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The potential role of antibodies against minor blood group antigens in renal transplantation.

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Abstract

Blood group antigens are red-blood cell (RBC) surface markers comprising specific carbohydrate moieties attached to the glycolipids and glycoproteins within the membrane. In addition to the major ABO blood group antigens, at least 35 minor blood group antigens have been defined to date. These antigens have immunogenic potential and may cause a transfusion reaction. There is evidence for renal expression of antigens from the Kidd, MNS, Duffy and Lewis groups and therefore the potential for antibodies directed against these antigens to cross-react in a transplanted kidney. In individuals lacking a specific RBC antigen, antibodies may develop after *de novo* exposure to that antigen, in addition to the potential presence of pre-existing innate antibodies. Relatively little attention has been paid to non-ABO-system antibodies, with most reports in the literature focusing on transfusion reactions rather than on any putative role in allograft rejection. Here we review each of these antigens in the context of renal transplantation and what limited evidence there is on how such immunological risk may be assessed and managed.

Introduction

In addition to the major ABO blood group antigens, at least 35 minor blood group antigens have been defined to date [1]. These groups are categorised by antigens that are under the control of a single gene or cluster of closely linked genes and result in the attachment of specific carbohydrate moieties to the glycolipids and glycoproteins within the RBC membrane. Some of these blood group antigens act as chemokine receptors and membrane transporters, although the function of many remains unknown [2].

Minor RBC antigens may induce alloimmunisation, occasionally manifest as severe haemolytic transfusion reactions. Alloimmunisation is generally a complication arising from previous RBC transfusion, pregnancy or solid organ transplantation but in some cases *de novo* antibody formation has been described. In contrast to the well-established role of anti-A and B antibodies in renal allograft rejection, the role of non-ABO system antibodies is not well defined. Of the common non-ABO system antigens, there is evidence for renal expression of antigens from the Kidd, MNS, Duffy and Lewis groups and therefore the potential for innate or acquired antibodies directed against these antigens to increase immunological risk. Indeed, there are a number of clinical and experimental observations in the literature supporting the supposition that these RBC antigens act as minor histocompatibility antigens and may cause antibody mediated rejection (AbMR). There is also evidence that polymorphisms in some of these antigens may affect long term graft outcomes through non humoral pathways [3, 4].

In the general population, the incidence of red blood cell immunisation after a single transfusion is up to 10% with the risk of alloimmunisation rising to 40% with increasing number of transfusions [5]. The HLA-DRB1*15 phenotype has also been shown to be associated with hyper-responsiveness associated with RBC and HLA immunisation [6].

Within the chronic kidney disease (CKD) population, the incidence of alloimmunisation is reported to range from 1.7% to 14% [7, 8] with antibodies against Rh and Kell being the most commonly documented [9]. Although it is routine practice to perform a RBC antibody screen for potential renal transplant recipients, detailed phenotyping of donor RBC antigens is not usually performed, even though patients transplanted with a kidney expressing these antigens may represent a rejection risk. Relatively little attention has been paid to non-ABO-system antibodies, with most reports in the literature focusing on transfusion reactions rather than on any putative role in allograft rejection and the importance of these antigens may well be under-recognised. Here we review each of these antigens in the context of renal transplantation and what limited evidence there is on how such immunological risk may be managed.

Lewis

The Lewis antigens are a group of antigens which are expressed on RBCs as well as on cells from a wide variety of other organs including renal epithelial cells [10]. These antigens (Le^a and Le^b) were first recognised in the 1940s after a case of haemolytic

disease of the newborn, secondary to an Le^a binding antibody was reported [11]. Le^b was subsequently discovered two years later.

The synthesis of Lewis glycoproteins occurs primarily in the gut and relies on the enzyme fucosyltransferase encoded for by the *FUT3* gene [12]. Individuals not expressing this antigen (Le^{a-b-}) have inactivating point mutations within this gene. The commonest phenotype Le^{a-b+} is present in 50-80% of all races whilst the rarest phenotype Le^{a-b-} is present in 6% of Caucasians but ~20% of African, Chinese, Indian and Arabic populations [2,13].

