Issac and El Nahid
Egyptian Journal of Medical Human Genetics (2023) 24:69
https://doi.org/10.1186/s43042-023-00449-3

Egyptian Journal of Medical Human Genetics

RESEARCH

Open Access

Association of *IL-1β* rs16944 and *IL-1RN* rs2234663 gene polymorphisms with graft function in renal transplant recipients

Marianne Samir Makboul Issac[1*] and Maggie S. El Nahid[2]

Abstract

Background After renal transplantation, renal graft function affects both patient and graft survival. There is growing evidence of the genetic association between interleukin-1β (*IL-1β*) or its receptor antagonist (*IL-1RN*) and graft function in renal transplantation. The objective of this study is to investigate the role of the recipient *IL-1β* and *IL-1RN* gene polymorphisms and their haplotypes on renal graft outcome.

Methods Using PCR, *IL-1β* (−511C/T) and *IL-1RN* (86 bp VNTR) gene polymorphisms were determined in 31 renal allograft recipients; eight cases with stable allograft function and 23 cases with early renal dysfunction as well as 26 age- and gender-matched healthy controls.

Results A statistically significant difference in *IL-1 β* (−511C/T) gene polymorphisms and *IL-1RN/IL-1β* haplotypes was observed on comparing renal allograft recipients with stable allograft function and those with early renal allograft dysfunction. However, the difference in the frequency distribution of *IL-1RN* gene polymorphisms, between these two groups, did not reach statistical significance. Also, no statistically significant difference was observed in comparing these two gene polymorphisms and their haplotypes between renal allograft recipients and healthy controls.

Conclusion The *IL-1β* −511 CT/TT polymorphic genotypes and *IL-1RN/IL-1β* polymorphic haplotypes are associated with early renal allograft dysfunction. These are observational data that can be repeated in larger studies. If the results obtained are consistent, this might open doors to personalized medicine where clinicians can take necessary measures to identify the renal transplant recipients' genotypes at risk of mounting an increased inflammatory response and hence administer the appropriate immunosuppressive protocol.

Keywords Renal transplantation, Graft function, *IL-1β* (− 511C/T), *IL-1RN* (86 bp VNTR), Gene polymorphisms

Background

Renal transplantation is the ideal treatment for patients with end-stage renal disease [1]. It has been suggested that in human renal transplantation, pro-inflammatory Th1 lymphocytes and their cytokines mediate allograft rejection, whereas the Th2 lymphocytes and their cytokines are involved in the process of tolerance induction [2]. The inter-individual differences in cytokine production that influence allograft rejection might be impacted by the polymorphisms within the encoding genes that can regulate the various inflammatory responses within the graft [3].

Interleukin-1 (IL-1) plays a crucial role in the inflammatory response [4]. During allograft rejection, an increase in IL-1 production precedes allograft dysfunction and injury [5]. The genes of the IL-1 complex, which are located on chromosome 2q13, encode for three

*Correspondence:
Marianne Samir Makboul Issac
mariannesamir@kasralainy.edu.eg
[1] Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, El Saray St., El Manial, Cairo 11956, Egypt
[2] Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

proteins: IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). It has been reported that IL-1α is approximately 3000 times less active than IL-1β [6]. Each of the genes is polymorphic, and there is evidence that specific alleles are associated with increased susceptibility to inflammation [7]. A single nucleotide polymorphism (SNP) (rs16944) has been identified at bp position − 511 in the promoter region of the *IL-1β* gene with a substantial influence on its serum levels [8]. IL-1β plays an important role in the development and progression of acute kidney injury (AKI) [9]. In renal tubular cells, inflammasome-mediated caspase-1 activation and IL-1β generation are induced by several intra- and extra-cellular stimuli such as ischemic-reperfusion injury, hypotonic stress, adenosine triphosphate, mitochondrial dysfunction, uric acid crystals and lysosomal rupture [10].

