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Genomics in Organ Transplantation

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The understanding of genetic diversities in humans by applying the state of the art genomic technologies has been accumulated and enriched since the last decades. Even in organ transplantation, these genomic technologies have not yet been widely applied and have less impact, except Human Leukocyte Antigen (HLA) matching. Pre- and post-operative care including surgical techniques in organ transplantation has improved reducing morbidity and mortality, but there are limitations and obstacles due to personal diversities coming from genetic variation. For this reason, the therapy combined with genomic information would be promising and beneficial in organ transplantation and would expect to give a new paradigm in personalized medicine in the near future. In this review, we introduce Next Generation Sequencing (NGS) technology and summarize potential benefits of these technologies in organ transplantation.

Key Words: Genomics; High-Thoughput Nucleotide Sequencing; Organ Transplantation; Graft Rejection

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INTRODUCTION

Since the first organ transplantation conducted in 1953, the overall processes of organ transplantation have been remarkably developed not only in surgical techniques but also in peri-surgical treatment including appropriate matching donor, immunosuppressive agents, etc. [1]. Many types of study associated with genomics have also developed (Table 1). By virtue of these successful improvements, there were more than 28,000 cases of organ transplantations including liver, heart, and kidney conducted in KOREA since 2000 (KOrean Network for Organ Sharing, KONOS). And now, organ transplantation is considered as a routine curative treatment for the end stage of diseases in kidney, heart, and liver. Even though these successful improvements in transplantation progresses, the acute or chronic rejection rate of allograft is still significant, and it is up to 60% [2].

The completion of the human genome project initiated the new era of translational medicine. The Human Genome Project (HGP) was performed to determine the chemical nucleotide sequences which consist of the human DNA and identify genes of the human genome physically and functionally. Since the completion at 2003, this information has been widely used to find disease related markers, discover genetic variations, and identify personal diversities [3]. Like beads array technology, the next generation sequencing (NGS) brought us a new insight into molecular biology. Especially the sensitivity of this technology made it possible to identify specific markers in a heterogeneous group of patients and supply customized medicine to take care of the different types of diseases. NGS technology shifts a paradigm from protocol-based medicine to personalized medicine. NGS technology can be applied to the patients suffering from organ failure and failed organ transplantation, estimating rejection rates using the specific biomarkers identified by NGS between patient and donors, finding the best matching donor and transplanting it to the patient, and achieving successful donor transplantation. In this review, we introduce the current available genomic technologies and summarize potential benefits of these technologies in organ transplantation.

Table 1. Definitions associated with genomics

Element	Definition
Genome	The entire genes of organism intrinsically, including its hereditary character.
Genomics	A field of studying the genome.
Genetics	Concerning heredity of features and properties of organism and how they are manifested.
Omics	Fields of studying biology associated of –omics (e.g. genomics, transcriptomics, proteomics, metabolomics).
Bioinformatics	A field of collecting and studying biological data, and application of it to solve biological problems concerned with molecular biology.
Biostatistics	The branch of science applies to statistics into biology including collecting, analysis, and interpretation of biological data.

GENERAL CONCEPTS OF GENOMICS IN ORGAN TRANSPLANTATION

The diversity of the human genome is as immense as the population of human beings on earth. Those diversities range from population to personal diversities caused from genomic variations like deletions, insertions, translocations, copy number changes, single-nucleotide polymorphism (SNP), etc. Among these variations, some variations have a causal relationship with certain diseases, and the importance of finding these variations has been raised along with the development of genomic technologies.