These gut derived antigens are absorbed into the circulation and are subsequently adsorbed onto RBCs. Lewis antigens become immunologically available when co-expressed with RBC glycolipids. Like A and B antigens, soluble forms of Le^b but not Le^a are also found in the saliva and urine (secretor). Whilst the significance of secretor status is currently cryptic, there appear to be links between this, host defences [14] and graft outcomes [15] at least in ABO blood group status.

Unlike naturally occurring AB antibodies which are almost ubiquitous, not all individuals have innate anti-Le antibodies with antibodies generally being found in individuals who are Le^{a-b-}. When present, these antibodies are usually IgM and have the capacity to be complement fixing and cytotoxic [2]. Of relevance to renal transplantation, Lewis antigens are also detectable on renal tubular epithelial cells and may be acquired by other renal cells including glomerular cells [16].

Because of its precursor homology to the ABH glycoproteins, Lewis antigens were the first to be recognised as being important in the renal transplant setting. Early studies showed a difference in graft survival between Le positive and negative recipients, with Le^{a-b+} recipients having significantly better survival than those who were Le^{a-b-} or Le^{a+b-}, an association which was preserved even when HLA matching was considered [17-19]. In a large retrospective study of 1,111 first renal allograft recipients, Gratama *et al* reported no difference in 1 year allograft survival between Lewis-negative and Lewis-positive recipients. However when corrected for HLA matching, they found that Lewis negative patients were at higher risk of graft failure when receiving HLA mismatched kidneys [20]. They concluded that in the case of Lewis negative recipients every effort should be made to prioritise optimally HLA matched grafts for these recipients.

Blood group antibody screening during transplant workup usually identifies pre-existing high titre anti-Le antibodies which may have been innate or induced by exposure to a foreign Lewis antigen on a previous graft or following blood transfusion. There are reports where the development of *de novo* complement fixing

anti-Le^a/Le^b antibodies have been associated with AbMR in the absence of other donor specific anti HLA antibodies [16]. Re-transplanting in the face of a previous allograft lost in the presence of an anti-Lewis antibody warrants attention to Lewis matching for subsequent grafts [21].

Kidd

The Kidd antigen (Jk^a) was first described in 1951 in a similar context to the Lewis antigen, following a case of haemolytic disease of the newborn where an antibody directed against a novel antigen was identified [22]. Antibodies directed to a similar antigen (Jk^b) were described in a transfusion reaction 2 years later [23]. The *SLC14A1* gene on chromosome 18 encodes the Kidd antigen. A single base transition is responsible for the two alleles, giving 3 common genotypes: Jk^{a+}Jk^{b-}, Jk^{a+}Jk^{a+}, and Jk^{b+}Jk^{b+}. One further ('null') phenotype has been described named Jk^{a-b-} (*Jk3*) and occurs due to inheritance of the silent gene at the Jk locus. This phenotype is very rare, with the exception of ethnic Polynesians (present in 1:400) and in Finnish populations [24]. The phenotype frequencies are Jk(a+b-) 26%, Jk(a+b+) 50%, Jk(a-b+) 23% in Caucasians, Indians and Chinese but 51%, 41% and 8% respectively in Africans and Saudis [2,13]. Complement-fixing antibodies (commonly IgG1 and IgG3) are measurable against the Jk^a and/or Jk^b antigens after sensitising events. Although these antibody levels wane and may later be undetectable, the IgG (and occasionally IgM) antibodies exhibit a very strong anamnestic memory response when re-challenged.

The Kidd antigen has almost complete homology to a urea transporter protein expressed in endothelial cells of the vasa recta within the kidney [25]. Interestingly patients with the Kidd-null phenotype also have RBCs that are resistant to osmotic stress induced by urea, but have normal permeability to other substances [26]. Such patients also have a urinary concentrating defect [27]. The urea transporter is highly conserved between species but mRNA for this human gene (hUT-B1) is found in a number of organs and is identical to the Kidd gene but for a base pair substitution and a deletion [28]. The fact that this is a persistent gene through species speaks to its value, so it is interesting that a null-mutant urea transporter is not phenotypically more obvious [29].

