

High-throughput Gene Expression Profiling: Its Application in Studying Transfusion-Transmitted Infections

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Since the discovery of the ABO blood groups, blood transfusion has been playing an important therapeutic role in clinical medicine. Similar to other therapeutic manipulations, blood transfusion always carries risks, which include transmitted infection threats and noninfectious hazards [1]. Microarray gene-expression profiling, a high throughput method that simultaneously examines gene expression changes at the transcript level has potential applications in screening for prognostic markers and in detecting multiple pathogens from a single sample. Previous studies demonstrated that gene expression profiling has shed light on unrecognized mechanisms of virus resistance that are deemed to be essential for the discovery of new drug targets.

Transfusion-related Risks

The AIDS epidemic in the mid-1980s heightened global concern about blood safety. With the development of more sensitive laboratory screening methods for blood donors, the morbidity and mortality of the Transfusion-Transmitted Infections (TTI) has been decreasing dramatically in the past several decades [2]. However, many new and emerging transfusion transmitted pathogens are the greatest threats to blood safety. Up till now, the transfusion-transmitted infectious diseases include: 1) virus infection: from traditional HIV, HBV and HCV to recently discovered arboviruses such as West Nile Virus (WNV), Dengue Fever Virus [3]; 2) parasitic infections: Malaria, Chagas disease and Babesiosis [4], etc; 3) bacterial contamination: *Escherichia coli*, *Staphylococcus epidermidis* [5] etc. Emerging pathogens in blood donors, undetected in the window period, would potentially result in future infections in the transfusion recipients. Wang et al. [6] examined the prevalence and incidence of HIV infections among donors whose blood samples were collected from five Chinese blood centers between 2008 and 2010. Although the declining HIV epidemic in China, estimated residual risks for transfusion transmitted HIV infections (5.4 per million) are still much higher than the residual risk of HIV (0.125 per million) in 3,936,925 whole-blood donations in Canadian Blood Services from 2006 to 2009 [7].

Introduction of Gene Expression Profiling

Since the 1990s, DNA microarrays have been used to study various infections, to diagnose diseases, and to delineate the virus-host interactions. There are three main types of DNA microarrays: 1) in-situ synthesized arrays: microarrays on which the probes are synthesized in situ directly onto the surface of the chip; 2) spotted arrays on glass: independent synthesized probes are printed on special glass slides; 3) self-assembled arrays: synthesizing DNA on small polystyrene beads and depositing those beads on the end of a fiber-optic array [8].

Application of Gene Expression Profiling in Studying Transfusion-Transmitted Infections

Simultaneous detection of multiple transfusion transmitted pathogens

DNA microarray allows simultaneous detection of different pathogens possible. Due to the outbreak of large-scale epidemics of

arboviral diseases in recent years, there is a pressing need to improve the detection and molecular analysis in urgent clinical situations where the rapid identification and characterization of the pathogen is essential. For example, resequencing DNA microarray (RMA) technology is able to detect single nucleotide polymorphisms (SNPs) within the gene of interest to characterize emerging pathogens. Berthet et al. [9] used high density Pathogen ID v2.0 RMA (PID2-RMA) to successfully detect dengue, West Nile, and Chikungunya viruses in spiked blood samples or sera from individuals infected with dengue virus.

Delineating virus-host interactions to identify new antiviral drug targets and to develop prognostic tools

DNA microarray technology has enabled genome-wide analysis of gene expression changes from clinical tissues and animal models. Previous studies have already shed light on the molecular mechanism of viral resistance. Interferon- α is approved as one of the main therapeutic treatments for chronic hepatitis B virus (HBV) infection, but only a small number of patients achieve Sustained Virological Response (SVR). The molecular basis for interferon (IFN)- α -tolerance is not clearly defined. Tsuge et al. [10] performed microarray analysis with human hepatocyte chimeric mouse livers to assess the direct impacts of HBV infection and IFN treatments on gene expression profiles. They were able to demonstrate that HBV infection attenuated the expression of IFN-stimulated genes (ISGs) under immune deficient condition, which suggests that HBV proteins are involved in viral escape mechanisms from innate and adaptive immunity.

More than 170 million people worldwide are chronically infected with HCV. Currently there is no vaccine and the most effective treatment is paginated IFN- α -combined with ribavirin and one of the direct acting antiviral (DAAs), which has morbid side effects, variable cure rates, and high costs [11]. Therefore it is necessary to understand molecular mechanisms of virus-host interactions and to predict treatment outcomes before initiating therapy. By comparing the pretreatment hepatic gene expression levels between treatment responders and non-responders of patients chronically infected with HCV, Chen et al. [12,13] identified 18 genes (out of 19,000 host genes or transcripts), whose differential expression levels are associated with treatment outcomes. More interestingly, they demonstrated that the cell-type specific protein expression of ISGs in a novel ubiquity

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in-like pathway (ISG 15/USP 18) correlated well with treatment outcomes, with prediction accuracy higher than that predicted by the polymorphism of IL28B [14,15]. Furthermore, they demonstrated that the pre-activation of the endogenous interferon signaling and the cell-type differential expression of ISGs are not unique for HCV. Similar findings were identified in patients chronically infected with HBV [15,16]. Put all these together, this is an excellent example on how gene expression profiling can be used to delineate virus-host interactions in order to better understand the molecular mechanisms of viral resistance, leading to the identification of new drug targets [17].

