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Dynamic Reprogramming of Signalling Networks – A New Challenge in Cancer Therapy

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The reprogramming of cellular signalling networks that leads to new phenotypes is a common phenomenon in morphogenesis, stem cell transformation, and tissue remodelling and cancer progression. Research in this area seeks to discover those newly activated and deactivated pathways, and in doing so obtain key drivers and biomarkers of the signalling network reprogramming and attendant cell transformation. This reprogramming of signalling networks is of growing importance in anti-cancer therapy design. The effects of reprogramming on cancer cell function can lead to oncogene addiction, aberrant epithelial-mesenchymal transitions, remodelling of tumor bioenergetics, changes in response to hypoxia, tumor invasion and others. Following substantial investigation into the genetic and epigenetic mechanisms of network reprogramming, key biomarkers for the majority of these transformations have been obtained and applied to cancer diagnostics, grading and prediction of therapeutic response to cancer therapy. An emerging issue in this field of research, stimulated by clinical observations of adaptive resistance to monotherapy regimes, is signalling network reprogramming induced by targeted drug therapy in cancer.

Genomic, transcriptomic and proteomic profiling can provide insight into these resistance mechanisms, such as up-regulation of distinct gene networks responsible for activation of otherwise redundant signalling pathways that lead cancer cells to circumvent the action of a single drug action. In the figure set below, we exemplify such gene expression alteration in cancer cells following a range of drug treatments. Figure 1A shows five heat maps of gene expression over a 14 day period following tamoxifen treatment in an ER+ ZR-75-1 breast cancer xenograft model [1].

We observed a high level of dynamism in gene regulation over the time period: genes up-regulated on one day were typically down-regulated on the other days. This combination of forward and feedback signalling can then be further modulated by the effects of circadian rhythms on the signalling processes and influence their response to therapy [2]. In Figure 1B, the kinome map represents reprogramming of the kinome in response to a MEK inhibitor(AZD6244) in SUM159 cells of triple-negative breast cancer [3]. Blue and red nodes show up- and down-regulated kinases and receptors tyrosine kinases (RTKs) determined by mass spectrometry.

This map shows kinome reprogramming through the activation of multiple kinase and RTKs: PDGFRβ, VEGFR2, HER2/3 and others that allow cancer cells to bypass MEK inhibition. Figure 1C shows volcano plots of gene expression following trastuzumab, pertuzumab and their combination targeting HER2 receptor in SKOV3 HER2+ positive human ovarian tumor xenografts [4,5]. Expression profiles for these three treatments differ despite the fact that they all target the same receptor, HER2. This analysis showed up-regulation of HER3 receptors that can sensitise the cells to pertuzumab, an inhibitor of HER2/HER3 signalling, and provides benefit in this combination therapy.

These data and other results of drug-induced changes in gene expression have shown that some inhibitors of specific kinases/receptors induce reprogramming of signalling networks in some cancer lines that leads to up-regulation of unique networks of kinases and receptors responsible for activation of signalling pathways not targeted by drug therapy. This reprogramming thus leads to new phenotypes of cancer cells which are resistant to primary drug therapies yet may be sensitive to other drugs targeting the newly activated networks [6,7].

Scenarios of dynamic reprogramming can be considered in terms of a hierarchical structure of kinase and RTK networks consisting of dominant and secondary signalling networks. After inhibition of a dominant network, signalling is rewired to activate a secondary network and the enhancement of expression of the secondary kinase/receptors occurs [8]. It is also possible that dominant and secondary RTK/kinase sub-networks cooperate with each other and drive cancer progression together. In this case, inhibition of the dominant kinase unmasks the rest of the signalling network and sensitises the cell to signalling through this network, and so sensitises cell to a second drug targeting that secondary network [7]. For example, trastuzumab sensitises HER2+ cancer cells to EGFR and HER3 targeted therapy [4,6].

