Keywords: on- man le koc te; Antibodies; K idne ; ransplantation

Abbreviations: Abs: Antibodies; A CA: Anti-ndot elial ec rso Cell Antibodies; ACA: Anti-ndot elial cell Antibodies; AM : Antibod ediated ejection; Anti-Col: Anti-Collagens; A 1 : Angiotensin pe 1 ecepto; Anti a1 t b lin: Anti b lin ; AVA: Anti- imentin Antibod ; C4d: Co plement Co ponent 4d; DSA: Dono- peci c Antibodies; EC: ndot elial Cell; LIS A: n me- inked noso bent Assa ; A : ndot elin- pe A ecepto; : ocal eg mental clo er losclerosis; A: man e koc te Antigen; MHC: Majo istoco patibilit Co ple ; MICA: Majo istoco patibilit Co ple Class C ain- elated ene A; on A abs: on man e koc te antibodies; M: Cross matc

Introduction

on A antigens incl de antigens e pressed on endot elial, epit elial cells, pa enc mal cells and ci c lating i mm ne cells [1-3]. on A abs can be di ected against a to- o allo-antigens and be eit er present pre-t ansplant o *de novo* fo med post t ansplantation [3]. t er o e, e ost epo ted on A abs incl de t ose di ected against Angiotensin pe 1 ecepto (A 1 -Ab), ndot elin pe A ecepto (A), C Class C ain- elated Antigen A (MICA-Ab), imentin (AVA) b lin (anti a1 t b lin), Collagens (anti-Col) Anti ndot elial Cell Antibodies (ACA), anti- eat s ock p otein, and anti-p osp olipid able 1) [4,5].

Mo eo e, t e t igge s of acti ation o t ansition of t ese on A abs to a d pat ogenicit a e like ac te ejection, pope f sion, isc e ia epe f sion, calcine in to icit , infection, and ec ent diseases [6].

on A abs a e a stronge ole in g a d sf nction and ejection; Antibod ediated ejection (AM) o C4d deposition in t e absence of ci c lating dono speci c on A abs t an pe io sl t o g t [1,5-7]. e ai of t is e ie is to s ed lig t on on A abs de elop ent, ec anis of action, clinical ele ance, and t eat ent.

Mechanism of NON-HLA antibodies production

nj r of g a endot eli b on A abs can lead to e pos e of neo-antigens ic consec ti el sti late t e p od ction of antibodies against non A antigens [1,4,5,7-9]. t e e, C tokine sto d ring b ain deat and in a mation associated it an isc e ia- epe f sion inj r , asc la inj r , and/o ejection ma ca se inc eased e pression of c ptic a toantigens, and ma sti late on A abs p od ction. Additionall , i m ne acti ation, tape ed i m nos pp ession in t ansplant ecipients ma sti late on A abs p od ction [10].

o e e, se eral st dies epo ted ot e a s of on A abs de elop ent ot e t an sensiti ation [1,11-13]. o e a ple, an A5.1 tation in t e dono , ic is elated to t e MICA*008 allele, is associated it a st ongl inc eased MICA e pression on dono endot elial cells co pa ed to ild t pe dono s and t e efo e t ese tated MICA molec les a e i po tant ta gets fo antibod fo mation [14]. Additionall , is atc ing on ce tain a ino acid esid es leads to inc eased MICA antibod fo mation and it can be t at based on t e 3D st ct e of MICA, t ese st ct es a e o e accessible fo antibodies [1,13].

HLA antibodies and NON-HLA antibodies correlation

Con e sel , in a mato esponse ind ced b on A abs co ld seq entiall p eg late A e pression, inc ease t e isk fo a patient to de op A-speci c antibodies and t s ake t e allog a o e s sceptible to an allo-i m ne esponse in ol ing bot mo al and cell la [1,2,4,5,8,15].

e o s st dies s o ed t at patients it bot A and non-A antibodies ad lo e g a s ival ates co pa ed to patients it eit e one of t e [16]. t is ass ed t at A and non A

antibodies ¡a e a s ne rgistic e ect [4,15].

