

**Keywords:** on-  $\mu$  and le koc te; Antibodies; K idne;

Abbreviations: Abs: Antibodies; A CA: Anti-Indot elial rec rsor Cell Antibodies; A CA: Anti-Indot elial Cell elia: Anti-Indot elial Cell; Indot elial Cell; In

abs: on man he koc te antibodies M: Cross matc

### Introduction

Moreo,  $e_r$ ,  $t_r$  e  $t_r$ iggers of acti, ation  $o_r$   $t_r$  ansition of  $t_r$  ese on f. A abs to  $a_r$ d pat ogenicit  $a_r$ e likel ac te rejection, poperf sion, isc  $t_r$ e  $t_r$  is a reperf sion, calcine  $t_r$  in to icit, infection, and rec  $t_r$  rent diseases [6].

on  $\overset{*}{\bullet}$  A abs , a e a stronger role in  $g_ra$  d sf nction and rejection; Antibod Wediated ejection (AMP) or C4d deposition in t e absence of  $ci_rc$  lating donor speci c on  $\overset{*}{\bullet}$  A abs t an  $p_re$ , io sl t o  $g_1t$  [1,5-7]. e  $ai_p$  of t is re, ie is to sped light on on  $\overset{*}{\bullet}$  A abs de eloppent, there arise of action, alinical relevance, and  $t_reat_p$  pert.

## Mechanism of NON-HLA antibodies production

C tokine  $sto_{r}$  in  $d_{r}$  ring  $b_{r}$  ain deat  $d_{r}$  and in a  $d_{r}$  mation associated it  $d_{r}$  an isc  $d_{r}$  in  $d_{r}$  reperf sion in  $d_{r}$  asc  $d_{r}$  in  $d_{r}$  rejection as a seincreased e  $d_{r}$  pression of  $d_{r}$  ptic a toantigens, and  $d_{r}$  as  $d_{r}$  at a  $d_{r}$  as  $d_{r}$  in  $d_{r}$  has  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$  and  $d_{r}$  as  $d_{r}$  and  $d_{r}$ 

\* o e e<sub>r</sub> se e<sub>r</sub>al st dies reported of e<sub>r</sub> as of on \* A abs de elongent of e<sub>r</sub> t an sensiti ation [1,11113]. o<sub>r</sub> e apple, an A5.1 m tation in t e dono<sub>r</sub> ic is related to t e MCCA\*008 allele, is associated it a strongle increased MCCA e pression on dono<sub>r</sub> endot elial cells doppared to ild t pe dono<sub>r</sub>s and t erefore t ese tated MCCA polec les are important targets for antibod for pation [14]. Additionall, prispate ing on certain appino acid resid es leads to increased MCCA antibod for pation and it can be t at based on t e 3D-st<sub>r</sub> ct re of MCCA, t ese st<sub>r</sub> ct res are pore accessible for antibodies [1,13].

## **HLA antibodies and NON-HLA antibodies correlation**

# A antibodies and lo et gra s r, i al rates compared to patients it eit er one of the loss. It is assumed that had non-

antibodies  $\mu_{V}^{a}$  e a s nergistic e ect [4,15].

## Non-HLA antibodies incidence and pathogenicity

on  $^{*}$  A abs ma f nction as complement- and non-complementing antibodies and the maind cealarge ariet of allogra in ries, relecting the comple it of their acte and chronic actions [17].

Complement-dependent and complement-independent mechanisms  $a_re$  not  $a_re$  tall e cl si e [8,18].  $a_re$  a mple, Anti-Vimentin Antibodies [AVA] seem to complement [19]. in initarly MYCA Absurate been sho in to be more e—cient at complement activation and a  $a_re$  been associated it, C4d. AMA [2]. In contrast, 40%-50% of clases, it is  $a_re$  ascalar changes  $a_re$  and  $a_re$  being an initial  $a_re$  and  $a_re$  and  $a_re$  and  $a_re$  and  $a_re$  in  $a_re$  and  $a_re$ 

Besides, antibodies can ind cell sis of target-cells, it is peoply and be not antibodies tyro gy activation of nat ral-killer cells, a process called antibod -dependent cell pediated c toto icit [1,22]. rt per pore, on A abs ma also contrib te to sport and long-ter port cral changes in the arterial all or d ct epit relia that propote clotting or and narro ing [8].

Additionall, excapabilit of on \$\tilde{A}\$ A abs to mediate allogra in \$r\$ ma depend on their specific and an interpretation in the excapability of the example antigen, and single period in the expansion of the exception in th

## Non-HLA Antibodies as Biomarkers of Injury

on the other hand, other st dies claimed that on hand a hand represent a marker for introper in moral activation rather than having independent pathogenic potential [2,11]. erefore, in the near fit re, on hand a hard be sed as biomarkers of ongoing implying ne response and herald the need for more sitable implying nos ppression [8].

