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Impact of inducible co-stimulator gene polymorphisms on acute rejection in renal transplant recipients: An updated systematic review and meta-analysis

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ABSTRACT

Background: Acute rejection (AR) is an adverse predictor of long-term allograft survival. Previous studies have suggested that single-nucleotide polymorphisms in inducible co-stimulators may be associated with AR in kidney transplantation.
Methods: We searched for studies using PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the dominant and recessive genetic models and the co-dominant and allele models.
Results: We observed significant associations between CTLA-4 +49A/G, −1147 C/T, −1661 A/G, −1722 T/C, CD28 IVS3 +17 T/C polymorphisms and AR in kidney transplantation (+49A/G: OR: 0.79, 95% CI: 0.63–0.98; $P = 0.034$; −1147 C/T: OR: 0.19, 95% CI: 0.077, 0.48; $P = 0.081$; −1661 A/G: OR: 0.059, 95% CI: 0.042, 0.084; $P = 0.00$; −1722 T/C: OR: 0.32, 95% CI: 0.11, 0.97; $P = 0.044$; CD28 IVS3 +17 T/C: OR: 1.47, 95% CI: 1.04, 2.09; $P = 0.03$). No significant associations between PDCD1, PTPN22 and CD86 polymorphisms and AR risk were identified.
Conclusion: +49 G/A, −1147 C/T, −1661 A/G and −1722 T/C polymorphisms in CTLA-4 and CD28 IVS3 +17 T/C polymorphisms may be associated with the risk of AR occurrence in kidney transplantation. Further large, well-designed studies are urgently needed.

Contents

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1. Introduction

Chronic allograft dysfunction (CAD) remains a challenge despite great strides in immunosuppressive protocols and surgical techniques (Zaidan et al., 2014). The most common correlate of CAD is acute rejection (AR) episodes, which occur in up to 25.6% of recipients during the first 90 days after kidney transplantation (Almond et al., 1993; Matas et al., 1994; Chhabra et al., 2012). Considerable evidence has demonstrated that various inducible co-stimulators, which regulate T cell-mediated immune suppression and injury through an intricate network of molecular signals, may be crucial in the occurrence of allograft AR (Misra et al., 2014; Karimi et al., 2012; Marder et al., 2003a; Marder et al., 2003b).

For the full activation of T cells, two signals are required: the first signal is specific and originates from the T cell receptor and human leukocyte antigen (HLA), whereas the second signal is non-specific and results from inducible co-stimulators on antigen-presenting cells (APCs) with their receptors (Greenfield et al., 1998; Haimila et al., 2009). The important inducible co-stimulators include cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), CD28, CD86, protein tyrosine phosphatase non-receptor 22 (PTPN22) and programmed cell death 1 (PDCD1), and mutations in these genes play an essential role in the occurrence of AR episodes (Duan et al., 2012; Salomon and Bluestone, 2001; Azarpira et al., 2010). Several studies have focused on inducible co-stimulators related to gene polymorphisms and AR episodes in kidney transplantation. One survival study conducted by Misra et al. (2014) reported that CTLA-4 variations might play an important role in the pathogenesis of end-stage renal diseases (ESRD), AR and delayed graft function (DGF). Canossi et al. (2013) also revealed that variations in CTLA-4 gene were significantly associated with the AR episodes. However, some controversial results were suggested that the variations in inducible co-stimulators genes were not associated with the adverse events following kidney transplantation, including AR episodes (Haimila et al., 2009; Dmitrienko et al., 2005). Therefore, the potential roles of genetic polymorphisms in inducible co-stimulators genes were still not clearly identified based on these findings.

As a result, we performed this systematical review and meta-analysis to evaluate the association between genetic polymorphisms in inducible co-stimulators genes and AR occurrence in kidney transplantation.

2. Methods

2.1. Literature search

PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (updated on July 15, 2015) were comprehensively searched by two independent authors (Liu K and Shuo G). The Mesh terms used were “kidney transplantation” or “renal transplantation”, “acute rejection”, “polymorphisms” and “inducible co-stimulators” or “CD28”, “CTLA-4”, “CD86”, “PTPN2”, “PDCD1”. The reference lists of all studies included in the meta-analysis and abstracts of annual meetings of the American Society of Nephrology, International Transplant Society and European Dialysis and Transplantation Association were also reviewed.