The IL-1 receptor antagonist gene (*IL-1RN*) has a penta-allelic polymorphic site in intron 2 (rs2234663) containing variable numbers of an 86-bp tandem repeat (VNTR) sequence. The IL-1 complex is highly distinctive because the IL-1 receptor antagonist (IL-1Ra) acts as a natural inhibitor that binds to the IL-1 receptor inhibiting IL-1α and IL-1β binding [5].

The clinical outcome of renal transplantation is impacted by the recipient's immune response to the transplanted kidney. The ability to manage a patient's clinical course depends on the ability to control the immune response through immunosuppressive therapy [11]. Inhibition of IL-1 production is one of the main mechanisms by which corticosteroids suppress the immune response. IL-1Ra production is also enhanced in stable human kidney graft recipients and hence, could be a crucial factor in the early down-regulation of the allogeneic immune response. Drugs targeting IL-1 such as recombinant IL-1RN (anakinra), IL-1β traps (rilonacept), and neutralizing anti-IL-1β antibodies (canakinumab) are currently in clinical use; targeting IL-1 has shown promising results in renal transplantation patients [12].

This research work aimed to determine the *IL-1β* and *IL-1RN* gene polymorphisms among a group of renal transplant recipients and to study whether there is an association between these polymorphisms and their haplotypes with renal graft outcome.

Methods

Subjects

Our study included 31 patients (age range 18–48 years; mean age 32.68 ± 10.47; 23 males and 8 females) who had undergone living-donor renal transplantation at Kasr Al Ainy Hospital, Faculty of Medicine, Cairo University as well as 26 age- and gender-matched healthy controls.

Inclusion criteria included male and female adult (18–60 years old) patients undergoing renal transplantation. All patients had ABO- and HLA-matched living donors. Exclusion criteria included any patient with pre-renal or post-renal causes of renal allograft dysfunction.

Twenty-three patients experienced early renal allograft dysfunction [13], based on clinical diagnosis, including persistent elevation of the patient's serum creatinine above their normal baseline, even after correction of hemodynamic status, urinary tract infections, and immunosuppressive drug level. Early dysfunction or failure occurring ≤ 6 months post-transplant can occur either immediately, during the initial hours and days post-transplant or within the first few weeks or months after transplant [13]. Eight patients had stable graft function (SGF).

Healthy controls for the study were recruited from the same geographical area, with no history of hypertension, diabetes, renal failure, vascular diseases, stroke, and/or cardiac diseases.

Laboratory methods

Blood samples and genotyping

Two milliliters of blood were collected in a tube containing EDTA as an anticoagulant for DNA extraction and stored at − 20 °C. Genomic DNA was isolated from peripheral blood leukocytes using a genomic DNA purification kit according to the manufacturer's instructions (Thermo Scientific, USA).

Genotyping of IL-1β (− 511 C>T) (rs16944) by PCR–RFLP

IL-1β − 511 C/T genotyping was performed as previously described [14] with the primer pair (forward, 5′-TGG CAT TGATCT GGT TCATC-3′, and reverse, 5′-GTT TAG GAATCT TCCCAC TT-3′) (Bioneer, Korea) with initial denaturation at 95 °C for 1 min followed by 30 cycles of 95 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s with a final extension at 70 °C for 7 min using a PCR Thermal Cycler (ThermoHybaid, UK). PCR products were digested by restriction endonuclease AvaI (ThermoScientific, USA) and visualized by electrophoresis on a 3% agarose gel stained with ethidium bromide. Alleles were coded as follows: T, 304 bp, and C, 190 and 114 bp.

