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Nanogenomics for Personalized Nanomedicine: An Application to Kidney Transplantation

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Abstract

Chronic Kidney Disease (CKD), defined by reduced glomerular filtration and/or albuminuria persistent for more than three months, is an important Public Health concern, being a real burden for the society. OMICS data generated by high-throughput technologies, converging together into the transpantomics approach, can face this issue, by enabling the discovery of predictive and personalized biomarkers. Using the Leader Gene algorithm, which takes into account gene expression, gene connectivities and biological pathways, we previously identified eight genes (namely, HTATIP/KAT5, c-JUN, TP53, ATF2, MAPK14, ARRB2, XBP1, and NPHS1), that we termed "hub genes". In the present contribution, we accessed the Gene Expression Omnibus (GEO) database, a public repository of micro-array experiments, looking for the expression profiles of the previously identified Leader Genes. We found that 5 out of 8 genes (62.5%; HTATIP, c-JUN, TP53, ARRB2, and ATF2) are able to distinguish between rejection and tolerance to kidney transplantation, being differentially expressed between the two groups of patients in a statistically significant way. Some of these genes (HTATIP, ARRB2, and ATF2) have been rarely described as predictors of clinical outcome to renal graft in the extant literature.

Keywords: Bioinformatics; Kidney transplantation; Leader gene algorithm; Microarray; Nanogenomics; Personalized medicine; Transplantomics

Introduction

Chronic Kidney Disease (CKD), clinically defined by reduced glomerular filtration and/or albuminuria persistent for more than three months, is an important Public Health concern [10], being a real burden for the society with an estimated prevalence of about 8-16% worldwide, which is constantly increasing [21] and reaches the 50% in underdeveloped areas [13], and consuming from 2-3% up to 6% of the national health expenditure.

Kidney transplantation is proposed as an effective treatment, being the pillar of the renal replacement therapy (RRT). Risk factors for CKD are represented by hypertension [46], diabetes [22], obesity [67], cardiovascular diseases [50] and also genetic anomalies play an important role [13,50].

However, despite the achievements and the advancements, there is an urgent need of immunosupressive drugs that are effective and with few adverse effects [18] since allograft rejection still persists.

Transplantomics is an emerging approach coined and pionereed by Jeremy Chapman, encompassing all the genomics and post-genomics disciplines (such as proteomics, transcriptomics, metabonomics or metabolomics, etc …) [3,45,55,59] with the aim to discover biomarkers for predicting transplant outcomes and to enable a personalized, tailored and targeted treatment instead of a population-based, "one-size-fits-all" healthcare approach [37-39].

Using the Leader Gene algorithm [7,8,42], which takes into account both gene expression, gene connectivities and biological pathways, we previously identified eight genes (namely, HTATIP/KAT5, C-JUN, TP53, ATF2, MAPK14, ARRB2, XBP1, and NPHS1) that we termed "hub genes" [9,23,47,57]. In the present contribution, we want to validate this list of previously identified Leader Genes, showing that nanogenomics can enable a personalized pathway toward the issue of kidney allograft [35,36].

Material and Methods

Gene Expression Omnibus (GEO), which is a repository of micro-array data, was accessed searching for the gene expression profiles. In case of different existing experiments studying the expression of the chosen gene, the data were normalized and then pooled together. Student's t-test for independent samples, Analysis of Variance (ANOVA)-one way and Pearson's correlation between gene expression in kidney and in peripheral blood were calculated with SPSS software V21.0.0 package (IBM) and using R environment. p-values were computed with SPSS, and values less than 0.05 were considered statistically significant.

Results

Pooled Gene expression profiles analysis revealed that HTATIP/KAT is able to distinguish between rejection and tolerance outcome, being differentially expressed between the two groups of patients with a *p-value* <0.001, both in kidney and in peripheral blood. Similar results were obtained with TP53 (*p-value* <0.001), C-JUN (*p-value* <0.001 in blood, *p-value* <0.05 in kidney). ARRB2 yielded a

statistically significant result only in kidney (*p-value* <0.05), such as ATF2 (*p-value* <0.05).