Non-HLA antibodies incidence and pathogenicity

on A abs a f nction as co ple ent- and non-co ple ent-ing antibodies and t e a ind ce a la ge a iet of allog a in ies, e ecting t e co ple it of t ei ac te and c onic actions [17].

Co ple ent-dependent and co ple ent-independent ec a-nis s a e not t all e cl si e [8,18]. o e a ple, Anti- i entin Antibodies [A A] see to co ple ent [19]. i ila l , CA Abs a e been s o n to be o e e– cient at co ple ent acti ation and a e been associated it C4d A [2]. n cont ast, 40%-50% of cases it se e e asc la c anges s c as b inoid nec osis a e C4d-negati e, i plicating in ol e ent of eit e non-co ple ent- ing antibodies o ot e ediato s, as noticed in of cases of A in t e p esence of 1 -Ab o A CA t at occ ed it o t e idence of co-ple ent acti ation [2, 20,21].

Besides, antibodies can ind ce l sis of ta get-cells it e b ane bo nd antibodies t o g acti ation of nat al-kille cells, a p ocess called antibod -dependent cell ediated c toto icit [1,22]. t e e o e, on A abs a also cont ib te to s o t and long-te st c al c anges in t e a te ial all o d ct epit elia t at p o ote clotting o/and na o ing [8].

Additionall , e capabilit of on A abs to ediate allog a in j r a depend on t ei speci cit and a– nit , densit of t e ta get antigen, and s ne g it A antibodies [2]. t is nlikel t at on-A abs can di ectl ind ce a o gra da age since e ac te ejection ind ced b t ese antibodies a el occ s able 2) [23-37].

Non-HLA Antibodies as Biomarkers of Injury

n t e ot e and, ot e st dies clai ed t at on A abs a ep esent a a ke fo in j o o al acti ation at e t an a ing independent pat ogenic potential [2,11]. e efo e, in t e nea f t e, on A abs a be sed as bio a ke s of ongoing i ne esponse and e ald t e need fo o e s itable i nos pp ession [8].

Compartment speci city

on A i ne esponses, incl ding anti- CA antibodies, e e detected against kidne co pa t ent-speci c antigens, it ig est post-t ansplant ecognition fo enal pel is and co te 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)	tubular atrophy [27, 40-41].
histocompatibility complex class gene: A	transplantations: well matched for the HLA) [1,7,42,44] * Contrary to expectations, patients with positive patients [1].
Anti-endothelial precursor cell antibodies (AEPCA)	serum creatinine levels at 3 and 6 months post-Tx [45].
1 receptor (AT1R)	*Associated with a higher incidence of graft loss [1,28,49], cellular mediated) and malignant hypertension [7,27,29,46]. *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]. *Patients with both anti-AT1R and DSA had lower graft survival than those with DSA alone [48].
Endothelin-1 type A receptor (ETAR)	*Associated with a higher incidence of graft loss and *Vasculopathy or arteritis were observed in patients with
Duffy antibody (a chemokine receptor)	
Agrin antibody	*Associated with transplant glomerulopathy [7].
antibodies	glomerulopathy, a chronic lesion characterized by 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

an of t e late gra fail res attrib table to non A e ects

(antibodies against antigens e pressed on bilical ein endot elial cells), A o o -cross atc tec niq es (antibodies against dono endot elial progen o s) able 4) [3].

At present, se of bot A and c toto icit assa s in parallel for pre-transplant testing see s j dicio s to allo a separation of anti- A fro anti-non A acti ities [14].

Current Treatment Modalities for Pathogenic Non-HLA Antibodies

e presence of on A abs are not an absol te contraindication to transplantation, b t rat er a s ggest pre io s or ongoing tiss e inj r , and a be sef l in identif ing patients o s o ld be treated eit er prior to transplantation or post-transplantation to a oid gra inj r [2].

C4d a magic marker? Nephrol Dial Transplant 18: 2232-2239.

21. Ming Y, Hu J, Luo Q, Ding X, Luo W, et al. (2015) Acute antibody-mediated