Genotyping of IL-1RN VNTR (rs2234663) by PCR

IL-1RN genotyping was performed as previously described [15] with the primer pair (forward, 5′-CTC AGC AAC ACT CCT AT-3′, and reverse, 5′-TCC TGG TCT GCA GGT AA-3′) (Bioneer, Korea) with initial denaturation at 94 °C for 4 min followed by 32 cycles of 94 °C for 1 min, 50 °C for 1 min, and 72 °C for 1 min with a final extension at 72 °C for 10 min using a PCR Thermal Cycler. PCR products were analyzed by electrophoresis on a 1.5% agarose gel stained with ethidium bromide. Alleles 1–5 (IL-1RN 1–IL-1RN 5) were detected according to their sizes relative to a 100-bp DNA ladder: allele 1

(four repeats), 410 bp; allele 2 (two repeats), 240 bp; allele 3 (five repeats), 500 bp; allele 4 (three repeats), 325 bp; and allele 5 (six repeats), 595 bp.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Mann–Whitney *U* test for independent samples. For comparing categorical data, the Chi-square (χ^2) test was performed. An exact test was used instead when the expected frequency was less than 5. *p* values less than 0.05 were considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Table 1 Demographic and clinical data of renal transplant recipients and healthy controls

	Renal transplant recipients (*n* = 31)	Healthy controls (*n* = 26)
Age (years)	32.68 ± 10.47	35.65 ± 8.85
Gender		
Male	23 (74.2%)	21 (80.8%)
Female	8 (25.8%)	5 (19.2%)
Body mass index (kg/m^2)	21.52 ± 2.37	20.5 ± 1.75
Causes of end-stage renal disease		
Hypertension	14 (45.2%)	
Pre-eclampsia	1 (3.2%)	
Reflux uropathy	2 (6.5%)	
Unknown	13 (41.9%)	
Ureteric stricture	1 (3.2%)	
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	15.55 ± 4.82	
Mean time of pre-transplantation hemodialysis, months (± SD)	32.15 ± 25.73	
Warm ischemia time (minutes)	30.97 ± 7.24	
Cold ischemia time (minutes)	42.58 ± 9.03	
Donor age (years)	35.29 ± 6.49	
Donor gender		
Male	25 (80.6%)	
Female	6 (19.4%)	

Qualitative data are represented as frequency (percentage), while quantitative data are represented as mean ± SD

Results

Characteristics of renal transplant cases and controls

The demographic and clinical data of the renal transplant cases and their age- and gender-matched healthy controls are shown in Table 1. Our renal transplant cases had a mean age of 32.68 ± 10.47 years with the majority (74.2%) being males. Around 45% of the cases developed end-stage renal disease as a result of hypertension. The mean time of pre-transplantation hemodialysis was 32.15 ± 25.73 months. The mean age of the donors was 35.29 ± 6.49 years, and the majority of donors (80.6%) were males (Table 1).

Causes and clinical characteristics of the early allograft dysfunction group

The causes of early allograft dysfunction, as revealed by renal biopsy, were acute tubular injury, acute rejection, and thrombotic microangiopathy. The main clinical characteristics observed in the allograft dysfunction group were the rise of serum creatinine, elevated renal resistivity index, recent hypertension, proteinuria, and hematuria. None of these clinical features have been observed in the stable renal allograft group (Table 2).

Frequency distribution of *IL-1RN* (VNTR) and *IL-1β* − 511C/T gene polymorphisms and *IL-1RN*/*IL-1β* haplotypes in renal transplant cases and healthy controls

The majority of our participants harbored the *IL-1RN* *1*1 genotype, while fewer cases displayed the less

Table 2 Clinical characteristics of the early renal allograft dysfunction group

Clinical characteristics	Renal transplant recipients (*n* = 31)	
	Stable allograft function (Group I) (*n* = 8)	Early renal allograft dysfunction (Group II) (*n* = 23)
Proteinuria	0 (0%)	7 (30.4%)
Recent hypertension	0 (0%)	11 (47.8%)
Hematuria	0 (0%)	6 (26%)
Rise of serum creatinine	0 (0%)	21 (91.3%)
Elevated renal resistivity index	0 (0%)	19 (82.6%)

