tumourigenic mechanisms throughout human breast cancer development from various genomic levels in a pathway-based approach.
Material and Methods: Data were collected from six breast cancer cohorts with distinctive clinical parameters to represent the heterogeneity of this disease (approved by the Ethics Committee in Norway). In total, 587 breast tissue samples (20 normal samples, 567 tumour samples from ductal carcinoma in situ to large aggressive breast tumours), with genome-scale DNA copy-number and mRNA expression profiles and with mutation status of selected genes (TP53 and PIK3CA), were investigated.
We identify significant DNA copy-number alterations in different stages of tumour progression; assess the correlation between gene copy number changes and the corresponding mRNA levels; and incorporate the mutation status of selected genes. We integrate these different data types and identify co-occurring and mutually exclusive alteration events, with the potential to distinguish "driver" events from incidental "passenger" events. Combining our findings on the gene-level with known signaling pathway data allows us to identify the molecular processes that drive the different stages of tumour development.
Results: Our study unveils the pathway signatures of human breast tumour progression. We identify candidate chromosomal regions with oncogenic alteration and associated core signaling pathways involved in distinctive stages of tumourigenesis. We also pinpoint the candidate events required for entering subsequent tumour developmental stage. Our analysis confirms that the aberrant alterations in breast cancer tend to occur in a cohesive fashion involving known cancer genes. In addition, new candidate "drivers" in breast cancer progression are also identified.
Conclusions: Alterations of multiple networking genes disrupt critical signaling pathways during breast cancer progression through cooperative mechanisms. The candidate genes identified based on the integrative information from multi-dimensional genomic data are likely to be the "driver" events in breast cancer tumourigenesis.
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824 Deuterium has a key role in tumour development – new target in anticancer drug development

G. Somlyai[1], A. Kovács[2], I. Guller[2], Z. Gyöngyi[3], K. Krempels[1], I. Somlyai[1], M. Szabó[4], T. Berkényi[5], M. Molnár[6]. [1]*HYD LLC for Cancer Research and Drug Development, Budapest, Hungary,* [2]*Saint John's Hospital, Urology, Budapest, Hungary,* [3]*University Medical School, Public Health, Pécs, Hungary,* [4]*Private Veterinary Surgeon, Budapest, Hungary,* [5]*Alpha-Vet Veterinary Hospital, Székesfehérvár, Hungary,* [6]*Semmelweis University of Medicine, Pathophysiology, Budapest, Hungary*

It is known that the deuterium/hydrogen (D/H) mass ratio is the largest of stable isotopes of the same element, causing differences in the physical and chemical behaviour between the two hydrogen isotopes. Although the concentration of D is more than 10 mM in living organisms the possible role of D had not been investigated for 6 decades after it's discovery in the early 30's.
In order to investigate the possible role of naturally occurring D in living organisms, in cell growth and tumour development, D-depleted water (DDW) was used.
The experiments with DDW revealed that due to D-depletion the cell growth of various cell lines (PC-3, human prostate; MDA, human breast; HT-29, human colon; M14, human melanoma) were inhibited *in vitro*. DDW caused tumour regression in xenotransplanted mice (MDA and MCF-7, human breast; PC-3) and induced apoptosis *in vitro* and *in vivo*. Deuterium depletion inhibited the expression of certain genes (c-myc, H-ras, COX-2) having key role in tumour development.
Breast tumours in 81 dogs and 14 cats showed a response rate higher than 70%; more than 50% of the pets were cured when DDW was used as a single treatment or in combination with surgery.
During the four-month-long DDW administration in the phase II, double blind clinical trial, 7 out of 22 of the prostate cancer patients achieved partial response (PR), while only one patient out of 22 showed PR in the control group (Armitage-test $p = 0.027$, Fisher-test $p = 0.046$). The one year survival was significantly higher in patients treated with DDW (logrank test, $p = 0.029$). The mortality rate decreased substantially in the treated group by the end of the first year (Fisher-test, $p = 0.034$).
The records of 74 women suffering from metastatic breast cancer (MBC) were retrospectively evaluated. Conventional cancer therapy was supplemented with *per os* (PO) DDW treatment, when the daily water intake of the patients was replaced with DDW. The administration of DDW parallel to the conventional treatment produced regression or halted progression in 74.3% of the 74 evaluated MBC patients, increasing the median survival time from the diagnosis of the distant metastasis up to 47.7 months.
We suggest that cells are able to regulate D/H ratio and its changes can trigger molecular mechanisms having key role in cell cycle regulation. The decrease in D-concentration can intervene in the signal transduction pathways thus leading to tumour regression.
We suggest that the recognition of the major importance of naturally occurring D in living organisms can serve as a new target in anticancer drug development.

