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Interleukin-17 receptor polymorphism predisposes to primary graft dysfunction after lung transplantation

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BACKGROUND: Primary graft dysfunction (PGD), with an incidence of 11% to 57%, is a major cause of morbidity and mortality within the first 30 days after lung transplantation (LTx). In this study, we postulate that recipient genetic variants in interleukin-17 and -23 receptor genes (IL-17R and IL-23R, respectively) may predispose LTx recipients to an increased risk for developing PGD.

METHODS: Seven genetic variants of IL-17R and IL-23R were successfully genotyped in 431 lung transplant recipients. Our primary end-point was PGD and secondary end-points were time to extubation, intensive care unit (ICU) stay, bronchoalveolar lavage neutrophilia and serum C-reactive protein.

RESULTS: The AA genotype of the rs882643 genetic variant of IL-17R was associated with higher PGD grades at 0 hour (adjusted $p = 0.042$), 12 hours (adjusted $p = 0.013$) and 48 hours (adjusted $p = 0.0092$) after LTx. The GG genotype of the rs2241049 genetic variant of IL-17R was associated with higher PGD grades at 48 hours (adjusted $p = 0.0067$) after LTx. For both genetic variants, no association was found with extubation time, ICU stay, post-operative BAL neutrophilia, serum CRP, chronic lung allograft dysfunction (CLAD) or graft loss.

CONCLUSION: Both genetic variants of IL-17R (rs882643 and rs2241049) were associated with PGD. This confirms a genetic predisposition toward PGD and suggests a role of IL-17 in driving neutrophilia in PGD.

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During the last 2 decades, lung transplantation (LTx) has become an established therapeutic option for selected patients with different forms of end-stage pulmonary disease. However, mortality rates after LTx remain relatively high.[1] Primary graft dysfunction (PGD), with an incidence of 11% to 57%, is a major cause of morbidity and mortality within the first 30 days after LTx.[1,2] PGD is characterized by pulmonary edema with diffuse alveolar damage, clinically manifesting as progressive hypoxemia with radiographic infiltrates.[2]

PGD has been variously referred to over a wide range of synonyms, such as ischemia-reperfusion injury, re-implantation response, reperfusion edema, primary graft

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failure, post-transplant acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). None of these terms are perfectly synonymous, and therefore in 2005 a working group of the International Society for Heart and Lung Transplantation (ISHLT) proposed a standardized definition for PGD, along with a grading system.[3] The defined criteria were radiographic pulmonary infiltrates and a partial pressure of oxygen/fraction of inspired oxygen (P/F) ratio assessed at certain time-points (0, 12, 24, 48, and 72 hours after LTx) with the exclusion of mechanical, immunologic and infectious causes that can mimic, modify or confound its definition and grading.[3] Injury inflicted on the donor lung by the transplant process (retrieval, preservation, implantation and reperfusion) in combination with other factors, such as acid aspiration, pneumonia and trauma from mechanical ventilation, contribute to the development of PGD.[2] This acute lung injury leads to alveolar flooding with protein-rich edema.[4] Furthermore, pulmonary injury will activate donor macrophages and pulmonary endothelial cells that recruit and activate recipient lymphocytes and neutrophils.[2] The inflammation leads to further epithelial damage and excessive cytokine secretion, which is probably the immunologic correlate of PGD and, ultimately, may even lead to graft loss.

The interleukin (IL)-17/IL-23 axis may play a key role in PGD, as demonstrated by Yoshida and colleagues, who showed that IL-17/IL-23-dependent memory T cells led to PGD-related bronchoalveolar lavage (BAL) neutrophilia.[5] Furthermore, genetic variants of IL-23R have been shown to be involved in chronic neutrophilic inflammatory diseases like rheumatoid arthritis, and Th17 cells are linked to several chronic inflammatory respiratory diseases, including chronic obstructive pulmonary disease, asthma, cystic fibrosis and bronchiolitis obliterans syndrome after LTx.[6–11] In the present study, we postulated that genetic variants in IL-17 receptor (IL-17R) and IL-23R genes may predispose LTx recipients to developing PGD after LTx.