Data are represented as frequency (percentage)

frequent genotype *1*2. However, the rare genotypes *2*2, *3*3, *1*3, and *2*4 were present in only four participants, so these genotypes were grouped as 'others' as shown in Table 3. Also, the less frequent haplotypes *1/T, *2/C, *2/T,*3/C, *3/T and*4/T were grouped as 'others'. No statistically significant difference was encountered in the distribution of *IL-1RN* ($p=0.270$) and *IL-1β* gene polymorphisms ($p=1.0$) and their haplotypes ($p=0.259$) between cases and controls (Table 3).

Association of *IL-1RN* (VNTR) and *IL-1β* − 511C/T gene polymorphisms and *IL-1RN*/*IL-1β* haplotypes with graft function in renal transplant recipients

Renal transplant recipients were further subdivided according to the graft function into stable allograft function (Group I) and early renal allograft dysfunction (Group II) as shown in Table 4. On comparing *IL-1RN* genotypes between the two groups, 87.5% of Group I were carriers of the *IL-1RN* *1*1 genotype versus 65.2% of Group II cases; however, the difference did not reach

Table 3 Frequency distribution of *IL-1RN* (VNTR) and *IL-1β* − 511C/T gene polymorphisms and *IL-1RN/IL-1β* haplotypes in renal transplant recipients and healthy controls

Gene polymorphism	Renal transplant recipients ($n=31$)	Healthy controls ($n=26$)	*p*-value
IL-1RN genotypes			
*1*1	22 (71%)	14 (53.8%)	0.270
*1*2 + others[†]	9 (29%)	12 (46.2%)	
IL-1β genotypes			
CC	7 (22.6%)	6 (23.1%)	1.000
CT + TT	24 (77.4%)	20 (76.9%)	
IL-1RN/IL-1β haplotypes			
*1/C	24/62 (38.71%)	24/52 (46.15%)	0.259
Others[‡]	38/62 (61.29%)	28/52 (53.85%)	

IL-1RN Interleukin-1 receptor antagonist, *IL-1β*, Interleukin-1β

[†] *IL-1RN* genotypes 'others' include the less frequent genotypes *IL-1RN* *2*2, *3*3, *2*4 and *1*3

[‡] *IL-1RN/IL-1β* haplotypes 'others' include the less frequent haplotypes *1/T, *2/C, *2/T, *3/C, *3/T and*4/T

p value ≤ 0.05 is considered to be statistically significant

Table 4 Association of *IL-1RN* (VNTR) and *IL-1β* – *511 C/T* gene polymorphisms and *IL-1RN/IL-1β* haplotypes with graft function in Renal Transplant Recipients

Gene polymorphism	Renal transplant recipients ($n=31$)		*p*-value
	Stable allograft function (Group I) ($n=8$)	Early renal allograft dysfunction (Group II) ($n=23$)	
IL-1RN genotypes			
*1*1	7 (87.5%)	15 (65.2%)	0.379
*1*2 + others[†]	1 (12.5%)	8 (34.8%)	
IL-1β genotypes			
CC	6 (75%)	1 (4.3%)	< 0.001
CT + TT	2 (25%)	22 (95.7%)	
IL-1RN/IL-1β haplotypes			
*1/C	11/16 (68.75%)	13/46 (28.26%)	< 0.001
Others[‡]	5/16 (31.25%)	33/46 (71.74%)	

IL-1RN Interleukin-1 receptor antagonist, *IL-1β* Interleukin-1β

[†] *IL-1RN* genotypes 'others' include the less frequent genotypes *IL-1RN* *2*2, *3*3, *2*4 and *1*3

[‡] *IL-1RN/IL-1β* haplotypes 'others' include the less frequent haplotypes *1/T, *2/C, *2/T, *3/C, *3/T and*4/T

p value ≤ 0.05 is considered to be statistically significant

statistical significance, $p=0.379$. As regards *IL-1β* genotype distribution, 95.7% of Group II were carriers of the *IL-1β* polymorphic genotypes CT + TT versus 25% of Group I cases; with a statistically significant difference, $p<0.001$. Interestingly, on comparing the *IL-1RN*/*IL-1β* haplotype between the two groups, 68.75% of Group I were carriers of the wild-type haplotype *1/C versus 28.26% of Group II, with a statistically significant difference, $p<0.001$ (Table 4).