As an example, a representative causal relationship of genomic diversities and disease could be found in a breast cancer. By the heterogeneous gene expression patterns, the cancer subtypes, treatment, and prognosis were determined [4]. This result provided a glimpse of insight that a certain kind of association could exist between genome and disease state. In 2005, a comparative study identified two significant SNPs by comparing DNA sequences between healthy and disease group of age-related macular degeneration [5]. This is known as the first significant result by applying genome-wide association study in clinical samples (GWAS), and subsequent studies have been identifying genomic variants in disease sample compared to control sample. GWAS is an approach to find association with a trait from common genetic variants in different individuals. Since 2002, when GWAS was first introduced from RIKEN, this method has been widely adapted in SNP studies and give us a clue for the association between SNPs and a certain disease, SNPs and drug resistance, etc. [6-8].

Microarray technology accelerates genomic studies including GWAS. Through microarray experiments, one can measure gene expression levels of thousands of genes simultaneously, identify genomic variations such as SNPs and copy number changes, and detect DNA protein binding sites more quickly. In organ transplantation, the cDNA microarray was applied to kidney transplantation in living donor, deceased donor and identified deceased donor specific inflammation target genes. Hause et al. [9] showed that post-ischemic acute renal failure was reduced when these target genes were repressed in deceased donor kidneys. This shows how genomics affects prognosis in organ transplantation.

NEXT-GENERATION SEQUENCING

NGS is high-throughput sequencing technology that parallels the sequencing process producing thousands or millions of sequences concurrently. Millions or billions of DNA transcripts can be sequenced simultaneously and provide more accurate and reliable results than Sanger sequencing. With these DNA sequences one can obtain gene expression profiling, identify genomic variants, and detect DNA/RNA protein binding, histone modification, and methylation sites. For more detailed review of NGS technology, please refer to the reference article [10-14].

Recently, with reasonable cost and advanced technology, NGS has become popular in genomic analysis and has been widely adapted. There are several different NGS applications. For population genomics, evolutional genomics, and identifying genomic variants in human diseases, whole genomic sequencing, whole exome sequencing and target re-sequencing can be applied, and for gene expression profiling, transcriptome sequencing, and RNA sequence analysis can be applied. There are a few studies applying transcriptome sequencing analysis in heart transplantation and the studies have identified 10 genes related to cardiac transplant rejection [15]. Splicing events, novel gene identification, fusion genes, and post transcriptional modification can be also identified by transcriptome sequencing. Besides these applications, NGS can also be applied in epigenetic studies.

By virtue of emerging NGS technology, we faced some technical and ethical issues such as lack of data analysts like bioinformatician, biostatistician and security problems to preserve personal genome sequence data. But the current NGS technology is sufficiently developed and adaptable for clinical data analysis, and it will provide a clue for customized health care service in the near future.

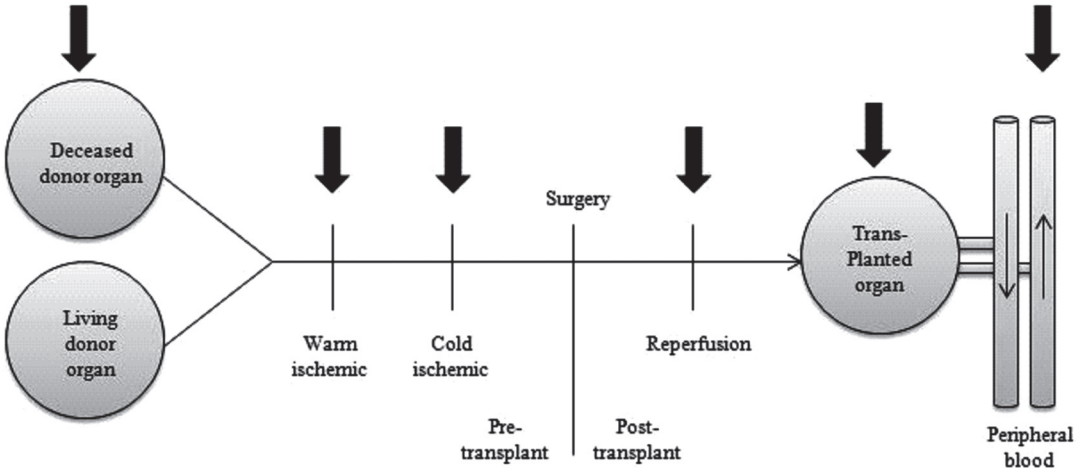

Fig. 1. Application of genomics in organ transplantation. Gathering samples are available in a point of time which are indicated by thick arrows.