Methods

Study design

In this retrospective analysis, we reviewed all LTxs performed at our hospital between January 2000 and December 2010. Approval for this study was granted by the institutional ethics committee of the University Hospitals Leuven (S54739) and all patients were asked to consent. The cohort consisted of 470 patients who received a single-lung (SLTx), sequential single-lung (SSLTx) or heart–lung (HLTx) transplant, and of whom clinical data, BAL fluid and blood were prospectively collected within our bio-bank (S51577).

Patients' characteristics or confounding factors included donor/recipient age, recipient gender, donor/receptor body mass index (BMI), bypass [cardiopulmonary bypass (CPB)/extracorporeal membrane oxygenation (ECMO)], donor P/F, ischemic time, surgery time, donor smoking history, sarcoidosis, type of LTx (SLTx vs SSLTx vs HLTx) and type of underlying lung disease. Clinical follow-up data included PGD, time to extubation (days), length of intensive care unit (ICU) stay (days), time to chronic lung allograft dysfunction (CLAD) and graft loss, BAL cell profile and serum C-reactive protein (CRP) as markers for pulmonary and systemic inflammation. PGD was graded at fixed time-points, 0, 12, 24 and 48 hours after LTx (T0, T12, T24 and T48), according to the ISHLT classification and based on P/F ratio (Grade 0 to 1: P/F >300 mm Hg; Grade 2: P/F 200 to 300 mm Hg; Grade 3: P/F <200 mm Hg). Post-operative (within the first week) bronchoscopies with BAL (2×50 ml of saline) in combination with cell count/differentiation were performed routinely, as previously reported.[12] The routine bio-banking of BAL at our center was started in 2001. Serum CRP values at 24, 48 and 72 hours were used for analysis. Retransplantation ($n = 18$) was considered as a separate transplantation for outcome analyses, because a second allograft was evaluated in an already genotyped recipient, as previously described.[13]

Genotyping

Of the total cohort of 470 lung transplant patients eligible for inclusion, recipient DNA was extracted from peripheral blood, or when unavailable from explanted lung tissue. DNA from blood samples was extracted using the QIAamp DNA Blood Midi kit, according to the supplier's instructions (Qiagen, Hilden, Germany). For DNA extraction from lung tissue embedded in paraffin blocks, paraffin was removed by xylene, followed by 2 washes with ethanol. After the paraffin-removal step, tissue was digested with proteinase K solution and DNA was extracted using a DNeasy Blood and Tissue kit (Qiagen). For control of DNA purity, 1 μl of genomic DNA was used to measure the 260/280 and 260/230 ratios with a Nanodrop 1000 (NanoDrop Technologies, Wilmington, DE). Only samples with a 260/280 ratio <2 and a 260/230 ratio <1 were accepted. DNA (5 ng/μl) was aliquoted into 384-well plates, and IL-17R and IL-23R genetic variants were genotyped in a blinded manner using iPLEX technology on a compact analyzer (MassARRAY; Sequenom, Inc., San Diego, CA), as reported previously.[7,11,14,15] In 16 patients, DNA extraction failed, and therefore no DNA was available for genotyping.

Genotyping for rs879574 (IL-17R gene), rs882643 (IL-17R gene), rs2241049 (IL-17R gene), rs2201841 (IL-23R gene), rs10489628 (IL-23R gene), rs2066808 (IL-23R gene) and rs134315 (IL-23R gene) was performed in a blinded manner using iPLEX technology on the compact analyzer (MassARRAY), as reported previously.[7,14,15] Automated genotyping calls were generated using the MassARRAY RTTM software and were validated by manual review of the raw mass spectra. Quality control was performed by genotyping 12 samples in duplicate, with a duplicate concordance of 100%. The success rate of genotyping within the remaining 454 patients was $>90\%$ (90% to 96%) for each of the 7 selected genetic variants.

Initially, an association between PGD at different time-points and any of the selected genetic variants was assessed. We could not find an association for any of the genetic variants in the IL-23R genes, but 2 genetic variants (rs882643 and rs2241049) of the IL-17R variant seemed to influence PGD after LTx and only those were investigated more closely. The success rate of genotyping within the remaining 454 patients was 95% for both single-nucleotide polymorphisms (SNPs; rs882643 and rs2241049), resulting in 431 patients for further analysis. The genetic variants are located in both coding (rs882643) and non-coding (rs2241049) regions of the IL-17R gene.

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