Discussion

Following renal transplantation, renal graft function is important for patient and graft survival. The immune response, to transplanted organs, is regulated by a network of cytokine interactions. However, the genes encoding these cytokines and their receptors are polymorphic. We attempted to study the impact of *IL-1β* and *IL-1RN* polymorphisms and their haplotypes on graft function. In the present study, we did not observe a statistically significant difference in the two studied gene polymorphisms between the healthy controls and renal transplant recipients. However, our results indicated that *IL-1β* − 511 C/T genotypes showed a statistically significant difference between stable allograft function and early renal allograft dysfunction, where 75% of the stable allograft function had the wild-type CC, compared to only 4.3% of the early renal allograft dysfunction. On comparing *IL-1RN* gene polymorphisms between the two groups, 87.5% of stable allograft function harbored the genotype *1*1 compared to 65.2% of early renal allograft dysfunction; however, the difference did not reach statistical significance. Interestingly, the *IL-1RN*/*IL-1β* haplotype showed a statistically significant difference when compared between the two groups, where 68.75% of those with stable allograft function were carriers of the haplotype *IL-1RN* *1/*IL-1β* *C versus 28.26% of those showing early renal allograft dysfunction.

Published results from previous studies were inconsistent as regards the role of *IL-1RN* and *IL-1β* polymorphisms and haplotypes on graft function and incidence of acute rejection (AR) in renal transplant recipients. Our findings contrasted those provided in a previous study from India by Manchanda et al. [16], where there was a significant difference in the distribution of *IL-1β* and *IL-1RN* genotypes between healthy controls and renal transplant groups. They stated that a statistically significant difference was also observed in *IL-1RN* genotypes when compared between stable graft function and delayed graft function groups whereas no significant difference in *IL-1β* − 511 promoter polymorphism was observed between these two transplant recipients' groups [16].

Bhat et al. reported that the *IL-1β* − 511TT genotype was more prevalent in renal transplant cases versus controls and those experiencing rejection episodes versus those with stable graft function in their study conducted on participants from Kashmeer valley [3]. Ding et al. stated that there was no significant difference between recipients with an AR episode and those with an absence of AR regarding *IL-1RN* and *IL-1β* polymorphisms in the studied Chinese population [17]. These discordant findings might be due to differences in ethnic and geographical backgrounds, sample size, different clinical diagnostic processes, and immunosuppressive protocols [18, 19].

Interestingly, our study showed that *the IL-1β* − 511 TT genotype was present at higher frequencies in the early renal allograft dysfunction versus stable allograft function group, and this has been reported in other research work [3, 16], assuming it represents a "high secretor" phenotype leading to increased pro-inflammatory activity in autoimmune and infectious diseases [20].

Previous studies [21–25], analyzing the impact of the *IL-1RN* genotypes on levels of IL-1β and IL-1Ra, have provided discordant results. Studies on epithelial/endothelial cells have shown that *the IL-1RN**1 allele is more anti-inflammatory with higher levels of IL-1Ra produced by cells harboring the *IL-1RN**1 allele [21]. This is following the findings of Santtila et al. [22] who stated that *the IL-1RN**2 allele is associated with increased IL-1 β release from peripheral blood mononuclear cells. Whereas Vamvakopoulos et al. [23] and Candiotti et al. [24] indicated that IL-1Ra concentrations were significantly higher in carriers of *IL-1RN**2* than in *IL-1RN**1* homozygotes. Also, they stated that *IL-1RN**2* homozygotes showed a decreased IL-1 β release, in a dosage-dependent manner [23]. Other researchers [25] have indicated that they failed to demonstrate any *IL-1RN* allelic effect on IL1Ra expression manner.

