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Meeting abstract

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A role for Fra1 in the control of transcriptional network reorganization following ras transformation

ST Seibt*[1], A Solf[1], C Steinhoff[2], S Kielbasa[2], E Szczurek[2], M Vingron[2] and C Sers[1]

Address: [1]University Medicine, Charité, Berlin, Germany and [2]Max Planck Institute for Molecular Genetics, Berlin, Germany
* Corresponding author

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RAS proteins act as molecular switches transmitting signals from the cell surface to the nucleus, thereby affecting several downstream signaling cascades. Among these cascades, the mitogenic MEK/ERK pathway affects a network of transcription factors such as SRF, ELK and AP1 components, largely known to play an important role in regulating cellular proliferation. While the targets of individual transcription factors have been identified, the structure of the transcription factor network down-stream of MEK/ERK signaling mediating transformation is not well understood. In addition, both gene activation and repression are necessary for tumor formation and it is unclear how certain MEK/ERK stimulated transcription factors participate in both processes.

We performed genome-wide gene expression analysis to identify transcription factors differentially regulated via MEK/ERK between immortalized and HRAS-transformed cells. Individual transcription factors such as Fra1, over-expressed in RAS-transformed cells and human tumors derived from lung or bone, were knocked-down using siRNA. A second gene expression profiling was used to determine the target genes of these transcription factors. TRAP (TRanscription factor Affinity Prediction), a biophysical model of transcription factor binding and gene set enrichment analysis (GSEA) was used to screen for genes with conserved binding motifs and for functional gene sets exhibiting similar regulation.

These approaches revealed novel insights into the role of Fra1 upon activation in RAS-transformed cells. We could define a previously unknown involvement of the MEK/ERK-dependent Fra1 transcription factor in governing the alteration of the transcriptional network in tumor cells: Fra1 seems to play a role in chromatin remodeling and in circadian functions. In addition, we observed a Fra1-dependent suppression of interferon target genes, which are known to be regulated via DNA methylation. These data suggest a key role for the AP1 complex and the Fra1 transcription factor in the reorganization of chromatin and the transcriptional network following oncogenic transformation.