A System-Biological Approach to Interferon-Based Therapies

Kazunori Miyazaki
kazun.miyazaki@toshiba.co.jp
Satoshi Itoh
satoshi.ito@toshiba.co.jp

Toshiba Corporation, Corporate Research and Development Center, Advanced Functional Materials Laboratory, 1, Komukai Toshiba-cho, Saiwai-ku, Kawasaki, Kanagawa 212-8582, Japan

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1 Introduction

Type I interferon (IFN) has been used for treatment of patients with viruses, HCV for example. The type I IFN is produced in virus-infected cells of many different types. The secreted IFN induces an antiviral state in the infected and uninfected neighboring cells. In the cultured cells, the intracellular signaling pathway triggered by the secreted type I IFN has been studied extensively. However, the antiviral mechanisms of IFN action in therapies remain elusive.

The efficacy of the IFN-based therapies is dissimilar depending on patients with HCV. This indicates that genetic polymorphisms will play an important role in the mechanisms. In fact, there are some genes in which polymorphisms were reported to relate to the efficacy of the IFN-based therapies [2,4,5,6,9]. They include genes that play a role in the type I IFN signaling pathway. Additionally genes whose relevance to the IFN signaling pathway remains unknown, for example Osteopontin, low molecular mass polypeptide (LMP) 7, and mannose-binding lectin (MBL) genes, are also included. These things indicate that the intracellular system activated in the IFN-based therapies is not as simple as only the type I IFN signaling pathway.

To figure out the intracellular system activated in the IFN-based therapies is important for understanding the antiviral mechanism of IFN action. And it would be useful for improvement in the efficacy of the IFN-based therapies and personalized therapies. In the present study, we show a system-biological approach to figure out the intracellular system. We retrieve biomedical literature concerning the IFN signaling pathways and the transcriptional regulation of the genes reported to relate to the efficacy of the IFN therapies. By gathering the information about the relationship between the genes and the IFN signaling pathway in the literatures, we construct a model for the intracellular system activated in the IFN-based therapies.

2 Method and Results

We first retrieved PubMed abstracts concerning the type I IFN signaling pathway and the transcriptional regulation of six genes (MBL, LMP7, Osteopontin, Myxovirus resistance protein A (MxA), double-stranded RNA-dependent protein kinase (PKR), 2’-5’ oligoadenylate synthetase (OAS) genes) reported to relate to the efficacy of the IFN therapies. We used “interferon” and the gene names to construct a PubMed query. Among the six genes, as was expected, there were three genes (OPN, LMP7, and MBL genes) which we were not able to find out the literature indicating that the transcriptional regulation of the genes is included in the type I IFN signaling pathway. However, as to LMP7 gene, some of the literatures show that the expression of the gene is induced by another type of IFN, type II IFN [3,7]. The type II IFN is also a cytokine involved in antiviral responses. Additionally, as to OPN, there were some noteworthy reports about the regulation of the expression. OPN is induced by NO which is produced by inducible nitric oxide synthase (iNOS) in murine macrophages which are stimulated by the type II IFN and lipopolysaccharide [10]. In contrast, OPN inhibits the induction of iNOS expression [8]. Guo et al. [1] shows that OPN gene will form a negative feedback loop with iNOS gene in murine macrophages. By gathering the information about type II IFN signaling pathways as well as about type I IFN signaling pathways and the transcriptional regulation of genes relevant to the efficacy of the IFN-based therapies, we constructed a model for the intracellular system activated in the
3 Discussion

In this paper, we assumed that the genes, in which polymorphisms related to the efficacy of the therapies, would play an important role in the intracellular system activated in the IFN-based therapies. We took particular note of the information about the association between the genes and the IFN signaling pathways. By gathering the information, we constructed a model which includes IFN signaling pathways and the genes with the exception of MBL gene. At that point in time when we retrieved the literature, the transcriptional regulation of MBL gene was not clear. Therefore, that may be the leading reason why MBL gene was not included in the present model.

Of course, it is necessary to estimate the validity of the present model by a molecular biological analysis, a genetic association study, or a system-biological simulation. For a preliminary estimation, we examined whether there are the information about the genetic association of iNOS gene, one of the critical molecule in the present model, with the efficacy of the IFN-based therapies. Recently, Yee et al. [11] investigated the association of iNOS gene haplotypes with the outcome of HCV infection. Their observation indicates that iNOS is included in the innate immune systems against HCV infection. In our future work, we plan to address the genetic association study of the polymorphisms in iNOS gene and the efficacy of IFN-therapies.

References