An acquired sensitivity to a second inhibitor targeting a drug-activated network suggests that the first drug action may significantly broaden signalling network activity. This increase in breadth of activity following drug-induced perturbation is manifest through the activation of various cross-talks, feedbacks, feed forwards, and gene regulation circuits. In general, inhibition of a module of signalling network can cause an increase in sensitivity to perturbation, e.g. through mutation or drug action, in the rest of the network modules [9]. Thus bioinformatic studies of signalling networks in response to drug intervention should consider much wider networks than for unperturbed networks alone, and experimental data on gene expression can unmask these expanded networks and unravel the mechanisms of the acquired sensitivity of the signalling network.

This concept of drug-induced reprogramming of signalling network activity significantly expands the conventional view on oncogene addiction in targeted therapy. Conventionally, cancer therapy involves targeting single key signalling pathways, e.g. cancer drivers such as PI3K/PTEN/AKT/mTOR, RAS/RAF/ERK and others, and inhibition of these oncoprotein pathways abrogates tumor growth. With drug-induced reprogramming of signalling networks, disruption of oncogenes by drugs fails, in many cases, to cause cell death and leads to cancer sensitivity to other kinase/receptor inhibitors. For example, not all HER2+ breast cancer cell lines are sensitive to anti-HER2 therapy, i.e. these lines do not exhibit addiction to the HER2 oncogene. Following targeted anti-cancer therapy, cancer cell line addiction to one oncogene can indeed be abolished yet the dependence on another gene may emerge due to dynamic reprogramming.

Thus bioinformatic studies of cancer signalling networks must determine the principles of signalling network rewiring mechanisms that enable cancer cells to change the dependence of tumor growth from one sub-network to another. A key deliverable from bioinformatics would be the mapping of cell line specific drug-induced reprogramming in protein-protein association networks for drugs targeting different signalling networks. Such mapped biomarkers of reprogramming dynamics could significantly impact on the development of combination drug therapy in cancer. First, unpicking the drug-activated sub-networks can help to identify new drug targets in designing combination therapy to overcome acquired resistance to monotherapy. As discussed above, a first drug may well broaden signalling network activity and thus expand the range of possible targets for a secondary drug in combination therapy. Second, it will help to define those signalling networks responsible for resistance to drug action and inform design of the optimal strategy of combination therapy to overcome de novo and adaptation resistance. Further research should be carried out to elucidate the role of the first drug as a primer to initiate network reprogramming. It has been established that the drug can retain its activity even at de novo resistance and activate network reprogramming in some cancer lines. For example, in the case of trastuzumab, it is assumed that this drug is active in primary trastuzumab resistance tumors and causes gene expression and reprogramming of signalling networks [6,7]. Moreover, a clinical trial of HER2+ breast cancer progression following HER2 inhibition by trastuzumab showed that chemotherapy in combination with trastuzumab was more effective than chemotherapy alone. This findings suggest that trastuzumab sensitises cellular response to a second drug despite the fact that cancer cells are insensitive de novo to trastuzumab and that there is therapeutic benefit to continue trastuzumab therapy in combination with other drugs beyond progression [10].

In order to develop drug therapy targeting dynamic reprogramming signalling networks in cancer cells, it is necessary to choose between two possible strategies: either to stop reprogramming of signalling networks and thus abrogate acquired resistance to the drug; or therapeutic exploitation of drug-induced reprogramming by targeting the attendant broader range of targets. While these strategies differ, both require combination treatment. Further, it is necessary to bind tightly drug development, diagnostics and therapy following companion diagnostics and drug co-development strategies in combination therapy design [11]. Novel compounds and their combinations must be developed in a combinatorial context, and not independently of diagnostic assays, in order to gain any integrative benefits with respect to tumor growth inhibition and suppression of adaptation drug resistance.

In conclusion we return to the initial discussion of reprogramming in stem cells and suggest that there are tight ties between drug-induced reprogramming of cancer cells and reprogramming of somatic cells to pluripotent stem cells induced by small molecules. A study of the common mechanisms of signalling network reprogramming in these systems could facilitate therapeutic applications of pluripotent stem cells on the one hand and initiate the development of a novel combination therapy strategy in cancer on the other.

