% confidence interval (CI) values, or sufficient data to calculate these, were reported; (3) genotyping and statistical methods were clearly described; and (4) the participants in the control group were in Hardy-Weinberg equilibrium (HWE). Studies were excluded if they were (1) non-case control studies; (2) duplicates of previous reports; (3) based on partial data; or (4) meta-analyses, reviews, or letters. Literature search and selection were performed by two authors (J.B. and H.L.) independently.

2.2. Data extraction

The following data were gathered from each study: first author's name, year of publication, country, ethnicity of study patients, genotyping method, cancer type, definition of the study patients (cases), source of the control group (controls), frequency of genotypes, sample size, and evidence of HWE in the controls.

2.3. Statistical analyses

ORs with 95% CI were used to assess the strength of the association between the CD28 rs3116496 polymorphism and cancer. The genetic models that were evaluated for pooled ORs were TT vs. TC, TC vs. CC, TT vs. CC, TT+TC vs. CC, TT vs. TC+CC, and T vs. C. Higgins' I^2 statistic and the chi-square-based Q-test were used to assess heterogeneity among studies [51]. A P value < 0.10 for the Q-test indicated significant heterogeneity, and at these instances, the random-effects model (the DerSimonian and Laird method) was used to calculate the pooled ORs; otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [52–56]. In a fixed-effect model, for any observed effect Y, $Y_i = \theta + \varepsilon_i$, where θ is true effect and ε_i is within-study error with $N(0, \sigma_i^2)$ [52]. However, in a random-effect model, for any observed effect Y_i, $Y_i = \theta_i + \varepsilon_i = \mu + \zeta_i + \varepsilon_i$, where true effect θ_i is determined by the mean of all true effects μ plus between-study error ζ_i with $N(0, \tau_i^2)$ [52]. The statistical significance ($P < 0.05$) of pooled ORs was determined by the Z-test. Publication bias in the literature was assessed by Egger's linear regression test, and visual inspection of asymmetry was performed in funnel plots [57]. If publication bias existed, p values examined by Egger's test would be resulted in less than 0.05 [57]. In order to correct publication bias, we employed 'trim and fill' method which was made to correct the funnel plot by imputing where the missing studies would be likely to be placed [58]. The correction for missing studies could lead to make relevant changes about the weighted mean effect, and thus, the influence of the publication bias for the statistical significance in the overall effects was evaluated [59,60].

All statistical tests were performed using the Review Manager (version 5.2; The Cochrane Collaboration, Oxford, UK) and Comprehensive Meta Analysis (Biostat, Englewood, USA) software.

3. Results

3.1. Study selection and characteristics

A total of 672 articles related to the search terms were initially identified (Fig. 1). Of these, 615 were excluded by screening titles and keywords, 42 were excluded by reviewing the abstracts, and the remaining 15 were reviewed in detail based on the inclusion and exclusion criteria. As a result, eight articles were ultimately selected for the meta-analysis of the CD28 rs3116496 polymorphism and cancer. The eight independent studies were based on three Asian and five European patient populations. The cancer types were breast cancer, non-small cell lung cancer, cervical cancer, malignant melanoma, colorectal cancer, B cell chronic lymphoblastic leukemia, and mucosa-associated lymphoid tissue lymphoma. All DNA samples were extracted from blood, and various genotyping methods were used, such as polymerase chain

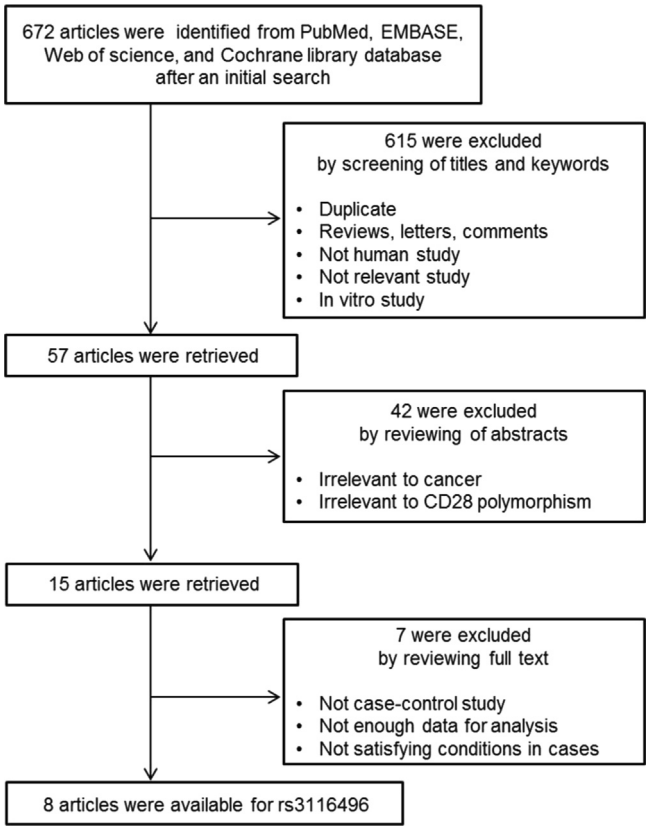

Fig. 1. Flow diagram of the study selection process for the meta-analysis.