Signaling Network of MIF Knockdown in Inhibiting Tumor Growth and Metastasis in Gastric and Colorectal Cancers

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Abstract

Macrophage migration inhibitory factor (MIF), one of the first discovered proinflammatory cytokines, has been implicated in the promotion of tumorigenesis by supporting tumor growth and tumor-associated angiogenesis. Given the observation that MIF was overexpressed in most tumor types inspected, we showed *in vitro* that suppression of endogeneous MIF expression by siRNA can significantly inhibit the growth and metastasis of human gastric epithelial (AGS) and colorectal (DLD-1) carcinoma cell lines. To elucidate the molecular mechanisms involved, we employed Affymetrix microarray to examine the genome-wide expression profiles of AGS and DLD-1 cells in response to the knockdown of MIF. Two-fold differentially expressed genes were then analyzed by Ingenuity Pathways Analysis tool.

We found that AGS cells were generally more sensitive to the MIF knockdown, in which 1130 genes were differentially expressed, compared to 147 genes in DLD-1 cells. In AGS cells, decreased MIF expression resulted in reduced growth and migration, and increased cell adhesion through the following pathways: (i) downregulation of AP-1 dependent transcription through EGR1/FOS, (ii) inhibition of dystroglycan/dystrophin transmembrane signaling, (iii) suppression of BTG1 expression, (iv) induction of ADAMTS3 expression and (v) induction of apoptosis by IGFBP3 and BCL10. On the other hand, DLD-1 cells worked through (i) downregulation of AP-1 mediated transcription via EGR1/JUN and (ii) downregulaton of CYR61 and CTGF (Figure 1).

Results from these studies revealed for the first time the common as well as differential mechanisms involved in the MIF-dependent control of gastric and colorectal cancers. We also identified important MIF responsive genes as potential biomarkers and therapeutic targets.

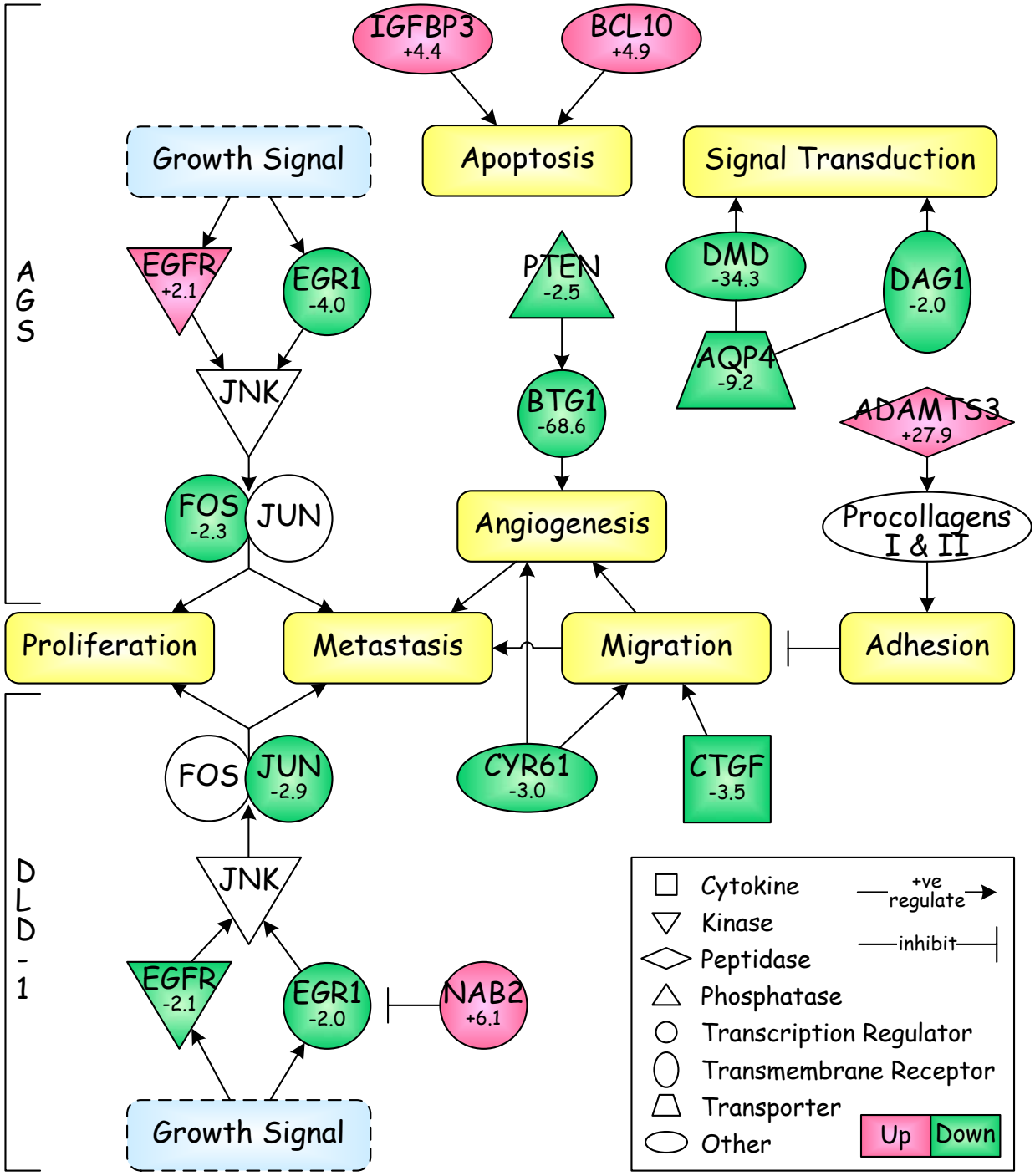

Figure 1. Signaling network of MIF knockdown in AGS and DLD-1 cells.