Year of publication 2015

Priscille Brodin, Elaine DelNery, Emmanuelle Soleilhac (2015 Mar 4)
[High content screening in chemical biology: overview and main challenges].
Médecine sciences : M/S : 187-96 : DOI : 10.1051/medsci/20153102016

Summary

The last two decades have seen the development of high content screening (HCS) methodology and its adaptation for the evaluation of small molecules as drug candidates or their use as chemical tools for research purpose. HCS was initially set-up for the understanding of the mechanism of action of compounds by testing them on cell based-assays for pharmacological and toxicological studies. Since the last decade, the use of HCS has been extended to academic research laboratories and this technology has become the starting point for numerous projects aiming at the identification of molecular targets and cellular pathways for a given disease on which novel type of drugs could act. This screening approach relies on image capture of fluorescently labeled cells therefore generating a large amount of data that must be handled by appropriate automated image analysis methods and storage instrumentation. These latter in addition to the integration and data sharing are current challenges that HCS must still tackle.

Year of publication 2013

Sardar Faisal Mahmood, Nadège Gruel, Elodie Chapeaublanc, Aurianne Lescure, Thouis Jones, Fabien Reyal, Anne Vincent-Salomon, Virginie Raynal, Gaëlle Pierron, Franck Perez, Jacques Camonis, Elaine Del Nery, Olivier Delattre, François Radvanyi, Isabelle Bernard-Pierrot (2013 Oct 22)
A siRNA screen identifies RAD21, EIF3H, CHRAC1 and TANC2 as driver genes within the 8q23, 8q24.3 and 17q23 amplicons in breast cancer with effects on cell growth, survival and transformation.
Carcinogenesis : 670-82 : DOI : 10.1093/carcin/bgt351

Summary

RNA interference has boosted the field of functional genomics, by making it possible to carry out ‘loss-of-function’ screens in cultured cells. Here, we performed a small interfering RNA screening, in three breast cancer cell lines, for 101 candidate driver genes overexpressed in amplified breast tumors and belonging to eight amplicons on chromosomes 8q and 17q, investigating their role in cell survival/proliferation. This screening identified eight driver genes that were amplified, overexpressed and critical for breast tumor cell proliferation or survival. They included the well-described oncogenic driver genes for the 17q12 amplicon, ERBB2 and GRB7. Four of six other candidate driver genes-RAD21 and EIF3H, both on chromosome 8q23, CHRAC1 on chromosome 8q24.3 and TANC2 on chromosome 17q23-were confirmed to be driver genes regulating the proliferation/survival of clonogenic breast cancer cells presenting an amplification of the corresponding region. Indeed, knockdown of the

expression of these genes decreased cell viability, through both cell cycle arrest and apoptosis induction, and inhibited the formation of colonies in anchorage-independent conditions, in soft agar. Strategies for inhibiting the expression of these genes or the function of the proteins they encode are therefore of potential value for the treatment of breast cancers presenting amplifications of the corresponding genomic region.

Kristine Schauer, Jean-Philippe Grossier, Tarn Duong, Violaine Chapuis, Sébastien Degot, Aurianne Lescure, Elaine Del Nery, Bruno Goud (2013 Aug 16)

A novel organelle map framework for high-content cell morphology analysis in high throughput.

Journal of biomolecular screening : 317-24 : DOI : 10.1177/1087057113497399

Summary

A screening procedure was developed that takes advantage of the cellular normalization by micropatterning and a novel quantitative organelle mapping approach that allows unbiased and automated cell morphology comparison using black-box statistical testing. Micropatterns of extracellular matrix proteins force cells to adopt a reproducible shape and distribution of intracellular compartments avoiding strong cell-to-cell variation that is a major limitation of classical culture conditions. To detect changes in cell morphology induced by compound treatment, fluorescently labeled intracellular structures from several tens of micropatterned cells were transformed into probabilistic density maps. Then, the similarity or difference between two given density maps was quantified using statistical testing that evaluates differences directly from the data without additional analysis or any subjective decision. The versatility of this organelle mapping approach for different magnifications and its performance for different cell shapes has been assessed. Density-based analysis detected changes in cell morphology due to compound treatment in a small-scale proof-of-principle screen demonstrating its compatibility with high-throughput screening. This novel tool for high-content and high-throughput cellular phenotyping can potentially be used for a wide range of applications from drug screening to careful characterization of cellular processes.

Julien Ablain, Magdalena Leiva, Laurent Peres, Julien Fonsart, Elodie Anthony, Hugues de Thé (2013 Mar 18)

Uncoupling RARA transcriptional activation and degradation clarifies the bases for APL response to therapies.

The Journal of experimental medicine : 647-53 : DOI : 10.1084/jem.20122337

Summary

In PML/RARA-driven acute promyelocytic leukemia (APL), retinoic acid (RA) induces leukemia cell differentiation and transiently clears the disease. Molecularly, RA activates PML/RARA-dependent transcription and also initiates its proteasome-mediated degradation. In contrast, arsenic, the other potent anti-APL therapy, only induces PML/RARA degradation by specifically targeting its PML moiety. The respective contributions of RA-triggered

transcriptional activation and proteolysis to clinical response remain disputed. Here, we identify synthetic retinoids that potently activate RARA- or PML/RARA-dependent transcription, but fail to down-regulate RARA or PML/RARA protein levels. Similar to RA, these uncoupled retinoids elicit terminal differentiation, but unexpectedly fail to impair leukemia-initiating activity of PML/RARA-transformed cells ex vivo or in vivo. Accordingly, the survival benefit conferred by uncoupled retinoids in APL mice is dramatically lower than the one provided by RA. Differentiated APL blasts sorted from uncoupled retinoid-treated mice retain PML/RARA expression and reinitiate APL in secondary transplants. Thus, differentiation is insufficient for APL eradication, whereas PML/RARA loss is essential. These observations unify the modes of action of RA and arsenic and shed light on the potency of their combination in mice or patients.