23rd Nantes Actualités Transplantation: "Genomics and Immunogenetics of Kidney and Inflammatory Diseases-Lessons for Transplantation"

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OVERVIEW OF THE MEETING

The 23rd annual "Nantes Actualités Transplantation" meeting took place in Nantes, France (May 31 to June 1, 2018; http://www.nat.nantes.inserm.fr/index.php/en/). This meeting focused on several "omic" approaches, spanning immunogenomics and epigenetics, to reveal key molecular factors involved in pathophysiological mechanisms of transplantation complications. This meeting brought together experts in the fields of genomics, epigenetics, and immunology. The different aspects of modern genetics from common (genomewide association study [GWAS]) to rare variants (next-generation sequencing [NGS]), as well as their regulations (epigenetics) were exposed in the context of inflammatory diseases to provide insights for the newly developing fields of nephrogenomics and transplantomics.[1] Indeed, large genetic explorations beyond HLA are still nascent in transplantation, and efforts are to be pursued to uncover new and unexpected mechanisms.

Because data are still sparse in transplantation, this meeting focused on reports developed in complex inflammatory diseases to draw the conclusions from these strategies and guide the future perspectives to be implemented in transplantation research.[2]

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GENOMICS AND IMMUNOGENETICS STEADY-STATE IN KIDNEY DISEASE

Contrary to kidney transplantation, genetic predispositions to kidney diseases were extensively explored during the past 10 years,[3] especially through GWAS on kidney function (eGFR). These studies discovered up to 90 associations in ethnically diverse backgrounds from the first study in Europeans in 2009[4] to transethnic data set in 2016.[5] At this point, there is no doubt that kidney genomics has led to numerous novel discoveries and elucidated new pathways; this meeting report will show that this step forward is envisioned in kidney transplantation as well.

Similarly, the few immunogenetic studies carried out in kidney transplantation were mainly about *HLA* and *KIR* mismatches between donor (D) and recipient (R).[6] Nevertheless, mismatches do not explain all rejections, and this meeting report will exemplify new data in transplantomics and epigenetics, which could be part of a global understanding of rejection.

PROGRESS IN IMMUNOGENETICS AND GENOMICS AS ESTABLISHED FIELD AND RESOURCES FOR BOTH CLINICAL AND BASIC APPLICATIONS

Hematopoietic stem cell transplantation using unrelated sources of cell donors has long stood as very peculiar immunological situation where immune genes play a central role in clinical success. As Patrice Chevallier (Centre Hospitalier Universitaire de Nantes, France) reminded us, transplantation success is highly dependent on the *HLA* matching level between D/R with a growing importance of permissive versus nonpermissive mismatches.[7,8] Jean-Luc Taupin (Hôpital St-Louis, Paris, France) highlighted the strong negative association between donor-specific anti-HLA antibodies, especially for the complement-driven mechanisms,[9] and kidney allograft survival.[10] A better understanding of HLA evolution history and allele complexity through immunogenetics is, therefore, of prime importance for improving matching and transplantation outcomes.[11] However, both speakers also emphasized the growing evidence implicating yet-to-be-discovered genomic non-HLA factors.

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Bioinformatics resources and databases from immunology-related issues have become, in a decade, key resources for both data and tools. James Robinson's (Anthony Nolan Research Institute, London, UK) work based on *HLA* NGS helped understand further this hypervariable region by visualizing the high levels of variation in *HLA*.[12] This representation allows us to grasp the origin of *HLA* complexity in multiple ways by comparing variability between genes and within genes and refining the *HLA* allele description.

HLA genes have always been explored in genetic association studies, and single-nucleotide polymorphisms have frequently hit the major histocompatibility complex (*MHC*) region through GWAS, yet the *MHC* region is often understudied because of its complexity. Jill Hollenbach (University of California, San Francisco, CA) stressed the relevance of high-resolution *HLA* typing and punctual *HLA* genetic variant for clinical outcomes. Her research team focused on comparing 2 closely related *HLA* alleles differing only by 1 amino acid, *HLA-DRB1*15:01* and *HLA-DRB1*15:03*, in the context of multiple sclerosis (MS). *HLA-DRB1*15:01* allele is strongly associated with MS, whereas *HLA-DRB1*15:*03 is not. Using a published crystal structure, they determined in silico that several metabolites would bind differently to these 2 *HLA-DRB1* alleles,[13] which might impact peptide presentation and T-cell responsiveness.