Previous reports of antibodies to the Kidd antigens causing rejection are rare but devastating [3,30-32]. Holt *et al* were the first to describe a case of rejection after blood transfusion and the subsequent development of a Jk^a antibody [30]. Further cases of plasma cell rich, acute cellular rejection (ACR) in the presence of a serum Jk^b antibody and histological evidence of Jk^b antibody binding to renal tissue has

been described [31,32]. Rourke *et al* described a patient developing late rejection, 10 years post-transplantation in the setting of poor compliance and the development of an anti-Jk^b antibody [33]. In a study examining 370 patients who had undergone renal transplantation to determine whether Kidd or Duffy antigen mismatches between donor and recipient caused increased rates of graft loss, no difference in graft survival was found between those with donor recipient mismatch and those who were matched. They did however show that Kidd antigen mismatches between donor and recipient was associated with more interstitial inflammation compared with those who were matched [34].

Avoiding sensitisation by prior transfusion appears sensible, but antibodies may not be detectable at the time of transplant and donor and recipient Kidd status is rarely known prior to transplantation. However, such antibodies are likely to be easily demonstrable and could be considered as potentially important where acute rejection occurs in the absence of a demonstrable anti HLA antibody.

MNSs

The MNSs blood group system is a group of trans-membrane receptors which are highly glycosylated (glycophorins) and have varying amino acid sequences. They serve as (negative) charge carriers and act as receptors for cytokines and pathogens including Malaria. The MNSs group consists of 43 antigens with the commonest comprising M, N, S and s antigens which are coded for on chromosome four [2]. Common phenotypes include M+N+S+s+ (24%), M+N+S-s+ (22%) and M-N-S-s+ (15%) [2,13]. In the general population 20-25% are M antigen negative regardless of ethnicity.

Anti-M antibodies were first described in 1933 and are the most frequent antibodies targeting the MNS system [35]. These antibodies are naturally occurring and can form without antigen exposure, similar to antibodies against blood group A or B antigens. Although Anti-M IgM is frequently seen, it is often ignored by transfusion laboratories because it rarely causes transfusion reactions, as binding is optimised in the cold and at low pH. The anti-M antibody reacts more strongly with homozygous cells (M+N-) compared with heterozygous cells (M+N+) [36].

The MNSs antigens are also expressed in the kidney on the renal endothelial and epithelial cell [37]. There is increasing evidence that antibodies against the MNSs blood group antigens may be relevant in some episodes of renal allograft rejection.

Organ transplantation creates an environment in which these antibodies could be induced to bind to renal endothelial or epithelial cells particularly at the time of reperfusion of a hypothermic, ischaemic allograft. The danger may be especially acute where a kidney from an M+ donor is transplanted into a recipient with a high titre of preformed anti-M Abs. Unlike anti-A & B antibodies which are almost ubiquitous, most patients do not develop anti-M antibodies despite 25% of the population not expressing the M antigen. The reason that natural antibodies develop in only a minority of people is unknown but at our institution, of the many thousands of patients screened for blood group antibodies between 1989 and 2017, only 149 patients expressed anti-M antibodies and of these 5 underwent renal transplantation. Anecdotally, we have achieved some success in transplanting 3 patients where pre-operative anti-M antibodies were identified in the recipient and the M status of the donor was known to be positive. This was achieved by peri-operative plasma exchange (PIEx) to reduce the anti-M titre and importantly re-warming the kidney by bathing it in warm saline for a few minutes prior to releasing the surgical clamp after re-anastomosis. However, these are our unpublished observations and we acknowledge that this was empirical therapy based on the theoretic risk and knowledge of the innate thermosensitive properties of these anti M antibodies. Pre-transplantation normothermic machine perfusion of an allograft may provide a further mechanism to avoid binding of thermosensitive anti-M antibodies to renal endothelium at the time of reperfusion.

Duffy

Duffy antigens are polymorphic with respect to a single nucleotide and a single amino acid substitution in a peptide. They are encoded on chromosome 1 by the *FY*A* and *FY*B* genes with 4 red blood cell phenotypes existing: Fy(a+b-), Fy(a-b+), Fy(a+b+) and Fy(a-b-). The Fy(a+b+) is the commonest phenotype in Caucasians (50%) followed by Fy(a-b+) (34%) and then Fy(a+b-) (17%). This is in contrast to Asian populations where the Fy(a+b-) phenotype has 80-90% prevalence and African Americans in whom Fy(a-b-) has a prevalence of 68% [38]. Anti-Duffy antibodies are usually of the IgG class and are often directed towards the Fya epitope [39].