These findings are reported in Figure 1 (gene expression in kidney) and Figure 2 (gene expression in blood).

On the contrary, MAPK14, XBP1 and NPHS1 expression profiles did not differ in a statistically significant way.

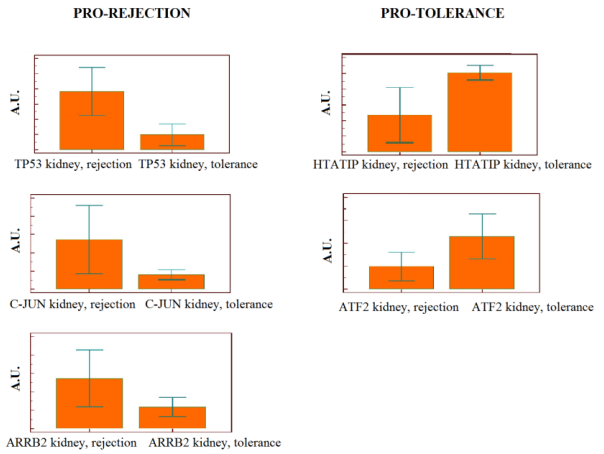

Figure 1: Gene expression in kidney (at left, genes whose upregulation leads to kidney allograft rejection; at right, genes whose upregulation leads to kidney transplant tolerance). Only genes able to distinguish between tolerance and rejection are reported.

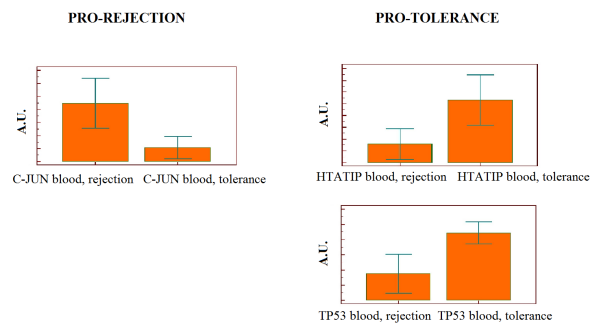

Figure 2: gene expression in blood (at left, genes whose upregulation leads to kidney allograft rejection; at right, genes whose upregulation leads to kidney transplant tolerance). Only genes able to distinguish between tolerance and rejection are reported.

Correlation between expression profiles in peripheral blood and in kidney was also studied, using Pearson's correlation. Only ATF2 tolerance profile in kidney and in blood yielded statistically significant results (r=-0.68, p-value <0.001) (Figure 3).

Discussion

5 out of 8 Leader genes (62.5%) are able to predict the clinical outcome of kidney transplantation. The lack of statistical significance for the remaining genes (namely, MAPK14, XBP1, and NPHS1) may due to the limited existing number of micro-array experiments.

As can be seen from the following extensive literature review, some of these genes have been rarely described as predictors of clinical outcomes to renal graft in the literature.

HTATIP/KAT5, a gene located at chromosome 11 (locus 11q13.1) and made up of 14 exons [31], encodes a protein of 513 amino-acids, termed as Tip60, a histone acetyltransferase (HAT) (EC 2.3.1.48), belonging to the MYST family of enzymes HATs. It was initially isolated as a 60 kDa HIV-1 Tat interactive protein and, due to its interaction with cPLA(2) and group IV cytosolic phosholipases A(2) [54,56], it is known also as cPLA(2)-interacting protein.