Conclusion

Although gene expression profiling suffers from concentration restriction in virtue of linear signal merely over a limited range of concentrations in solution and its detection only being available for DNA or RNA based on complementary sequence on the array [18] it offers the advantage of being able to detect multiple pathogens in parallel in blood. Moreover, as a useful tool to delineate the virus-host interaction and virus resistance, gene expression profiling is likely to play an increasingly important role in the future development of drug discovery.

References

- Alter HJ, Klein HG (2008) The hazards of blood transfusion in historical perspective. *Blood* 112: 2617-2626.
- Perkins HA, Busch MP (2010) Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. *Transfusion* 50: 2080-2099.
- Glynn SA, Busch MP, Dodd RY, Katz LM, Stramer SL, et al. (2013) Emerging infectious agents and the nation's blood supply: responding to potential threats in the 21st century. *Transfusion* 53: 438-454.
- Dodd RY (2012) Emerging pathogens and their implications for the blood supply and transfusion transmitted infections. *Br J Haematol* 159: 135-142.
- Bloch EM, Vermeulen M, Murphy E (2012) Blood Transfusion Safety in Africa: A Literature Review of Infectious Disease and Organizational Challenges. *Transfus Med Rev* 26: 164-180.
- Wang J, Liu J, Yao F, Wen G, Li J, et al. (2012) Prevalence, incidence, and residual risks for transfusion-transmitted human immunodeficiency virus Types 1 and 2 infection among Chinese blood donors. *Transfusion*.
- O'Brien SF, Yi QL, Fan W, Scalia V, Fearon MA, Allain JP (2012) Current incidence and residual risk of HIV, HBV and HCV at Canadian Blood Services. *Vox Sang* 103: 83-86.
- Bumgarner R (2013) Overview of DNA Microarrays: Types, Applications, and Their Future. *Curr Protoc Mol Biol* 22.
- Berthet N, Paulous S, Coffey LL, Frenkiel MP, Moltini I, et al. (2013) Resequencing microarray method for molecular diagnosis of human arboviral diseases. *J Clin Virol* 56: 322-327.
- Tsuge M, Takahashi S, Hiraga N, Fujimoto Y, Zhang Y, et al. (2011) Effects of Hepatitis B Virus Infection on the Interferon Response in Immunodeficient Human Hepatocyte Chimeric Mice. *J Infect Dis* 204: 224-228.
- Shepard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 5: 558-567.
- Chen L, Borozan I, Feld J, Sun J, Tannis LL, et al. (2005) Hepatic gene expression profiling discriminates responders and non-responders in treatment of chronic hepatitis C viral infection. *Gastroenterology* 128: 1437-1444.
- Chen L, Borozan I, Sun J, Guindi M, Fischer S, et al. (2010) Cell-type specific gene expression signature in liver underlies response to interferon therapy in chronic hepatitis C infection. *Gastroenterology* 138: 1123-1133.
- Randall G, Chen L, Panis M, Fischer AK, Lindenbach BD, et al. (2006) Silencing of USP18 Potentiates the Antiviral Activity of Interferon Against Hepatitis C Virus Infection. *Gastroenterology* 131: 1584-1591.
- Zhu Y, Qin B, Xiao C, Lu X, Chen L (2012) Cell-type specific interferon stimulated gene staining in liver underlies response to interferon therapy in chronic HBV infected patients. *Dig Dis Sci* 57: 2355-2361.
- Xiao C, Qin B, Chen L, Liu H, Zhu Y, et al. (2012) Preactivation of the interferon signalling in liver is correlated with nonresponse to interferon alpha therapy in patients chronically infected with hepatitis B virus. *J Viral Hepat* 19: e1-e10.
- Chen L, Shilin L, Li YJ, Xiaoqiong D, McGilvray ID (2012) Genome-wide Gene Expression Profiling: An Excellent Tool to Study Virus- Host Interactions. *Journal of Biochips & Tissue Chips* 2: e118.
- Petrik J, Coste J, Fournier-Wirth C (2011) Advances in transfusion medicine in the first decade of the 21st century: Advances in miniaturized technologies. *Transfus Apher Sci* 45: 45-51.