The polymorphism of *IL-1RN* consists of perfect tandem repeats of a conserved 86–base pair sequence, which has been reported to contain putative protein-binding sites; an α-interferon silencer A, a β-interferon silencer B, and a short-term phase response element [24]. These binding sites may influence gene expression; however, the exact mechanism is under investigation.

It has been postulated that it is not only the *IL-1β* or *IL-1RN* genotypes but the haplotype of the *IL-1RN* and *IL-1β* that play a role in modulating the susceptibility to certain disease conditions [26]. In any individual, an SNP at a given locus may be a part of a haplotype that affects protein expression or function, whereas the same SNP in another individual may not form part of the functional haplotype. Haplotyping of *IL-1* reflects that patients carrying high-producing alleles of *IL-1β* and low-producing alleles of *IL-1RN* are at higher risk of progression to rejection of allograft [26].

Our study has numerous strengths; we recruited 31 consecutive Egyptian live-donor renal transplant recipients and 26 age- and gender-matched healthy controls from the same geographical area. They represent an under-studied population, and there is a crucial need to shed light on the underlying gene polymorphisms which impact graft function in our studied groups. To the best of our knowledge, this is the first study investigating the impact of *IL-1β* and *IL-1RN* gene polymorphisms on graft function in Egyptian renal transplant recipients.

This study is not without limitations and our conclusion should be interpreted with caution due to the relatively small sample sizes. Although the sample size was relatively small, statistically significant results as regards the association of gene polymorphism with graft function were provided. However, this study should be replicated with a larger sample size before translating this information into clinical guidelines. Also, we did not measure the levels of IL 1 in renal transplant recipients and correlate it with the different *IL-1β* or *IL-1RN* genotypes and their haplotypes. Based on our results as well as others [3, 16, 20, 21], we assume that specific genotypes are 'high' or 'low' secretors.

Conclusions

This study sheds some light on the importance of detecting the underlying genetic polymorphisms that might impact graft function. Herein, we show that the *IL-1β*−511 CT/TT polymorphic genotypes and *IL-1RN*/*IL-1β* polymorphic haplotypes were associated with early renal allograft dysfunction. To the best of our knowledge, this is the first report from Egypt suggesting that a high producer *IL-1β* genotype and a combination of low producer of *IL-1RN* with high producer *IL-1β* haplotype might act as risk factors for graft rejection. Thus, the measurement of IL-1 production in disease states might serve as a marker of the clinical course of the disease or can be used in the evaluation of therapeutic efficacy. Moreover, post-transplant down-regulation of IL-1 bioactivity, to reverse ongoing rejection, could provide an efficient therapeutic modality.

The results presented herein are observational data, and this is an exploratory research question that perhaps can be followed up prospectively and might open new avenues for personalized medicine. If the results of future studies were consistent with ours and in order to reduce the occurrence of graft dysfunction, clinicians can take necessary measures to identify the renal transplant recipients' genotypes at risk of mounting an increased inflammatory response and hence administer the appropriate immunosuppressive therapy. Studies recruiting large numbers of renal transplant recipients, with prolonged periods of follow-up, are required before translating these findings to clinical guidelines for renal transplant recipients.

