

Pathway Studio Use-Case

The microglial gene regulatory network activated by interferon-gamma

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Microglia are the immune cells of the central nervous system (CNS). Like macrophages and dendritic cells they are derived from myeloid progenitor cells but migrate to the CNS during embryonic development. Microglial cells play a very important role in CNS functioning as they are rapidly activated in response to even minor stimuli and are a key factor in the defense against infectious diseases, trauma, ischemia, neoplastic transformations, and neurodegeneration [1]. The very broad range of conditions that result in activation of microglia and expression of major histocompatibility complex (MHC) class II molecules raises the question of how the underlying molecular mechanisms may differ between disease conditions.

The authors of this study specifically investigated the effect of interferon gamma (IFN- γ), a well known activator of microglial cells [2]. To further investigate details of response to interferon at a molecular level, microarray transcription profiling was performed. Pathway Studio software was used to build a molecular network formed by the genes found to be differentially expressed in the microarray gene expression experiments. Network diagram (Figure 1) greatly facilitates understanding and interpretation of the results. Moreover, causative relations and interactions existing among the differentially expressed genes and mined using Pathway Studio from the ResNet database provide strong additional evidence in support of the observations: it is likely that differential expression of gene products tightly inter-connected in a pathway represent a true finding rather than false due to noise on the microarray.

Indeed, up-regulation of interferon regulatory factor 1 (IRF1), a known downstream target of IFN- γ /STAT1 signaling (Figure 1) is observed along with up-regulation of STAT1 itself. It is interesting to note here that while STAT1 is initially activated by phosphorylation (IFN- γ induced the JAK-STAT pathway), it not only activates IRF1 transcription but is also further up-regulated upon IRF1 activation through a feedback loop [3]. Lipoprotein lipase (LPL) promoter binds STAT1 and, LPL was previously observed to be repressed upon STAT1 activation [4]. Expression of ICAM-1/VCAM-1 cell-adhesion molecules is also a known marker of inflammation and does occur in response to interferon signaling.

The results of microarray experiments performed in this work also show concerted down-regulation of extracellular matrix (ECM) proteins such as cathepsins D (CTSD) and L (CTSL) and fibronectin (FN1). The molecular network of Figure 1 does provide some further cross-validation of the observations as, e.g., CTSD mRNA was reported to be up-regulated by fibronectin [5] and thus down-regulation of the both does not contradict previous findings. Furthermore, IRF1 does directly bind the promoter and up-regulates cathepsin S (CTSS) expression [6], in line with the observations made in this work (Figure 1).

In summary, interpretation of the experimental data in the context of molecular interactions analysis helps to better understand interrelations among the observed

differentially expressed genes, to build a mechanistic pathway-level picture, and to cross-validate the findings against the volume of existing knowledge about molecular mechanisms. [Please refer to the original article for additional discussion of the findings.]

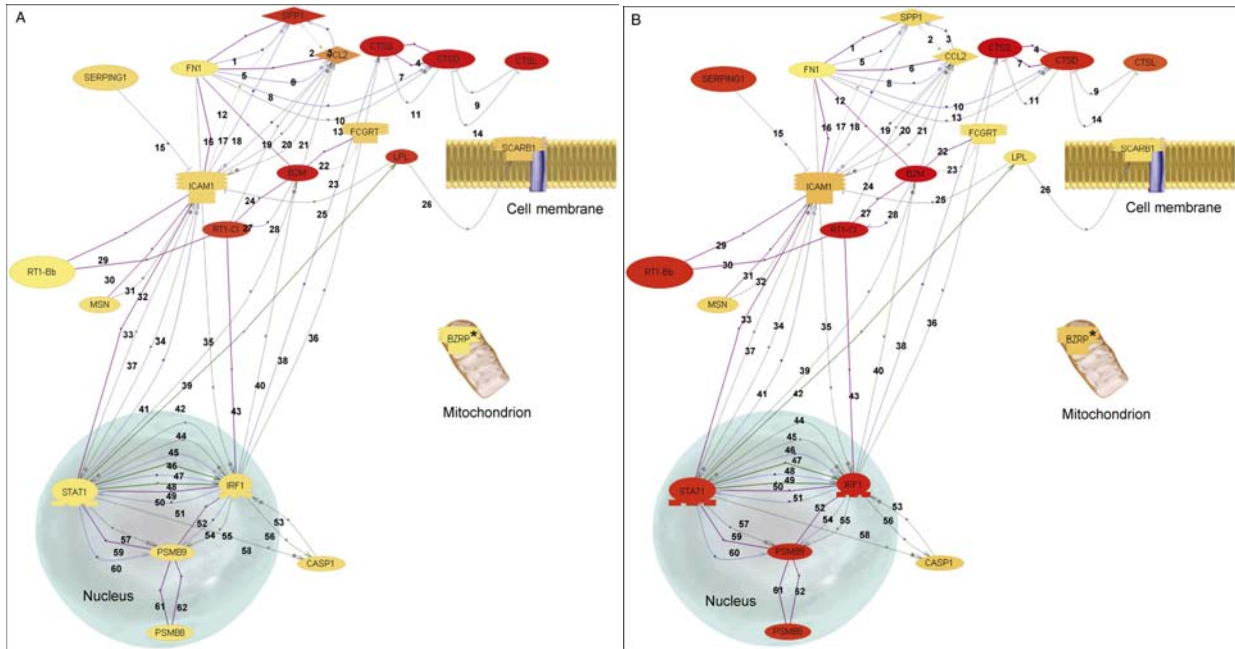


Figure 1. Gene expression in control (A) and IFN- γ treated (B) samples overlaid with molecular network. Higher expression levels are colored with red.

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