CURRENT STATE OF APPLICATION OF GENOMICS IN ORGAN TRANSPLANTATION

Application of genomic technology in organ transplantation includes not only pre-transplanted intervention, but also detection and monitoring post-transplanted rejection. Samples obtained from graft biopsy have many problems (Fig. 1). These procedures are not suitable for frequent monitoring because of its invasiveness and therefore minimally invasive tools are needed. Recently, genomes in urine or peripheral blood samples are used to detect early organ rejection. In this section, we introduce the applications of genomic technologies in three organ transplantations (heart/liver/kidney).

DNA of the transplanted organ is different from the recipient's DNA, so it can be used to monitor the organ's healthy state. Acute cellular rejection existing in transplanted heart biopsy can be found in the recipient's peripheral blood. And cell-free DNA from the donor genome is also significantly increased in recipient's plasma [16]. This study shows that genome monitoring can be used to access the health state of transplanted organ and can be used as a minimally invasive tool to evaluate it. A study on prediction of acute cardiac rejection from genome probe of donor biopsy sample and recipient's pre-transplant whole blood, showed better results than other 8 traditional clinical variables (recipient and donor age, cold and warm ischemic time HLA mismatch, gender mismatch, blood type mismatch, and panel-reactive antibody) [17].

Liver is different from the other organs, since liver has its unique regenerative potential. Many processes in organ transplantation like donor status, ischemia/reperfusion injury, regeneration, rejection are used in gene expression profiling. Distinctive gene expression patterns found in these processes can be used to develop new tools including reducing organ injury and rejection and raising regeneration potential. According to recent studies, differentially expressed genes in pre/post transplanted living donor organ are 1,324 and in deceased donor organs there are 579 genes. There are merely 126 commonly differentially expressed genes between the living and deceased donor group [18]. It shows significant discrepant properties between living and deceased donor organs. By using genome profiling, some expressed genes can be classified as a cluster and specific pathways that are related can be found [18].

Rejection of transplanted kidney is diagnosed by biopsy according to histologic classification. The existing gold standard method is the Banff criteria [19] and it has some problems like intrinsically containing invasive biopsy. Several groups have tried to delineate biomarkers of rejection by using the omics technique [20]. Using genomics, David Perkins and coworkers [21] reviewed that genetic biomarkers obtained from urine and peripheral blood samples can be used to monitor or diagnose of rejection by minimally invasive tools.

FUTURE PERSPECTIVES

Many types of omics associated studies in organ transplantations are developing and have become popular in its territory nowadays. Genomic architectures are built up based on genomic technologies and understanding genomic mechanisms. Unlike other bio-

markers such as proteins and metabolites, a subtle change in genome can be preceded by pathologic changes in the molecular level. Understanding these subtle changes can initiate individualized or personalized medicine. Development of genomic research in organ transplantations can help in enhancing accomplishment of the goal of long-term function of allograft. More active studies are necessary to progress genomics in transplantation. NGS, bioinformatics, and biostatistics are becoming available and are used to drive the new era of genomics.

CONCLUSION

Until recently, genomic approaches are not actively applied in organ transplantation. Finding potential genes and biomarkers related to a certain disease entity and understanding their mechanisms are not easy and are time consuming tasks. Novel high throughput sequencing technology dramatically reduces these times and efforts. Application of NGS approach in organ transplantation is expected to be increased as in other clinical studies. These technologies provide molecular insight of each individual patient and enhance customized healthcare. Knowing personal variants is more crucial and important in organ transplantation. Therefore, we need to prepare and adapt these new demands in the near future.

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