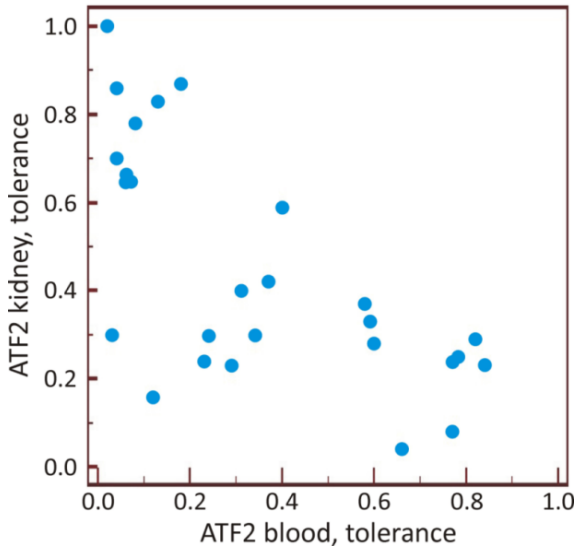

Figure 3: Pearson scatter-plot showing correlation between blood and kidney expression level of ATF2, *p-value* <0.001.

It is the catalytic subunit of the Tip60 histone acetyltransferase complex which is homologous to the Nu4 HAT complex in yeast and which includes also Tip60 splice variants (Tip60b/PLIP), p400/Domino, β-actin, TRRAP, RuvBL1, RuvBL2, Mrg15, MrgX, MrgBP, Brd8/TRCp120, Epc-1, EPC-like protein, YL-1, DMAP, Gas41, FLJ11730 [54], BAF53a (Brg1/Brahma Associated Factor-53a)/ACTL6A [28], and ING3 [54].

HAT plays an important role in regulating chromatin remodeling, transcription and other nuclear processes by acetylating histone (H4, H3, H2A.X/H2A.Z) [29] and non-histone proteins.

Particularly, it remodels p53 gene, being both responsible of the maintenance of a constant basal pool of p53 proteins and being its co-activator [54]. Moreover, it remodels type I interferon genes [16], Upstream Binding Factor (UBF), c-MYC, ATM and class I nuclear receptors (among the others, the androgen receptors) [54]. This modification may both alter nucleosome–DNA interactions and promote interaction of the modified histones with other proteins which positively tune transcription.

HTATIP is a nuclear protein expressed in testis, heart, brain, kidney, liver and lung, while is not expressed in muscles and spleen [30].

In kidney, HTATIP is expressed at the peri-capillary level, and its involvement in the kidney transplantation network may explain the mesangial expansion that some patients experience after the allograft [69], and may be an earlier signal of it [40].

Moreover, since it interacts with VHL and HIF-1α [53], it may be involved in the fibrosis and hypoxia pathways linked to allograft rejection [4,5,70], as well as in the apoptosis [12,31] and in the endoplasmic reticulum (ER) stress [51] networks, playing a role similar to that of SMILE/TMTC3.

It is involved in DNA repair mechanisms too, induced by genotoxic stress and in regulation of cell cycle (contributing to G2 checkpoint) [31]. Interacting with ATM [6], it may be involved in disease-related kidney senescence [14].

TP53 encodes the Cellular tumor antigen p53 (known also as tumor suppressor p53, phosphoprotein p53 or antigen NY-CO-13). Being an oncogene, it acts as a tumor suppressor in many tumor types, induces growth arrest or apoptosis depending on the physiological circumstances and cell type. It is involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a vast array of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression (393 amino-acids).

p53 has been linked several times to kidney transplant [15,59] and its up-regulation may lead to allograft rejection, even though its role may be more complex [58,60].

ARRB2 regulates beta-adrenergic receptor function. Beta-arrestins seem to bind phosphorylated beta-adrenergic receptors, thereby causing a significant impairment of their capacity to activate G(S) proteins (421 amino-acids). Arrestin b2 is known to have a significantly reduced expression in monocytes during kidney graft rejection as it has been recently demonstrated in humans [68].