The Duffy antigen is a receptor on the surface of RBCs used by the malaria parasite *plasmodium vivax*. It has also been shown to bind chemokines and was subsequently renamed Duffy Antigen Receptor Chemokines or DARC. In addition to being found on the surface of RBCs, DARC is also expressed on renal endothelial cells, in the peritubular capillaries, and post capillary venules [39]. Although DARC

binds some chemokines, it differs from other chemokine receptors in that it does not lead to a classic G-protein coupled signal transduction [38]. Early work showed that DARC^{-/-} mice showed an enhanced inflammatory response in a number of organs in a model of endotoxaemia, where there is increased production of chemokines [40]. Such a role may have relevance in the context of delayed graft function (DGF) and ischaemia reperfusion injury (IRI), where chemokine production and leucocyte recruitment may induce immunological and non-immunological injury. DARC may attenuate these processes, but its absence may exacerbate these insults. This putative role of DARC is supported by a study showing that DGF had no apparent impact on graft failure for patients with Duffy blood group (a+b⁻), (a-b⁺) or (a+b⁺), but reduced rates of graft survival were observed in those who were Duffy (a-b⁻) [4]. In a study using the UNOS database, Katznelson *et al* showed that DGF had a more deleterious effect on graft survival in African Americans, 68% of whom are Duffy (a-b⁻) compared with Caucasians where the prevalence of Duffy (a-b⁻) is less than 1% [41]. Lerut *et al* examined allograft outcomes in matched vs mismatched Duffy antigen donor/recipient status and observed that Duffy negative grafts had higher tubulointerstitial fibrosis and arteriolar hyalinisation scores [42]. Thus, consideration of the Duffy status may have relevance for the acceptance of allografts from donation after cardiac death donors (DCD) or extended criteria donors (ECD), particularly in recipients of African heritage. Machine perfusion technologies offer exciting potential to reduce IRI and may particularly benefit those who may lack the protective effect of DARC.

Discussion

Despite the theoretical and anecdotal evidence that non-ABO blood group antibodies may be associated with higher rates of rejection and inferior allograft outcomes, the routine screening for donor recipient phenotype matching at the time of deceased donor transplantation is not widespread. Data regarding their significance is relatively sparse and some antibodies are highly anamnestic and may not be readily detectable in the circulation at the time of transplantation. Hence at this stage for the general transplant recipient population, there is no recommendation for donor recipient RBC Ag phenotypic matching, not least because it would substantially reduce the donor pool size. There may however be some circumstances under which more detailed screening for recipient RBC antibodies and phenotyping of the donor is warranted (summarised in Table 1).

In the case where a histological diagnosis of AbMR with C4d staining has been made but no donor specific antibodies (DSA) have been identified, a RBC antibody screen

to exclude *de novo* RBC alloimmunisation as a cause of the rejection episode should be considered. A recent post transfusion reaction prior to the diagnosis of AbMR may heighten suspicion that RBC alloimmunisation may have precipitated the humoral response [30]. Regardless, a diagnosis of acute AbMR in the presence or absence of a DSA is usually treated with plasma exchange, which would effectively remove any anti-RBC antibodies present.

In cases where anti-RBC antibodies have been implicated in AbMR and the loss of an allograft, there is evidence of poor outcomes for re-transplantation where donor recipient RBC Ag phenotypic matching is not undertaken [21]. In practical terms, the frequency of donors who have a null phenotype for any of the minor RBC antigens is low in the general population and it may be difficult therefore to find a matched negative donor. In such cases an effort should be made to phenotype the donor RBC although this may not always be feasible, especially in the case of a deceased donor. However, a pre specified immunosuppression plan can be in place to pre-emptively plasma exchange the recipient both pre- and post- transplantation and to maintain higher levels of immunosuppression at least for the first few months post transplantation (unless the donor has been found not to express the relevant RBC antigen).

