Application of Gene Expression Trajectories Initiated from ErbB Receptor Activation Highlights the Dynamics of Divergent Promoter Usage

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 3589721
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Year 2015
Title Application of Gene Expression Trajectories Initiated from ErbB Receptor Activation Highlights the Dynamics of Divergent Promoter Usage
Journal PLoS ONE
Volume 10
Number 12
Pages / **Article-Number** e0144176
Mesh terms Apoptosis, genetics; Breast Neoplasms, genetics; Cell Cycle, genetics; Cell Differentiation, drug effects; Cell Line, Tumor; Cell Proliferation, drug effects; Enzyme Activation, drug effects; Epidermal Growth Factor, pharmacology; ErbB Receptors, metabolism; Extracellular Signal-Regulated MAP Kinases, metabolism; Female; Focal Adhesions, genetics; Gene Expression, drug effects; Gene Expression Profiling; Gene Expression Regulation, genetics; Humans; MAP Kinase Signaling System, genetics; MCF-7 Cells; Neuregulin-1, pharmacology; Promoter Regions, Genetic, genetics; Tumor Suppressor Protein p53, genetics
Understanding how cells use complex transcriptional programs to alter their fate in response to specific stimuli is an important question in biology. For the MCF-7 human breast cancer cell line, we applied gene expression trajectory models to identify the genes involved in driving cell fate transitions. We modified trajectory models to account for the scenario where cells were exposed to different stimuli, in this case epidermal growth factor and heregulin, to arrive at different cell fates, i.e. proliferation and differentiation respectively. Using genome-wide CAGE time series data collected from the FANTOM5 consortium, we identified the sets of promoters that were involved in the transition of MCF-7 cells to their specific fates versus those with expression changes that were generic to both stimuli. Of the 1,552 promoters identified, 1,091 had stimulus-specific expression while 461 promoters had generic expression profiles over the time course surveyed. Many of these stimulus-specific promoters mapped to key regulators of the ERK (extracellular signal-regulated kinases) signaling pathway such as FHL2 (four and a half LIM domains 2). We observed that in general, generic promoters peaked in their expression early on in the time course, while stimulus-specific promoters tended to show activation of their expression at a later stage. The genes that mapped to stimulus-specific promoters were enriched for pathways that control focal adhesion, p53 signaling and MAPK signaling while generic promoters were enriched for cell death, transcription and the cell cycle. We identified 162 genes that were controlled by an alternative promoter during the time course where a subset of 37 genes had separate promoters that were classified as stimulus-specific and generic. The results of our study highlighted the degree of complexity involved in regulating a cell fate transition where multiple promoters mapping to the same gene can demonstrate quite divergent expression profiles.

Publisher Public Library of Science
ISSN/ISBN 1932-6203

edoc-URL http://edoc.unibas.ch/43849/
Full Text on edoc No;
Digital Object Identifier DOI 10.1371/journal.pone.0144176
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/26658111
ISI-Number WOS:000366715900029
Document type (ISI) Article