Abbreviations

IL-1	Interleukin-1
IL-1Ra	IL-1 receptor antagonist protein
IL-1RN	IL-1 receptor antagonist gene
SNP	Single nucleotide polymorphism
AKI	Acute kidney injury
AR	Acute rejection
VNTR	Variable number of tandem repeat
SGF	Stable graft function

Acknowledgements

We would like to thank Dr. Shady Ramez for his participation in the collection of patient samples and their clinical data.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by ME, while laboratory studies and molecular analysis were performed by MI. The first draft of the manuscript was written by MI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive any grant from funding agencies.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Institutional Research Ethics Committee as well as the relevant guidelines and regulations and adhere to the tenets of the Declaration of Helsinki as revised in 2013. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

Received: 14 November 2022 Accepted: 16 October 2023
Published online: 31 October 2023

References

1. Seyhun Y, Mytilineos J, Turkmen A, Oguz F, Kekik C, Ozdilli K et al (2012) Influence of cytokine gene polymorphisms on graft rejection in Turkish patients with renal transplants from living related donors. Transplant Proc 44(6):1670–1678. https://doi.org/10.1016/j.transproceed.2012.05.046
2. Stepkowski SM (2000) Immunobiology of allograft rejection. In: Kahan BD, Ponticielli C (eds) Principles and practice of renal transplantation. Blackwell, Malden, pp 41–87
3. Bhat MA, Parry MA, Nissar S, Sameer AS, Bhat IA, Shah ZA et al (2017) Association of IL1 beta gene polymorphism and allograft functions in renal transplant recipients: a case–control study from Kashmir Valley. BMC Nephrol 18(1):111. https://doi.org/10.1186/s12882-017-0526-5
4. Oliviero F, Sfriso P, Punzi L, Dayer J-M (2019) Editorial: IL-1 inhibition. Front Pharmacol 10:87. https://doi.org/10.3389/fphar.2019.00087