Particular attention needs to be given to the perioperative management of planned transplant recipients with pre-existing anti-M antibodies. These antibodies are thermosensitive with binding optimised in the cold and at low pH. The standard cold storage method of preserving donor allografts may increase the risk of antibody binding immediately post anastomoses of the donor to recipient vessels. Theoretically this risk may be reduced by warming the kidney prior to transplantation and as noted above, we have had anecdotal success with adopting this approach. The increased availability of normothermic machine perfusion may also reduce the risk of early anti-M induced allograft rejection.

The phenotypic frequencies of various blood-group antigens differ between individual ethnic groups and therefore impacts on their risk of alloimmunisation. Particular attention needs to be paid to potential recipients of African ethnicity. In the USA, African Americans have higher rates of allograft rejection and a 30 to 40% decreased graft survival compared with Caucasian groups [43]. While this discrepancy in outcomes is multifactorial, there are reports that Lewis and Duffy blood group antigen phenotypes are associated with varying renal allograft survival particularly in African Americans who have a higher frequency of Duffy (68%) and Lewis (49%) null phenotypes. Although there are disparate results from studies regarding the

frequency of humoral mediated rejection in the face of Lewis and Duffy antigen mismatching [3,44] there are interesting data regarding poorer long-term outcomes in African Americans who are Duffy negative and have DGF. As outlined in detail above, DARC is thought to have an anti-inflammatory role by acting as a chemokine sink. DGF and ischaemia reperfusion injury increases cytokine and chemokine production resulting in recruitment of leucocytes to the graft which can induce immunological and non-immunological damage to the transplanted kidney. DARC may attenuate this process by sequestering chemokines and may explain why Duffy-negative African American recipients with DGF have shorter allograft survival. One approach to mitigate this adverse outcome might be to embrace machine perfusion technologies which have been shown to reduce DGF [45]. The finding that Lewis and Duffy antigen phenotypes may be associated with inferior allograft survival in African Americans builds on the accumulating body of evidence for the role of genetic variation in the increased risk of ESKD and poor transplant outcomes in this ethnic group. This is perhaps best highlighted by the important discovery of apolipoprotein L1 (APOL1) gene variants and their association with kidney disease in African Americans. In the context of renal transplantation, like the Duffy negative genotype, it has been shown that donor APOL1 high risk genotype status is associated with significantly worse allograft survival [46]. There is need for further prospective studies to examine the impact of these genetic variants on longterm allograft outcomes which could potentially pave the way for with the development of specific therapeutics.

Within the context of the multicultural population of Australia and New Zealand the Polynesian ethnic group have a high frequency of the Jk^{a-b-} phenotype which is otherwise rare. This group could be at enhanced increased risk of developing anti-Kidd antibodies and therefore of developing AbMR. We suggest such patients warrant early renal biopsy and testing specifically for anti-Kidd antibodies in the first months post transplantation if there is graft dysfunction.

The risk of alloimmunisation is proportional to the number of transfusions an individual has had [7]. The common advice is to use rEPO and iron to avoid transfusion in any patient in whom transplantation may be needed to avoid sensitisation. In addition, using a lower threshold before transfusion is given and only giving a single unit is also good practice. Despite this, a number of patients will receive a blood transfusion and although RBC antigen phenotype and matching to prevent alloimmunisation post transfusion is possible, it is largely impractical. Factors

influencing the risk of RBC alloimmunisation include donor-recipient mismatch and the relative immunogenicity of a given antigen (Kell being the most immunogenic) [9]. Other factors such as age, immune state and HLA class II allelic phenotype can all influence the propensity to become alloimmunised. In a multicultural country such as Australia it would be difficult to achieve population wide minor RBC donor-recipient phenotypic matching. A study from India calculated that 230 units of blood have to be crossmatched to get two compatible RBC units [9]. However, the knowledge of HLA-DRB1*15 hyper-responder status [6] may in time influence the decision to limit potential blood transfusions to highly compatible units. Phenotyping the donor population to develop a rare blood donor register in the event there is a need to provide antigen negative units is sensible.

