

MAPK Pathway Signatures in OncoMine™

The Mitogen-activated protein kinase (MAPK) pathway links extracellular signals with cellular response mechanisms to control essential cellular functions such as growth, proliferation, differentiation, migration and apoptosis. Deregulation of the MAPK pathway is an important area in cancer research, as many human cancers exhibit activating

MAPK pathway mutations. Many global gene expression profiling studies on human tumors have been conducted to elucidate the role of the MAPK pathway in cancer, but given that gene expression patterns in tumors are influenced by many factors, it is difficult to identify the specific set of genes that are activated by the MAPK pathway. An alternative approach is to begin with cell lines that have been transfected with activated MAPK pathway genes, and then use genomic profiling to compare the gene expression pattern of those cells with controls. In this case, any differences in gene expression are directly attributable to the activation of the gene. This approach pioneered by Bild et al., has been used to develop gene signatures for a number of oncogenic pathways, including H-RAS, that when applied to human tumor populations, can accurately predict pathway activity and suggest opportunities for targeted therapy¹.

A second study by Creighton et al., took a similar experimental approach, but assessed the effects of constitutively activating genes that act at different specific points in the MAPK pathway (Figure 1), including EGFR, ERBB2, RAF-1, and MEK-1². This approach led to the generation of individual gene signatures for each of the different points in the MAPK pathway, as well as a general MAPK activation signature that includes only those genes that are over- or under- expressed under each of the four conditions.

Data from these two studies can be examined in OncoMine, along with data from 26 additional studies comprising cancer specimens with known mutations in various components of the MAPK pathway (Table 1). This represents a unique opportunity to study the deregulation of the MAPK pathway in diverse experimental and clinical contexts. The OncoMine Concepts Map provides a platform to analyze such gene expression signatures and identify associations among pathways, tumors and drugs.

To begin our OncoMine analysis, we attempted to validate the MAPK activation signature. As expected, the signature

was most significantly associated with an activated H-Ras signature from an independent study. Furthermore, the MAPK signature was significantly associated with several tumor populations and sub-populations with known MAPK activation. For example, the signature was strongly associated with pancreatic tumors, which harbor K-Ras mutations, and glioblastoma, which often harbors EGFR amplifications. Also, both the MAPK signature and the ERBB2-specific signature were significantly associated with ERBB2-positive breast cancer. These observations support the notion that gene expression signatures can serve as a universal readout to link in vitro pathway analyses with clinical tumor populations.

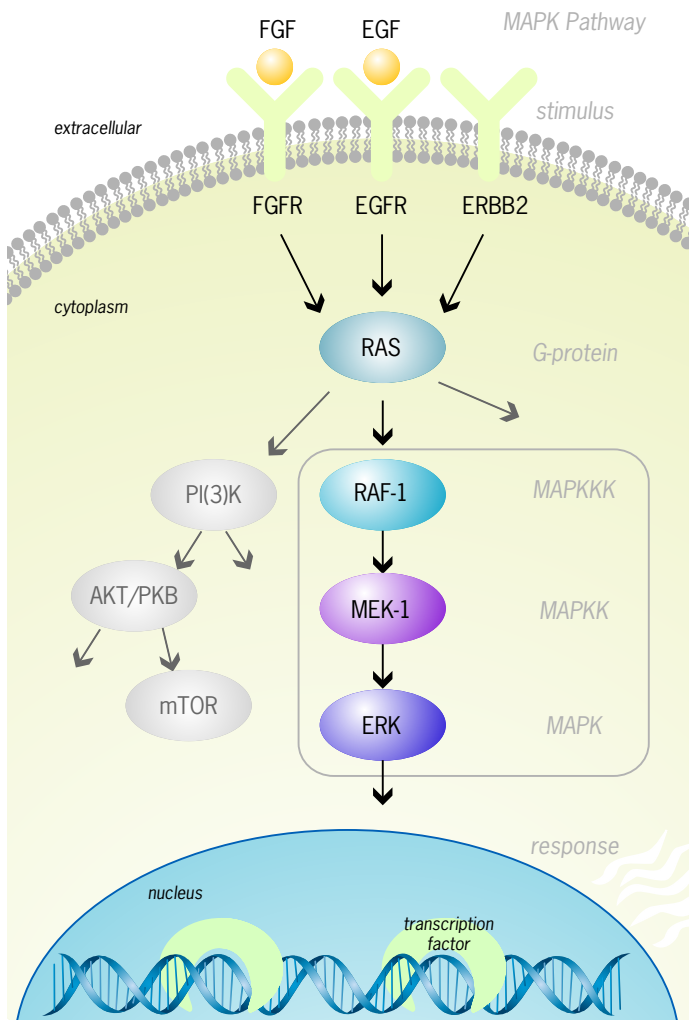


FIGURE 1: MAPK Pathway

¹ Bild et al., *Nature* 2006; 439:(19)

