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Association between Immunoglobulin Receptors, Antigen C and Elevated Risk of Chronic Liver Rejection

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Abstract

Chronic liver rejection poses a complex challenge in transplantation, as some patients do not respond to increased immunosuppression. Killer cell immunoglobulin-like receptors and their interactions with Class I Human Leukocyte Antigens (HLA-I) play a crucial role in predicting Natural Killer (NK) cell alloreactivity and influencing acute liver graft rejection. However, their relevance in CR remains a subject of debate. In this study, we investigated KIR and HLA genotypes in 513 liver transplant recipients using sequence-specific oligonucleotide (PCR-SSO) methods. We examined KIRs, human leukocyte antigen C (HLA-C) genotypes, KIR gene combinations, and KIR/HLA ligand interactions in the entire cohort and compared them between CR (n=35) and no-ongoing rejection (NCR=478) cases. It was found that the presence of activating KIR (aKIR) genes in recipients (rKIR2DS2+ and rKIR2DS3+) increased the risk of CR compared to the NCR group (p=0.013 and p=0.038). Inhibitory KIR (iKIR) genes in recipients, particularly rKIR2DL2+, significantly elevated the CR rate compared to their absence (9.1% versus 3.7%, p=0.020), and KIR2DL3 also had a significant impact on increasing CR (13.1% versus 5.2%; p=0.008), with no effect on NCR. Furthermore, CR was observed in cases with HLA-I mismatches (MM), and the absence of the donor (d) HLA-C2 ligand (dC2–) increased the risk of CR compared to its presence (13.1% versus 5.6%; p=0.018). A significant increase in CR was noted in cases with rKIR2DL3+/dC1– (p=0.015), rKIR2DS4/dC1– (p=0.014), and rKIR2DL3+/rKIR2DS4+/dC1– (p=0.006) combinations. Long-term patient survival was significantly lower in recipients with rKIR2DS1+rKIR2DS4+/dC1– at 5-10 years post-transplant. This study highlights the influence of rKIR/dHLA-C combinations and aKIR gene variations in increasing the risk of CR, as well as the impact of KIR2DS1+/C1-ligands and KIR2DS4+/C1-ligands on long-term graft survival.

Keywords: Executioner cell immunoglobulin-like receptors • Human leucocyte antigen • Liver transplantation

Introduction

Continuous liver rejection is a phenomenon that requires ongoing attention due to the fact that many patients do not respond to increased immunosuppression, often leading to retransplantation or mortality. Despite these challenges, CLR occurs in 3-17% of liver transplant recipients, primarily due to the use of more advanced immunosuppression regimens. The pathogenesis of CLR is complex, characterized by obliterative arteriopathy and ductopenia [1].

Recent research has highlighted the potential involvement of natural killer (NK) cells, both adaptive and innate, in immune responses within the liver. The liver houses the largest population of NK cells, which play a crucial role in monitoring for infections and liver-related pathologies. The behavior and capabilities of these innate lymphocytes have been a subject of considerable interest. NK cells express a balance of activating and inhibitory receptors, and their alloactivation is influenced by various models of interactions between killer immunoglobulin-like receptors (KIR) and their ligands, including KIR/HLA-C-ligand interactions. The interplay between inhibitory and activating killer cell immunoglobulin-like receptor (iKIR and aKIR) diversity may have implications for graft-versus-host disease and liver graft survival [2].

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In the context of organ transplantation, several studies have suggested the role of KIR/HLA-C-ligand interactions in liver and kidney transplants and their relevance to acute rejection and short-term liver allograft injury. Previous research has revealed that NK cells can serve a dual role after solid organ transplantation, enhancing immunity in immunocompromised conditions while also exacerbating the rejection process by amplifying immune responses associated with rejection. NK cells have been found to significantly contribute to the pathogenesis of both acute and chronic antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR), representing a key player among all immune cells involved in allograft rejection [3].

Literature Review

Elevated NK cell cytotoxicity was associated with kidney allograft rejection, as evidenced by increased expression of CD107a and interferon (IFN-) production in patients experiencing acute and chronic renal transplant rejection, as compared to those with well-functioning grafts. Killer immunoglobulin-like receptors (KIRs) are glycoproteins expressed on NK cells and certain T lymphocyte subsets. These KIR receptors play a crucial role in regulating NK cell activity by interacting with specific epitopes on HLA-I molecules. KIR receptors transmit inhibitory (iKIR) or activating (aKIR) signals within the cell through their long or short intracytoplasmic tails. There are eight genes encoding iKIR receptors (KIR2DL1-3 and KIR2DL5 and KIR3DL1-3) and six genes encoding aKIR receptors (KIR3DS1 and KIR2DS1-5). Notably, KIR2DL4 encodes a receptor with dual functionality [4].