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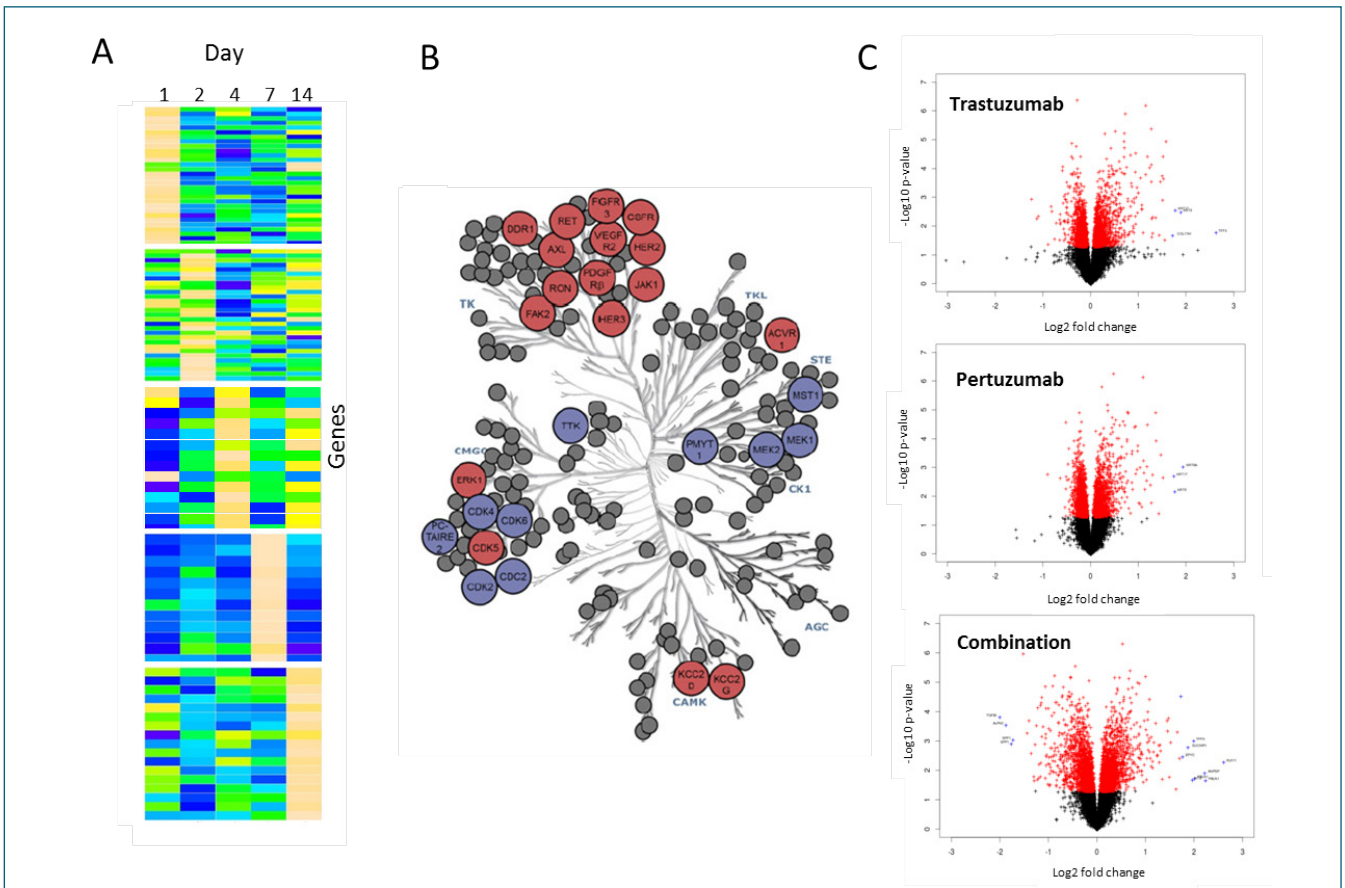

Figure 1. Gene expression in cancer cells following treatments by tamoxifen (A), MEK inhibitor (B) and anti-HER2 drugs, trastuzumab, pertuzumab and their combination (C).

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