Poster L-21

Integrative Analysis of NCI-60 Panel Reveals Candidate Key Genetic Regulators Affected by Genomic Alterations

Authors:
Doron Lipson (*CS Dept, Technion, Israel*)
Mark Reimers (*National Cancer Institute, Bethesda, MD*)
Anya Tsalenko (*Agilent Laboratories, CA*)
Amir Ben-Dor (*Agilent Laboratories, CA*)
Kimberly Bussey (*National Cancer Institute, Bethesda, MD*)
William Reinhold (*National Cancer Institute, Bethesda, MD*)
Michael Barrett (*Agilent Laboratories, CA*)
John Weinstein (*National Cancer Institute, Bethesda, MD*)
Zohar Yakhini (*Agilent Laboratories, CA*)

Short Abstract: Integrating new high-resolution DNA copy number data on the NCI-60 cell-line panel with existing expression and drug activity data we identify genomic alterations affecting key genetic regulators, by searching for those genes that exhibit noticeable downstream effects, as well as correlation with phenotypic characteristics.

Long Abstract:

The NCI-60 panel [1], which consists of 60 human cancer cell lines derived from 9 different tissues of origin, has been characterized by a wide variety of methods at the DNA, RNA, protein, and functional levels [see e.g., 2-6]. The cells have also been profiled by exposure to more than 100,000 different chemical agents. Recent studies have shown that integration of the different types of data can lead to identification of novel genetic regulators and drug targets [3,7,8] as well as elucidation of control mechanisms [9]. In this study we integrate new high-resolution DNA copy number data [10] on the NCI-60 panel with existing expression and drug activity data [3] to identify DNA copy number changes that are affecting key genetic regulators. We demonstrate that genomic aberrations can have a broad effect on the expression levels of resident genes. Many genes with known roles in carcinogenesis (e.g. NRAS, MAPK1, TP53, and CDKN2A) are affected by DNA copy number. However, it is expected that many other affected genes are only bystanders that are not directly involved in the carcinogenesis process. We filter the large number of candidate genes with significantly affected expression levels by searching for genes whose altered behavior has a noticeable downstream effect. The downstream effects are assessed by correlation with the expression levels of genes that are in-trans to the candidate genomic locus. Several known oncogenic regulators exhibit such a behavior pattern, e.g. FGFR3, BRCA2, and TP53. In parallel we identify candidate genes whose DNA copy number and expression level show significant correlation with phenotypic charac-teristics, namely treatment sensitivity as measured over a large panel of chemical agents. The expression levels of a number of key genes, including the multi-drug resistance gene ABCB1 (MDR1) and the MYB oncogene, are significantly correlated with a large number of potential chemotherapeutic agents. Finally, integrating the results of the in-trans correlation assessment with the drug sensitivity correlation results reveals a small number (~100) of putative key genetic regulators among the initial set of

candidate genes whose expression level is significantly altered by genomic aberrations. Enrichment analysis of GO terms in the in-trans affected genes suggests possible control mechanisms of some of the putative genetic regulators. For example, histone binding protein SLBP and its close neighbor TACC3 in 4p16.3 seem to play active roles in the regulation of RNA metabolism and processing. In addition, their overexpression shows significant correlation with RNA/DNA antimetabolites such as pyrazofurin. The zinc finger MIZF, located in 11q23.3, appears to be implicated in regulation of mitotic cell cycle, and in parallel its expression shows significant concordance with sensitivity to the anti-cancer drug ellipticine. The implication of MITF as a lineage survival oncogene [7], as well as the related SOX10, are also identified by our approach. (Supported in part by the Center for Cancer Research, NCI.)

References

1. M.R. Grever et al, Semin. Oncol. 19, 622–638 (1992).
2. J.N. Weinstein et al., Science, 275:343-349 (1997)
3. U. Scherf et al, Nat Genet. 24:208-9 (2000).
4. Ross, et al., Nat. Genet. 24:227-35 (2000).
5. S. Nishizuka, et al., PNAS. 100:14229-34 (2003).
6. A.V. Roschke et al., Cancer Res. 63:8634-7 (2003).
7. J.N. Weinstein, Breast Disease 19:11-22 (2004).
8. L.A. Garraway et al, Nature 436:33-5 (2005).
9. A.S. Adler et al, Nat Genet. 38(4):421-430 (2006).
10. Barrett et al, in preparation