5. Conti F, Breton S, Batteux F, Furlan V, Houssin D, Weill B et al (2000) Defective interleukin-1 receptor antagonist production is associated with resistance of acute liver graft rejection to steroid therapy. Am J Pathol 157(5):1685–1692. https://doi.org/10.1016/S0002-9440(10)64805-5
6. Ferreira SH, Lorenzetti BB, Bristow AF, Poole S (1988) Interleukin-1 beta as a potent hyperalgesic agent antagonized by a tripeptide analog. Nature 334(6184):698–700. https://doi.org/10.1038/334698a0
7. Serdaroğlu G, Alpman A, Tosun A, Pehlivan S, Ozkinay F, Tekgül H et al (2009) Febrile seizures: interleukin 1beta and interleukin-1 receptor antagonist polymorphisms. Pediatr Neurol 40(2):113–116. https://doi.org/10.1016/j.pediatrneurol.2008.10.004
8. Kira R, Torisu H, Takemoto M, Nomura A, Sakai Y, Sanefuji M et al (2005) Genetic susceptibility to simple febrile seizures: interleukin-1beta promoter polymorphisms are associated with sporadic cases. Neurosci Lett 384(3):239–244. https://doi.org/10.1016/j.neulet.2005.04.097
9. Konno T, Nakano R, Mamiya R, Tsuchiya H, Kitanaka T, Namba S et al (2016) Expression and function of interleukin-1β-induced neutrophil gelatinase-associated lipocalin in renal tubular cells. PLoS ONE 11(11):e0166707. https://doi.org/10.1371/journal.pone.0166707
10. Masood H, Che R, Zhang A (2015) Inflammasomes in the pathophysiology of kidney diseases. Kidney Dis 1(3):187–193. https://doi.org/10.1159/000438843
11. Girnita DM, Burckart G, Zeevi A (2008) Effect of cytokine and pharmacogenomic genetic polymorphisms in transplantation. Curr Opin Immunol 20(5):614–625. https://doi.org/10.1016/j.coi.2008.08.002
12. Afsar B, Covic A, Ortiz A, Afsar RE, Kanbay M (2018) The future of IL-1 targeting in kidney disease. Drugs 78(11):1073–1083. https://doi.org/10.1007/s40265-018-0942-2
13. Goldberg RJ, Weng FL, Kandula P (2016) Acute and chronic allograft dysfunction in kidney transplant recipients. Med Clin N Am 100(3):487–503. https://doi.org/10.1016/j.mcna.2016.01.002
14. di Giovine FS, Takhsh E, Blakemore AI, Duff GW (1992) Single base polymorphism at −511 in the human interleukin-1 beta gene (IL1 beta). Hum Mol Genet 1(6):450. https://doi.org/10.1093/hmg/1.6.450
15. Tarlow JK, Blakemore AI, Lennard A, Solari R, Hughes HN, Steinkasserer A et al (1993) Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. Hum Genet 91(4):403–404. https://doi.org/10.1007/BF00217368
16. Manchanda PK, Bid HK, Kumar A, Mittal RM (2006) Genetic association of interleukin-1β and receptor antagonist (IL-Ra) gene polymorphism with allograft function in renal transplant patients. Transpl Immunol 15(4):289–296. https://doi.org/10.1016/j.trim.2006.01.004
17. Ding S, Xie J, Wan Q (2016) Association between cytokines and their receptor antagonist gene polymorphisms and clinical risk factors and acute rejection following renal transplantation. Med Sci Monit 22:4736–41. https://doi.org/10.12659/msm.898193
18. Lv R, Hu X, Bai Y, Long H, Xu L, Liu Z et al (2012) Association between IL-6-174G/C polymorphism and acute rejection of renal allograft: evidence from a meta-analysis. Transpl Immunol 26(1):11–18. https://doi.org/10.1016/j.trim.2011.10.003
19. Hu X, Bai Y, Li S, Zeng K, Xu L, Liu Z et al (2011) Donor or recipient TNF-A-308G/A polymorphism and acute rejection of renal allograft: a meta-analysis. Transpl Immunol 25(1):61–71. https://doi.org/10.1016/j.trim.2011.04.004
20. Hurme M, Lahdenpohja N, Santtila S (1998) Gene polymorphisms of interleukins 1 and 10 in infectious and autoimmune diseases. Ann Med 30(5):469–473. https://doi.org/10.3109/07853899809002488
21. Dewberry R, Holden H, Crossman D, Francis S (2000) Interleukin-1 receptor antagonist expression in human endothelial cells and atherosclerosis. Arterioscler Thromb Vasc Biol 20(11):2394–2400. https://doi.org/10.1161/01.atv.20.11.2394
22. Santtila S, Savinainen K, Hurme M (1998) Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. Scand J Immunol 47(3):195–198. https://doi.org/10.1046/j.1365-3083.1998.00300.x
23. Vamvakopoulos J, Green C, Metcalfe S (2002) Genetic control of IL-1beta bioactivity through differential regulation of the IL-1 receptor antagonist. Eur J Immunol 32(10):2988–2996. https://doi.org/10.1002/1521-4141(2002010)32:10%3c2988::AID-IMMU2988%3e3.0.CO;2-9
24. Candiotti KA, Yang Z, Morris R, Yang J, Crescimone NA, Sanchez GC et al (2011) Polymorphism in the interleukin-1 receptor antagonist gene is associated with serum interleukin-1 receptor antagonist concentrations and postoperative opioid consumption. Anesthesiology 114(5):1162–1168. https://doi.org/10.1097/ALN.0b013e318216e9cb
25. Clay FE, Tarlow JK, Cork MJ, Cox A, Nicklin MJ, Duff GW (1996) Novel interleukin-1 receptor antagonist exon polymorphisms and their use in allele-specific mRNA assessment. Hum Genet 97(6):723–726. https://doi.org/10.1007/BF02346180
26. Hurme M, Santtila S (1998) IL-1 receptor antagonist (IL-1Ra) plasma levels are co-ordinately regulated by both IL-1Ra and IL-1beta genes. Eur J Immunol 28(8):2598–2602. https://doi.org/10.1002/(SICI)1521-4141(199808)28:08%3c2598::AID-IMMU2598%3e3.0.CO;2-K

Publisher's Note