² Creighton et al., *Cancer Research* 2007; 66:(7)

Perhaps more exciting is the opportunity to use this compilation of MAPK data and MAPK signatures to develop therapeutic approaches to inhibiting the pathway in specific patient populations and sub-populations. Our analysis indicated that MAPK pathway activation was associated with both gefitinib and dasatinib sensitivity in cell lines, providing a biological rationale for sensitivity and suggesting a potential biomarker for predicting sensitivity in patients. Notably, we observed significant associations between MAPK activation and patient survival in breast, lung and ovarian cancer, suggesting that tumors with activated MAPK pathway are less responsive to conventional therapy and may benefit from new targeted therapies such as gefitinib and dasatinib. While this analysis focused specifically on the general MAPK activation signature, future Oncomine analyses should attempt to delineate the effects of activating different components of the pathway in the context of tumor sub-populations and drug sensitivity.

TABLE 1: MAPK PATHWAY STUDIES IN ONCOMINE

Gene	Normal vs Aberrant Oncomine Analyses	Tissue Type	Experiment Type	# of Samples in Analysis	
EGF and FGF	Lee_Brain	Glioblastoma Primary Cell Line	Treated with EGF and FGF	40	
EGFR	Coldren_CellLine	Head and Neck Squamous Cell Carcinoma	EGFR Mutation	25	
	Coldren_CellLine	EGFR Mutant Lung Adenocarcinoma Cell Line	Gefitinib Sensitivity	8	
	Creighton_CellLine	MCF7 Breast Adenocarcinoma Cell Line	EGFR Transfection	6	
	Zhou_CellLine	Gefitinib Sensitive Non Small Cell Lung Carcinoma Cell Line	EGFR Status	5	
	Chung_Head-Neck	Head and Neck Squamous Cell Carcinoma	EGFR Immunohistochemistry	57	
	French_Brain	Glioma	EGFR Amplification	27	
ERBB2/HER2/neu	Creighton_CellLine	MCF7 Breast Adenocarcinoma Cell Line	ERBB2 Transfection	6	
	Neve_CellLine	Breast Cell Line	HER2 Overexpression	50	
	Bild_Breast	Breast Carcinoma	HER2 Status	140	
	Bittner_Breast	Breast Carcinoma	HER2/neu Status	26	
	Chin_Breast	Breast Carcinoma	ERBB2 Amplification Status	79	
	Hess_Breast	Breast Carcinoma	HER2/neu Status	132	
	Ma_Breast	Breast Ductal Carcinoma	HER2 Status	18	
	Ma_Breast_3	Breast Carcinoma	HER2/neu Status	55	
	Minn_Breast_2	Breast Carcinoma	HER2 Status	88	
	Perou_Breast	Breast Ductal Carcinoma	HER2 Status	30	
	Richardson_Breast_2	Breast Carcinoma	HER2/neu Status	37	
	Saal_Breast	Breast Carcinoma	HER2 Amplification Status	102	
	Zhao_Breast	Breast Ductal Carcinoma	HER2 Status	31	
FGFR	Lindgren_Bladder	Bladder Carcinoma	FGFR3 Mutation Status	75	
RAS	Bild_CellLine	Human Mammary Epithelial Cells	Activated H-RAS Transfection	20	
	Coldren_CellLine	Non-Small Cell Lung Carcinoma	K-RAS Mutation Status	45	
	Ince_CellLine	Human Mammary Epithelial Cells	H-RAS Transfection	10	
	Ince_CellLine	Breast Primary Epithelial Cells	H-RAS Transfection	11	
	Beer_Lung	Lung Adenocarcinoma	K-RAS Mutation Status	85	
	Bild_Lung	Non-Small Cell Lung Carcinoma	RAS Mutation Status	74	
	Hoek_Melanoma	Cutaneous Melanoma	N-RAS Mutation Status	8	
	Koinuma_Colon	Colorectal Carcinoma	K-RAS Mutation Status	40	
	Pavey_Melanoma	Melanoma	N-RAS Mutation Status	52	
	Valk_Leukemia	Acute Myeloid Leukemia	N-RAS Mutation Status	278	
	Valk_Leukemia	Acute Myeloid Leukemia	K-RAS Mutation Status	282	
	RAF	Creighton_CellLine	MCF7 Breast Adenocarcinoma Cell Line	Activated RAF-1 Transfection	6
		Haqq_Melanoma	Metastatic Melanoma	B-RAF Mutation Status	16
Hoek_Melanoma		Cutaneous Melanoma	B-RAF Mutation Status	8	
Koinuma_Colon		Colorectal Carcinoma	B-RAF Mutation Status	40	
Pavey_Melanoma		Melanoma	B-RAF Mutation Status	50	
MEK	Creighton_CellLine	MCF7 Breast Adenocarcinoma Cell Line	Activated MEK Transfection	6	