Genomewide association studies represent a major revolution in the genetic field with >10 000 robust associations identified in hundreds of diseases and traits over the past 10 years.[14,15] A recent GWAS focusing on >2000 individuals failed to identify genetic factors associated with kidney allograft survival outside the *HLA*.[16,17] Surprisingly, given the heterogeneity of clinical situation, this sample size may not have the sufficient statistical power—compared with autoimmune traits, including MS and Crohn's disease, that were largely discussed in the meeting, larger studies will be required to reach the robust trail of discoveries obtained by international genetic consortiums.[18]

Nevertheless, discussions in the meeting highlighted that there are limitations and challenges for the unbiased GWAS strategy, especially on study design and statistical power. Taking MS as an example, Sawcer[19] (University of Cambridge, UK) highlighted the key parameters impacting GWAS statistical power and success ($P < 5 \times 10^{-8}$ are necessary to claim significance for a GWAS): disease prevalence, frequency of the associated allele, effect size, and cohort size. The genetic journey of MS exemplifies these perfectly. In the early days, only strong associations were detected, especially within the *MHC* locus.[20-23] Increasing sample size and developing a very large consortium of >15 000 patients later allowed the discovery of novel genetic associations, with up to 201 signals explaining 35% of the variance.[24] Sawcer[25] also alerted the audience on the limited value of predictive genetic score at the individual level for complex diseases due to the multiplicity of genetic factors and their modest effect.[25] Multifactorial genetics of common variants is too often interpreted based on monogenic concepts, such as "mutations," whereas interaction of multiple commons variants with subtle functional implications remains hard to disentangle.

Following the same line of reasoning in phenotype of Crohn's disease (rather than mere susceptibility) and bridging the gap with infectious disease, James Lee (University of Cambridge, UK) and Jean-François Zagury (Conservatoire National des Arts et Métier, Paris, France) advocated for an alternative strategy to overcome lack of statistical power by designing studies with precise, homogeneous, and extreme phenotypes. Indeed, all diseases show some extent of clinical outcome variability, from mild to severe outcomes, and most genetic studies have focused on disease susceptibility rather than disease course. By focusing on extreme Crohn's disease phenotypes of progressive forms or extreme severity, James Lee's research group identified 4 novel associations that had not been described with large cohorts exploring disease susceptibility.[26] This means that disease initiation is not only temporally distinct from active symptomatic disease but governed by distinct genetics and probably driven by different biology.[26] Indeed, they compared Crohn's disease patients with mild (no surgery) versus severe (surgery) phenotypes and identified single-nucleotide polymorphisms associated with severe phenotypes and, interestingly, none of these polymorphisms were identified in susceptibility studies. Jean-François Zagury exposed that apart from the prototypical *CCR5* 32-bp deletion,[27] no convincing genetic association was identified with human immunodeficiency virus infection even when highly exposed seronegative individuals were studied and when combining multiple cohorts.[28-30] However, progression of human immunodeficiency virus disease revealed new associations when focusing on individuals with extreme disease outcomes, such as the long-term nonprogressors or rapid progressors from the Génétique de la Résistance face à l'Infection par le VIH cohort.[31-33]

Genomic contributions to immune phenomena go largely beyond coding portion of genes. As an example, Julien Textoris (BioMerieux, Lyon, France) underlined the importance of endogenous retroviruses (ERV) that represent a large fraction of the human genome (~8%)[34] and can play a major role in development and diseases, such as lymphoma. They developed a method to uncover ERV from 1000 Genomes project (1KG) data;[35] this will become an interested addition to the Ferret 1KG extraction tool.[36] Using an ERV-specific array, his group presented a method to uncover the ERV expression patterns in the context of immune activation and septic shock (unpublished data). Interestingly, ERV expression patterns have been associated with immune activation, depending on epigenetic modifications,[37,38] emphasizing the need to consider integrative strategies to uncover the whole complexity of pathophysiological mechanisms.