The role of antibodies against minor blood group antigens in renal allograft rejection and the development of tubulointerstitial fibrosis may be under recognised. In order to further elucidate their putative pathological role, there is a need for larger scale in vitro studies using immunohistochemistry to demonstrate binding of labelled antibodies to minor blood group antigens expressed in renal tissue from routine biopsy specimens. Furthermore, it would be interesting to see if this antigen expression or antibody binding may be upregulated in patients with ATN, ACR or AbMR. In cases where AbMR occurs in the absence of an identifiable DSA, the routine screening for and demonstration of an antibody against a specific minor blood group antigen in the circulation and the confirmation of antibody binding to renal epithelium and endothelium in diagnostic allograft biopsy specimens would support a true pathological role for these antibodies. While we know that in vivo anti M antibody is thermosensitive, it would be informative to replicate this in vitro by observing whether there is a difference in binding of anti M antibody to renal tissue expressing M antigen in the cold and at 37°C. Furthermore, as outlined in other sections in this paper, an interesting clinical study would be to test if machine perfusion technologies could be used to reduce the risk of immediate anti M antibody binding to the allograft following re-establishment of circulation post transplantation.

In summary although data on the impact of RBC alloimmunisation on both short and long-term outcomes is sparse, it is possible that the impact of these minor RBC histocompatibility antigens is greater than has previously been recognised. Awareness of the potential role of these antibodies in both humoral and non-humoral pathways of renal injury should lead to increased testing for antibodies particularly in the context of AbMR and the absence of an identified DSA. Other work is continuing

to enable us to understand the immunobiology of the antigens in better detail, and particularly how they interact with the immune response.

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Antigen Group	Antigen subtypes	Genetic loci	Renal tissue expression	Ab class	Association with allograft dysfunction	At risk phenotypes	Potential therapeutic strategies
<i>Lewis</i>	Le ^a Le ^b	FuT3 gene Chromosome 19	Tubular epithelium and glomerular cells ¹⁶	Le ^a IgM Le ^b IgM	ACR & AbMR ³⁰⁻³² Interstitial inflammation ³⁴	Le ^{a-} Le ^{b-} 20% of African, Chinese and Indian ethnicity ^{2,13}	Optimise HLA match for Le ^{a-} Le ^{b-} recipient. If anti Le ^a IgM or Le ^a IgM detected, type donor & consider PIEx
<i>Kidd</i>	JK ^a JK ^b JK ^{a+} JK ^{b-} JK ^{a+} JK ^{a+} JK ^{b+} JK ^{b+} JK ^{a-b-} (Null)	SLC14A1 gene Chromosome 18	Endothelial cells of vasa recta. Kidd antigen almost complete homology to urea transporter protein	JK ^a : IgG & IgM JK ^b :IgG & IgM	ACR & AbMR ³⁰⁻³³	JK ^{a-b-} (Null phenotype) Ethnic Polynesians Finnish populations	Recipients with the Null phenotype and Anti-Kidd antibodies, test Donor Kidd phenotype & consider PIEx

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Table 1 Summary of minor blood group genotypes, association with allograft dysfunction and potential therapeutic strategies

<i>MNSs</i>	43 antigens with commonest being M,N,S & s	GYPA & GYPB genes Chromosome 4	Renal endothelial and epithelial cells ³⁷	Anti-M IgM (cold reacting) Anti-M IgG Anti-N: IgM,IgG Anti-S: IgG Anti-s: IgM, IgG	In presence of cold reacting Anti-M IgM, acute AbMR at time of reperfusion of hypothermic, ischaemic allograft	Those with anti-M IgM (can be naturally occurring without prior antigen exposure)	In the presence of Anti-M IgM, consider warming the allograft possibly with normothermic machine perfusion prior to re-establishing circulation
<i>Duffy (DARC)</i>	Fy ^{a+b-} Fy ^{a-b+} Fy ^{a+b+} Fy ^{a-b-}	FY ^A & FY ^B genes Chromosome 1	Renal endothelial cells, peritubular capillaries and post capillary venules ³⁹	Fy ^a IgG Fy ^b IgG	Increased rate of tubulointerstitial fibrosis in recipients of Fy ^{a-b-} allografts ⁴² Reduced allograft survival in Fy ^{a-b-} recipients	Fy ^{a-b-} phenotype 68% African Americans	Duffy status may have relevance when considering the use of DCD or ECD kidneys Machine perfusion technologies may benefit those who lack protective effect of DARC.

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