MAPK14 encodes the Mitogen-activated protein kinase 14 [EC 2.7.11.24], known also as mitogen-activated protein kinase p38 alpha (MAP kinase p38 alpha), cytokine suppressive anti-inflammatory drug-binding protein (CSAID-binding protein; CSBP), or MAX-interacting protein 2 (MAP kinase MXI. It responds to activation by environmental stress, pro-inflammatory cytokines, and lipopolysaccharide (LPS)] by phosphorylating a number of transcription factors, such as ELK1 and ATF2, and several downstream kinases, such as MAPKAPK2 and MAPKAPK5. It plays a critical role in the production of some cytokines, e.g., IL-6 (360 amino-acids) and other pro-inflammatory cytokines.

It is expressed at peri-capillary level [64]. Its involvement in kidney transplantation is manifold: both immune tuning and control [52]. Its inhibition results into better clinical outcomes [41,62].

ATF2 encodes the Cyclic AMP-dependent transcription factor ATF-2 [activating transcription factor 2; cAMP response element-binding protein CRE-BP1, HB16]; transcriptional activator, probably constitutive, which binds to the cAMP-responsive element (CRE; consensus: 50-GTGACGT[AC][AG]-30), a sequence present in many viral and cellular promoters. Interaction with JUN redirects JUN to bind to CRES preferentially over the 12-Otetradecanoylphorbol-13-acetate response elements (TRES) as part of an ATF2-c-Jun complex (505 amino-acids).

ATF2 is mutated in patients with autosomal dominant polycystic kidney disease, as well as is involved in the pathogenesis of diabetic nephropathy [19].

XBP1 encodes the chaperone X-box protein type 1. It is a transcription factor essential for hepatocyte growth, the differentiation of plasma cells, the immunoglobulin secretion, and the unfolded protein response (UPR). It acts during endoplasmic reticulum stress (ER) by activating UPR target genes via direct binding to the UPR element (UPRE). It binds DNA preferably to the CRE-like element 50-GATGACGTG[TG]N(3)[AT]T-30, and also to some TPA response elements (TRE). It binds also to the HLA DR-alpha promoter and to the Tax-responsive element (TRE) of HTLV-I.

It has been sometimes associated with liver [34] and human islet cells [33] transplant. It has been poorly described as a biomarker of kidney transplant [48].

C-JUN is a proto-oncogene belonging to the Transcription factor AP-1 (activator protein 1) complex and was initially studied as V-jun avian sarcoma virus 17 oncogene homolog. Known also as p39, it is a transcription factor that recognizes and binds to the enhancer heptamer motif 50-TGA[CG]TCA-30 (331 amino-acids).

It is involved in peritubular capillary endothelial cells activation, their subsequent swelling and loss, and interstitial fibrosis, thus resulting in chronic antibody mediated rejection (CAMR) [25,26]. c-JUN is putatively involved in both apoptosis and fibrosis pathways [61], it correlates with tubular ischaemia/reperfusion injury [24]. Moreover, c-JUN expression may reflect phenotypic changes induced by cyclosporine [43], and mycophenolic acid [2] treatment.

NPHS1, located at chromosome 19 (locus 19q12-q13.1), encodes the nephrin, a type 1 transmembrane protein of 185-200 kDa, which is a member of the immunoglobulin superfamily, having eight extra-cellular immunoglobulin-like type C2 domains. This class of cell adhesion molecules functions in the glomerular filtration barrier in the kidney, being the structural component of the glomerular slit diaphragm [27]. This cellular junction has a porous structure, acting as a "molecular filter", and nephrin is an important component of it, being termed as a "signature molecule of the glomerular podocyte" for its importance [66]. It fosters activation of stress-activated protein kinase 38 and JUN which acts in complex with FOS [20]. In competition with the binding of Nephrin to the podocin, Arrestin b2 mediates Nephrin endocythosis and therefore its functioning reduction (47, and references therein). Note that the Arrestin b2 activation is via MAP kinase and down-regulates the TGF-b signaling pathway. Moreover, nephrin as signalling molecule interacts with a lot of partners: such as the Nck adaptor proteins that link nephrin to the actin cytoskeleton of kidney podocytes, which is required for nephrin-dependent reorganization of actin. Other interactions of nephrin with CD2AP, podocin (NPHS2), adherens junction proteins, Fyn, phosphoinositide 3-OH kinase, dendrin and vascular endothelial growth factor (VEGF) have been found and described. Binding of nephrin to dendrin and VEGF may have a role in the prevention of programmed cell death (apoptosis). Its polymorphism cause the Finnish-type steroid-resistant nephrotic syndrome (being involved in all the known variants, the congenital, the infantile and the childhood forms) [17] and other glomerulopathies, such as the focal segmental glomerulosclerosis (FSGS) [1,11,49], characterized by proteinuria and kidney impairment and dysfunction. The molecular basis of these