All these presentations should encourage the transplantation community to pursue their efforts on genetic association studies, not only with *HLA* but also with the whole genome as a playground. Finally, the genome should not only be studied as an independent compartment; notably, the tight control exerted by epigenetics regulations should also be considered.

PROGRESS IN EPIGENETICS: FINE-TUNING CELL TYPE-SPECIFIC GENE REGULATION IN CELLULAR DIFFERENTIATION AND IMMUNE MEMORY

Cell type-specific gene regulatory mechanisms are at the nexus of cellular differentiation and cellular plasticity and enable adequate responses to changing environmental

conditions. This is particularly important for immune cells that undergo constant differentiation processes (egg, differentiation from naïve T cells into effector or memory cells). Thus, understanding the epigenetic mechanism of these processes is crucial. Julia Polansky (Charité, Berlin, Germany) shared a detailed view of how epigenetics mechanisms contribute to T-cell maturation, using the fascinating example of *FOXP3* regulation that controls the differentiation of naive T cells into regulatory T cells. The demethylation of specific CpG sites in a *FOXP3* enhancer drives *FOXP3* expression activation and the differentiation from naive T cells into regulatory cells.[39] Additionally, Dr. Polansky showed that global DNA methylation loss drives T-cell differentiation into memory cells.[40]

Another interesting example of transforming vision of epigenetics was delivered by Silvia Monticelli (Institute for Research in Biomedicine, Bellinzona, Switzerland). She showed that 5mC and 5hmC DNA methylation is massively lost through an active mechanism during the T-cell differentiation processes into effector cells. The underlying mechanisms are likely to be associated with cell proliferation, but the functional consequences remain elusive and are now actively being investigated. Interestingly, these results and CRISPR/Cas9 fused to enzymes regulating DNA methylation could target important genes, such as FOXP3, and be used for immune cell therapy applications.

The work of Hendrik Stunnenberg's group (Radboud University, Nijmegen, The Netherlands) outlined the concept of trained immunity by which monocyte-derived macrophages acquire either a "trained" (induced by β-glucan priming) or "tolerant" state (induced by lipopolysaccharide exposure).[38] Importantly, the trained cells acquire a stronger and faster immune response and exhibit a very distinct epigenetic pattern (as marked by H3K4me1 and H3K27ac).[38] Because monocytes circulate only a few days in the blood and then move into the tissues, inducing the tolerant or trained state could be used to modulate tissue inflammatory processes in patients.[41]

Progress in epigenetics highlighted the importance of underlying newly identified mechanisms for cellular differentiation and memory. Experiments geared toward the medical exploitation of such states for cell therapy are being actively pursued, and initial results are encouraging. For example, the epigenetic differentiation of patient-derived T cells into regulatory T cells[42] could be a promising avenue for reducing the immune response autoimmune diseases and transplantation rejection.

HOPES AND SHORTCOMINGS OF "NEPHROGENOMICS" AND "TRANSPLANTOMICS"

The developing field of nephrogenomics consists of improving the understanding of renal pathologies, leading to kidney failure and kidney transplantation using genomic strategies. In transplantation, some studies showed the great power that could mount genetic studies in understanding different outcomes, such as initial pathology or D/R compatibility. However, so far, example with clinical relevance is rather monogenic.

Genetic progress in complement system is under the clear influence of genomic development for large-scale low-cost sequencing. As an example, Véronique Frémeaux-Bacchi (Inserm UMRS 1138, Paris, France) described the numerous complement disorders covering a large range of kidney pathologies from susceptibility to infections to atypical hemolytic uremic syndrome (aHUS). Atypical hemolytic uremic syndrome is a rare and heterogeneous disease that can lead to renal failure and kidney transplantation. Using targeted exome sequencing, rare causal variants were identified in genes of the alternative complement pathway in over 50% of aHUS cases.[43] Kidney transplantation can trigger inflammation and complement activation, which can unleash complement-mediated damages and graft rejection.[44] The development of drugs blocking the complement, such as eculizumab that targets C5, could not only improve the management of aHUS[45] but also kidney transplant-related complications.[44,46]