825 Towards a systems-level view of breast cancer through the joint analysis of multi-dimensional data

C. Curtis[1], S.F. Chin[1], S.P. Shah[2], S. Tavaré[1], S. Aparicio[2], C. Caldas[1], METABRIC Consortium[1]. [1]*University of Cambridge & Cancer Research UK Cambridge Research Institute, Oncology, Cambridge, United Kingdom,* [2]*British Columbia Cancer Research Agency, Molecular Oncology, Vancouver, Canada*

Background: The advent of new technologies has enabled researchers to interrogate genomes at unprecedented resolution, probing their structure and function. However, these data remain largely underutilized due to a lack of scalable methods to detect sparse signals in multi-dimensional datasets. Here we describe the joint analysis of multiple data types to obtain a systems-level view of the genomic architecture of breast cancer in 1000 cases.
Methods: High-density Affymetrix SNP 6.0 arrays were employed to assay allele-specific and total copy number on 1000 fresh frozen tumours and 500 normal samples. Matched RNA from 824 samples was hybridized to Illumina HT-12 arrays for gene-expression analysis. The mutational spectrum of critical cancer loci was surveyed through deep sequencing of a subset of cases. We developed a regularized regression approach to detect aberration hotspots on a genome-wide basis and learn their interaction networks.
Results: Through the integrative analysis of diverse data types, we identified novel breast cancer subtypes with distinct clinical outcomes. We further characterized the genomic landscape of breast cancer in terms of aberration hotspots, ploidy, and preferential allelic amplification. By interrogating alterations at both the DNA and mRNA level in a robust regression framework, we generated a genome wide CIS and TRANS regulatory map of breast cancer. The projection of these events onto pathways yielded a systematic overview of pathway perturbation amongst subtypes, suggesting novel therapeutic targets in patient sub-populations.
Conclusions: The dataset described herein constitutes an invaluable resource to dissect the complexity of cancer. By mining the relationships between multiple data types and associating patient-level data with key clinical variables, we have uncovered new insights into breast cancer biology.

826 Integrated cell cycle and DNA repair signalling network modelling for identification of key molecular regulators in basal-like breast cancer

I. Kuperstein[1], P. Vera-Licona[1], A. Zinovyev[1], G.C. Tucker[2], T. Dubois[3], E. Barillot[1]. [1]*Institut Curie, INSERM U900, Mines ParisTech, Department of Bioinformatics Biostatistics Epidemiology and Computational Systems Biology of Cancer, Paris, France,* [2]*Institut de Recherches Servier, R&D department, Croissy sur Seine, France,* [3]*Institut Curie, Département de Transfert Laboratoire de Signalisation Hôpital Saint-Louis, Paris, France*

Background: Basal-like breast cancer (BLC) is associated with a poor prognosis and there is a lack of targeted therapy to treat it when it fails to respond to first-line chemotherapy. Pathways involved in cell cycle and DNA repair are highly perturbed in BLC, thus facilitating cell survival capacity despite accumulated DNA damage. Cell cycle and DNA repair mechanisms contain a variety of signalling pathways that do not act in isolation, but create molecular networks. Identification of the common molecular regulators will guide the discovery of new strategies to induce synthetic lethality of malignant cells.
Methods: In order to understand in greater detail the orchestration between cell cycle and DNA repair molecular mechanisms, we used a systems biology approach to represent biological processes as comprehensive models based on experimental data retrieved from literature and transcriptomic data on breast tumours. The network is created using the CellDesigner software, which is adapted to further mathematical modelling and studies of signalling network dynamics.
Results: We have constructed an integrated cell cycle and DNA repair molecular signalling network composed of three interconnected layers. The first layer represents core cell cycle pathways and checkpoint proteins. The second layer includes DNA repair pathways related to direct repair, trans-lesion bypass, single strand and double strand DNA repair. The third layer is composed of common regulators and modulator enzymes for cell cycle and DNA repair, such as kinases, phosphatases, etc. that ensure reciprocal influence between cell cycle and DNA repair. We further integrated transcriptomic data from breast tumours into the network and highlighted specific DNA repair pathways, cell cycle checkpoint proteins and common players modified in the disease. To verify the network, we simulated, *in silico*, the familial BRCA1-negative phenotype and inhibition of the base excision repair protein PARP to prove that our model recapitulates some well-described physiological situation.
Conclusions: A comprehensive reconstruction of the cell cycle and DNA repair signalling network allows the integration of multiple crosstalk between