disorders are nephrin misfolding, altered subcellular localization (endoplasmic reticulum instead of plasma membrane) and altered mobility, reduced nephrin trafficking. NPHS1 is useful for distinguishing between minimal-changes disease and FSGS [32].

Podocin-to-nephrin ratio (PNR) is an emerging biomarker of acute kidney injury (AKI). Moreover, NPHS1 together with NPHS2 is able to predict recurrence rate of nephrotic syndrome after kidney transplant [44,63, 65]. Changes in nephrin expression are related to the effect of immunosuppressive treatment [58].

Conclusions

Our approach has underpinned 8 highly interconnected genes that may be involved in kidney transplantation. In the extant literature, only few genes have been experimentally associated with allograft response (namely, TP53, MAPK14 and c-JUN), whilst the others have been only indirectly linked with kidney transplant.

Mining the GEO database, we managed to confirm that TP53 and c-JUN are useful for distinguishing the clinical response to allograft while we were not able to replicate this finding for MAPK14. In addition to these genes, we found that also HTATIP, ARRB2 and ATF2 may be involved in kidney transplant networks.

Using Gene Ontology tool, we speculate that this panel of genes may be putatively responsible of biological processes, such as apoptosis, cell cycle regulation, ER stress, interstitial fibrosis and mesangial expansion leading to kidney allograft reject (Figure 4).

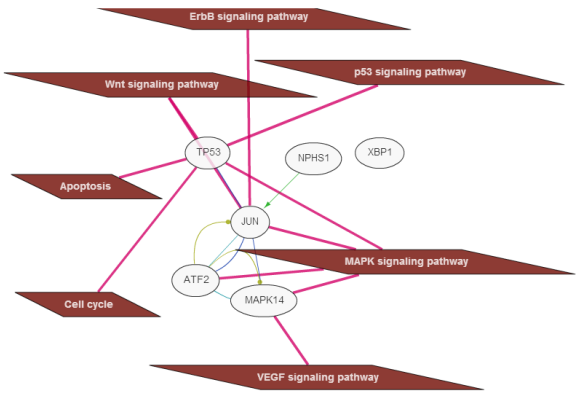

Figure 4: Gene Ontology map of the previously obtained hub genes, showing the networks and pathways they are involved in, and which may lead to kidney allograft rejection.

In conclusion, 5 of our previously obtained "hub genes" are helpful in distinguishing between kidney transplant tolerance and rejection. Further experiments are needed to confirm and replicate our findings.

As a final conclusive comment, we would like to speculate about the success of our bioinformatics leader genes algorithm, at least applied in this case. In the past, we have conducted bioinformatics analysis in two ways: an approach completely *ab initio* being purely theoretical, and another method that could be called semi-theoretical being based in part on microarray experiments and in part of their theoretical expansion and reconstruction of gene-gene interactions and networks by integrate these findings with further ones by means of data-mining.

It is noteworthy to underline that we never used text-mining in order to avoid wrong inferences about gene functions and their biological meanings. We decided to attain to the evidences so far collected to have more reliable and rigorous conclusions.

We believe the success of this approach in this case is due to the particularly robust experimental background of our bioinformatics analysis. However, in the future we will conduct also a similar approach for data deriving from pure *ab initio* investigations, in order to compare the two approaches. For this reason as well for the reasons previously explained, further research is necessary for shedding light on this topic.

Acknowledgments

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