

A systems biology approach to regulation of apoptosis by type I interferons

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Introduction

Type I interferons (IFNs) are cytokines that have antiviral, antiproliferative and immunomodulatory effects. There are many type I IFNs including interferon α , interferon β , interferon κ and interferon ω . All type I IFNs bind to the same receptor. These molecules are widely used in the treatment of hepatitis C, multiple sclerosis and various types of cancer.

In the case of multiple sclerosis only 50% of the patients respond to the therapy. The cause of this lack of efficacy is not known. It will be of great clinical value to find markers of response to this drug in order to begin an early intervention in the responders and develop new molecular targets for non-responders.

In this work we studied type I IFN signalling pathway taking special account on its role in apoptosis modulation.

Analysis tools

We reconstructed the protein interactions of the type I IFN pathway based on experimentally validated published results. To analyze the structure of the pathway we employed CellnetAnalyzer (Max-Planck Institute for Dynamics of Complex Technical Systems). In particular we centered in the group of nodes (proteins) indispensable for the occurrence of a particular cellular action, called minimal cut sets. The target nodes elected were those related with cell survival and apoptosis.

Using previous published models and measured protein kinases concentrations, we have created a computational model for the signalling pathway dynamics of the type I interferon receptor. The outputs of the system are TRAIL mRNA concentration and BAD, BCL2 phosphorylation levels. The model was implemented in Jdesigner (Keck Graduate Institute)

We performed the following simulations:

1. Wild type
2. Single knockout (STAT, PI3K, p38)
3. Double knockout (STAT/PI3K, STAT/p38, PI3K/p38)

Results and conclusion

The results show three possible ways that connect IFN with pro or anti-apoptosis. Two of them involve PI3K-signalling: one leads to apoptosis and the other prevents it. The third one inhibits apoptosis through MAPK-signalling. This could explain the observed double effect of type I interferons on apoptosis regulation. Laboratory experiments are underway to confirm these

predictions. An important observation is that all MCS block effects mediated by STAT (the “classical” pathway associated to IFN). Thus, it can be concluded that effects on apoptosis are intrinsic of interferon signalling. Compared to interferon α , interferon β shows a stronger gene expression activation by focusing on TRAIL(Apo2 ligand) mRNA concentration. The results also indicate a preponderance of PI3K signalling pathway in the control of TRAIL gene expression activated by type I IFNs receptor. The simulations also suggest a distribution of the signal control over the three branches activated by IFN (JAK/STAT, PI3K, p38).

The dynamic and structural analysis highlights the importance that multiple interventions could have in manipulating IFN type I signalling pathway. This is a theoretical orientation to the use of combination therapy in MS.