KIR genes exhibit extensive haplotypic diversity in terms of gene number and allelic polymorphism across all human populations. Among iKIRs, KIR2DL1 recognizes a lysine at position 80 on the α-helix of alleles belonging to the HLA-C2 allotype, while KIR2DL2/3 recognizes asparagines at the same position on HLA-C1 alleles. The specific recognition of HLA-C ligands has been documented for only KIR2DS1 and KIR2DS4, with the former recognizing C2 ligands and the latter recognizing both C2 and a limited subset

of C1 ligands, while ligands for other aKIRs remain unknown. Genotyping of KIR/HLA-C in both the graft and the recipient's liver can aid pathologists in predicting rejection responses and estimating the patient's survival, enabling timely clinical interventions to preserve the graft and enhance the quality and longevity of the transplant recipient. This study examines the impact of KIR/HLA-I on the development of continuous rejection (CR) and survival, with a focus on recipient KIRs (rKIR) and donor HLA (dHLA) class I ligands [5,6].

Discussion

In this comprehensive review, we have undertaken an analysis of KIR/HLA-C gene variations in a cohort of liver transplant patients and explored their potential correlation with the development of continuous rejection (CR) and graft survival, marking the first study of its kind in this context. The incidence of CR in liver transplants is relatively low, ranging from 3% to 17%, in stark contrast to acute rejection (AR) episodes observed in other solid organs such as the heart (25-60%), pancreas (20-40%), or kidney (30-70%). In our study, we observed a CR rate of 6.8%, which falls within the typical range for liver transplants. Despite a declining trend in CR rates over recent decades, several contemporary factors warrant continued vigilance regarding this complication. Risk factors for CR encompass the donor's advanced age, the autoimmune nature of the pretransplant condition, and the reduction or deliberate cessation of immunosuppressive therapy.

Therefore, the meticulous selection of donors in liver transplantation emerges as one of the most pivotal factors contributing to transplant success. Implementing a reasonable age limit of 65 years for liver donation is advisable. Notably, the average age of liver donors has been increasing, reaching 61.3 years for adults. In our study, the mean age of donors was 51.2 ± 0.9 years, aligning with recommended guidelines. However, our data underscore a noteworthy association between younger donors (average age of 44.09 ± 3.61 years) and a higher incidence of CR development in the non-CR group (mean age of 51.8 ± 0.9 years). Conversely, some prior investigations have found no impact of donor age on patient survival, although a heightened rate of delayed graft non-function has been reported with older donors. Numerous publications have linked KIR/HLA-I receptors to the outcomes of AR and patient survival in various organ transplants. Nevertheless, no studies to date have explored the influence of CR on liver grafts.

Conclusion

In this study, we examined the prevalence of KIR genes within donor-patient pairs. A notable observation was the elevated occurrence of the KIR2DS5 gene among healthy control subjects, although it did not exhibit any association with the development of continuous rejection (CR). Conversely, individuals experiencing CR displayed a higher and statistically more significant prevalence of KIR2DL2/S2 and KIR2DS3 genes. Nevertheless, previous investigations of acute rejection (AR) failed to establish a link between the presence or absence of specific KIR genes in liver grafts. In contrast, further research on AR in kidney transplants noted a protective effect associated with the KIR2DS5 gene and an association with the KIR2DS4 gene.

References

1. Choudhary, Narendra S, Sanjiv Saigal, Rinkesh K Bansal and Neeraj Saraf, et al. "Acute and chronic rejection after liver transplantation: What a clinician needs to know." *J Clin Experim Hepat* 7 (2017): 358-366.
2. Angelico, Roberta, Bruno Sensi, Tommaso M Manzia and Giuseppe Tisone, et al. "Chronic rejection after liver transplantation: Opening the Pandora's box." *World J Gastroenterol* 27 (2021): 7771.
3. Rodríguez-Perálvarez, Manuel, Jose M Rico-Juri, Emmanuel Tsochatzis and Patrizia Burra, et al. "Biopsy-proven acute cellular rejection as an efficacy endpoint of randomized trials in liver transplantation: A systematic review and critical appraisal." *Transplant Internat* 29 (2016): 961-973.
4. Blakolmer, Karin, Andrew Clouston and Amar Paul. "Update of the International Banff Schema for Liver Allograft Rejection: Working recommendations for the histopathologic staging and reporting of chronic rejection." *Hepatol* (2000): 792-799.
5. Gruttadauria, S, F Vasta, L Mandala and D Cintorino, et al. "Basiliximab in a triple-drug regimen with tacrolimus and steroids in liver transplantation." *Transplant Proc* 37 (2005): 2611-2613.
6. Armenian, Patil, Kathy T Vo, Jill Barr-Walker and Kara L Lynch. "Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review." *Neuropharmacol* 134 (2018): 121-132.

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