Multiple fields have been renovated by growing knowledge of diverse mutation of clinical interest. Corinne Antignac's (Inserm U1163, Paris, France) presentation focused specifically on hereditary forms of focal segmental glomerulosclerosis (FSGS), a podocytopathy associated with proteinuria. Unbiased sequencing technologies allowed the discovery of up to 30 independent genes associated with this hereditary nephropathy, mostly in genes encoding structural podocyte proteins and their regulators.[47-50] She emphasized how the use of targeted NGS panel can help provide a precise diagnosis and genetic counseling to guide treatment and improve prognosis, notably in the assessment of recurrence risk after kidney transplantation.[49,51,52] As for complement disorders, there are still some FSGS patients without any identified mutations. Agnostic strategies, such as NGS, will, therefore, help uncover new candidate genes. Establishing the causality and clinical significance of novel genetic variants will require a close collaboration between clinicians, geneticists, and biologists, and/or clinicians with additional education in genetics.

The relevance of genetic ancestry to nephrogenomic study was illustrated by Sophie Limou (CRTI, Nantes, France): she presented the exceptional story of *APOL1* variants association with primary and collapsing FSGS in African Americans using an unbiased admixture-mapping scan.[53] These *APOL1* variants were positively selected in West Africa and can protect against *Trypanosoma brucei rhodesiense* infections,[53] hence representing a typical example of balancing selection (protection from trypanosome infection versus increased risk for end-stage kidney disease).[54] As kidney allografts from high-risk *APOL1* donors tend to fail more rapidly,[55] *APOL1* genotyping could benefit recipients and participate in better graft allocation, as recently demonstrated.[56]

In the field of transplantation matching, Laurent Mesnard's (Inserm UMR 1155, Paris, France) research group aimed at summarizing non–HLA-coding differences between D/R into an allogenomics mismatch score.[57] This score compares minor antigens (amino-acid mismatches) between D/R from whole-exome data and was shown to correlate with graft dysfunction. If the results have yet to be confirmed and synergized with *HLA* data, this very promising strategy opens the avenue for personalized medicine and development of innovative transplantomic strategies.

CONCLUSIONS AND FUTURE PERSPECTIVES

This 23rd Nantes Actualités Transplantation meeting provided a wonderful platform to exchange knowledge between geneticists, epigeneticists, and transplant immunologists. Even if we feel we entered the post-GWAS era, an important number of genetic associations are still to be made, especially in the transplantation field where cohorts have not reached the critical statistical power. All speakers advocated for 2 fundamental goals: increase sample size and define precise phenotypic entities. Of course, genomics does not explain everything, and epigenetic research will profoundly impact translational research. In particular, the links between genetic variations, environment, epigenetics, and other integrative strategies are likely to contribute to a better understanding of phenotypic variation.

The exciting results obtained from nephrogenomics, *APOL1* associations, and allogenomics reveal the power of "omics" in bridging fields to improve transplantation outcomes and promise additional remarkable discoveries in a near future. The development of these large-scale strategies in transplantation, as for many other fields of biology, requires a growing number of computational experts and data analysts to manage and extract biological meaning from the enormous amount of information generated.

From this meeting, we were able to extract triple key directions for transplantation: (1) large and homogeneous genomics studies, including genotyping (GWAS) and whole exome sequencing, will allow the discovery of new genetic associations not only with rejection outcomes but also with D/R matching; (2) HLA remain the major histocompatibility antigens but new evidence identifies non–HLA-related alloimmune responses; (3) the exploration of transplanted individuals by new "omics" techniques, such as epigenomics, will bring additional knowledge on rejection outcomes. However, some key challenges are still to be overcome: (1) the simplest to envision is expanding cohort sample size to grant discovery of smaller effect size associations, (2) but the most interesting challenge would be combining diverse large-scale approaches into a global "omics" study (systems biology strategy) to fully understand the graft survival mechanisms and interactions with the recipient's genome and environment.

This meeting report highlights the key points that will empower the transplantation community to reveal new pathophysiological molecular factors from large-scale genetic and epigenetic studies. All fields of biology are at a turning point; the integration of large-scale data will require a global collaborative effort between clinicians and biologists and a growing need for computational biologists and data analysts.

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