2.2. Study selection

The inclusion criteria for the included studies were as follows: (Zaidan et al., 2014) case-control studies designed to compare at least one gene polymorphism of inducible stimulators, including “CD28”, “CTLA-4”, “CD86” and “PTPN2”, between recipients with stable graft function and recipients with acute rejection after kidney transplantation; (Almond et al., 1993) the frequencies of the genotype or allele in the case and control groups were reported; (Matas et al., 1994) the controls were derived from a population within the same geographic area and ethnic background as the cases, two authors (Liu K and Shuo G) assessed and selected trials for the final analysis independently, and discrepancies were resolved by consensus.

2.3. Data extraction

Relevant data were extracted from all selected studies independently by two authors (Liu K and Shuo G). The following characteristics were collected: first author's name, year of publication, nationality/race, number of recipients (acute rejection/stable), proportion of males, graft source, immunosuppressive protocols, genotyping method and polymorphism results. Missing data were obtained by contacting the first or corresponding author.

2.4. Statistical analysis

The pooled data were used to assess the strength of the association between gene polymorphism and acute rejection by the pooled odds ratios (ORs) with 95% confidence intervals (95% CIs). The association between gene polymorphism and acute rejection was analyzed using a dominant model, a recessive model, a co-dominant model and an allele model. A P value <0.05 was considered statistically significant. The heterogeneity among trials was assessed by I^2, which was defined as $100\% * (Q - df) / Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom, with a fixed-effects model set at low statistical inconsistency ($I^2 < 25\%$); otherwise, we selected a random-effects model, which is better adapted to clinical and statistical variations (Biondi-Zoccai et al., 2011). Egger's regression test and the Begg-Mazumdar test based on Kendall's tau were used to assess publication bias. Cumulative meta-analysis was performed by the year of publication. All statistical analyses were performed using Stata (release 12.0; College Station, TX, USA).

3. Results

3.1. Characteristics of the included studies

After the initial screening of titles and abstracts, 29 studies were selected for full-text review. Twelve studies were excluded because they did not meet our inclusion criteria.

A total of 17 case-control studies including 3326 renal recipients were eligible for our systematic review and meta-analysis (Fig. 1) (Misra et al., 2014; Haimila et al., 2009; Canossi et al., 2013; Dmitrienko et al., 2005; Gorgi et al., 2006; Krichen et al., 2009; Gao et al., 2012; Kim et al., 2010; Wisniewski et al., 2006; Gendzekhadze et al., 2006; Domanski et al., 2012; Kusztal et al., 2010; Ruhi et al., 2015; Krichen et al., 2011; Domanski et al., 2011; Sfar et al., 2009; Pawlik et al., 2014). The characteristics of the studies included in our analysis are described in Table 1.

3.2. The CTLA-4 gene polymorphism

Thirteen case-control studies investigated the association between the CTLA-4 gene variant and acute rejection after kidney transplantation, and 8 gene variants (+49 G/A, −318 C/T, −1147 C/T, −1661 A/G, +6230 A/G, −1722 T/C, −658 C/T, and 3′UTR G/A) were included for review and meta-analysis. Of these, 6 variants (+49 G/A, −318 C/T, −1147 C/T, −1661 A/G, +6230 A/G, −1722T/C) could be summarized for quantitative synthesis (Table 2); otherwise, due to the limited number of eligible studies, −658C/T and 3′UTR G/A could only be systematically reviewed.

In the quantitative data synthesis, we identified an association of the +49A/G variant with AR (OR: 0.79, 95% CI: 0.63–0.98; $P = 0.034$) in the recessive genetic model (AA/AG vs. GG) (Fig. 2A); furthermore, in the analysis of allele contrast, associations of the −1661 A/G variant with AR (OR: 0.059, 95% CI: 0.042, 0.084; $P = 0.00$) and the −1722 T/C