## Compartment speci city

on hA i ha i ne responses, incl ding anti-MACA antibodies, ere detected against kidne compartment-speci c antigens, it is est post-transplant recognition for renal pel, is and corte speci c

### Targets for Non-HLA Antibodies

- •
- Antibodies against G Protein-Coupled Receptors (GPCRs): AT1R
  - (ETAR)
- Antiendothelial cell antibodies (AECAs)
- Anti endothelial precursor cell antibodies (AEPCA)
- LG3 (Perlecan)
- •
- Antivimentin: Intermediate Filaments Vimentin (AVA)

| Clinical Relevance of Non-HLA antibodies |  |  |  |  |  |
|--|--|--|--|--|--|
| Antibody                                 | Clinical Relevance   |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| Antivimentin (AVA)                       |  |  |  |  |  |
| 7 and 7 and 7 to 7 ty                    | tubular atrophy [27, 40-41].   |  |  |  |  |
|  |  |  |  |  |  |
| hiata aa maa atibilitu                   |  |  |  |  |  |
| histocompatibility complex class         | transplantations: well matched for the HLA) [1,7,42,44]                      |  |  |  |  |
| gono: A                                  | * Contrary to expectations, patients with positive                           |  |  |  |  |
| gene: A                                  | ,                                      |  |  |  |  |
|  | patients [1].  |  |  |  |  |
|  | panome [1].  |  |  |  |  |
| Anti-endothelial                         |  |  |  |  |  |
| precursor cell antibodies                |  |  |  |  |  |
|  | serum creatinine levels at 3 and 6 months post-Tx [45].                      |  |  |  |  |
| (AEPCA)                                  |  |  |  |  |  |
|  | *Associated with a higher incidence of graft loss [1,28,49],                 |  |  |  |  |
|  | cellular mediated) and malignant hypertension [7,27,29,46].                  |  |  |  |  |
|  | cellular mediated) and malignant hypertension [1,21,25,40].                  |  |  |  |  |
|  | *Patients with bothAT1R-Ab and HLA-DSA had greater                           |  |  |  |  |
|  | incidence of allograft damage and graft loss [29,46-47].                     |  |  |  |  |
|  | *Patients with anti-AT1R Abs level >9 U/ml run a higher risk                 |  |  |  |  |
|  | of graft failure independently of classical immunological risk factors [28]. |  |  |  |  |
|  | 1001013 [20].  |  |  |  |  |
| 1 receptor (AT1R)                        | *Patients with both anti-AT1R and DSA had lower graft                        |  |  |  |  |
|  | survival than those with DSA alone [48].                                     |  |  |  |  |
|  | *Associated with a higher incidence of graft loss and                        |  |  |  |  |
|  |  |  |  |  |  |
| Endothelin-1 type                        | *Vasculopathy or arteritis were observed in patients with                    |  |  |  |  |
| A receptor (ETAR)                        |  |  |  |  |  |
| Duffy antibody                           |  |  |  |  |  |
| (a chemokine                             |  |  |  |  |  |
| receptor) Agrin antibody                 | *Accordated with transplant alemorule pothy [7]                              |  |  |  |  |
| Agriii aritibuuy                         | *Associated with transplant glomerulopathy [7].                              |  |  |  |  |
|  | glomerulopathy, a chronic lesion characterized by                            |  |  |  |  |
| antibodies                               | duplication of glomerular basement [27,50].                                  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| Antiendothelial cell                     |  |  |  |  |  |
| antibodies (AECA)                        |  |  |  |  |  |
|  | [53].  |  |  |  |  |

Table 3: Clinical relevance of non-HLA antibodies.

# Non-HLA antibodies monitoring and gra failure prediction

 $\label{eq:lambda} \text{Man} \quad \text{of } t_{1\!\!p} e \ \text{late} \ g_r a \quad \text{fail} \ _r \text{es} \ \text{att}_r \text{ib} \ \text{table to} \ \text{non} \ ^{\frac{2}{n}} \ ^{r} \!\!\!\! A \ e \ \text{ects}$ 

(antibodies against antigens e pressed on publical, ein endot elial cells), which A  $o_r$  o  $-c_ross_patc_p$  techniq es (antibodies against donor endot elial progenitors) ( able 4) [3].

At present, se of bot,  $^{\text{MK}}$  A and c toto icit assa s in parallel for pre-transplant testing see as; dicio s to allo a separation of anti- $^{\text{MK}}$  A from anti-non- $^{\text{MK}}$  A acti, ities [14].

# **Current Treatment Modalities for Pathogenic Non-HLA Antibodies**

e presence of on  $\stackrel{*}{\bullet}$   $^{t}$  A abs are not an absol te contraindication to  $t_r$  ansplantation, b t $_r$  at  $_t$  er $_r$  ma s ggest pre $_t$  io s or ongoing tiss e in; r , and ma be sef lin identif ing patients of sold be treated eit per prior to transplantation or post-transplantation to a oid grain; r [2].

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