COMBINING BIG DATA WITH CELL CULTURE ON THE 3D NICHOID TO DISCOVER NEW THERAPEUTIC STRATEGIES AGAINST CANCER

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Introduction

In recent years, the concept of synthetic lethality (SL) has gained increasing interest in the field of cancer therapeutics [1]. Here, we employed SL concept to discover new possible targets for the repurposing of so-called "migrastatics" drugs, agents which prevent cell spreading from the primary tumor site, to contrast the formation of metastases, and that can be used in combination with conventional "cytostatic" drugs that mainly target proliferation [2]. Moreover, in order to perform a drug repurposing operation, biological and medical big data could be exploited for computer-based approaches, which means to investigate new therapeutic possibilities for drugs that have already been approved for use in patients and are on the market [3]. After having computationally integrated these three concepts, we finally tested the resulting drugs in wet, treating cancer cells plated in the Nichoid, an innovative bioengineered micro-scaffold, able to mimic the structural niche of adhering cells in 3D culture [4].

Methods

Several types of data were retrieved from different databases (i.e. gene-disease associations from DisGeNET, SL couples from SynLethDB, drugs from DrugBank) and integrated. A specific scoring scheme allowed to extrapolate a set of genes associated with metastases, the SL couples in which they are contained and the drugs targeting SL partner genes. Then we selected two PARP-inhibitors (Olaparib and Veliparib) and two statins (Simvastatin and Lovastatin) for drug testing on BRCA1-mutated ovarian (OVPA8) and breast cancer (HCC1937) cell lines. Cells were expanded both on the Nichoid micro-scaffold fabricated by two-photon laser polymerization, and on conventional flat substrates, for viability comparison between the 2D and the 3D culture environment.

Results

We extrapolated a total of 63 genes associated to metastases, in turn contained in 168 SL couples and for which the partner genes turned out to be targets of 102 drugs. Among these drugs, our attention was drawn to statins, normally administered to lower lipid levels but, according to retrospective studies, with an unexplained connection to an improvement in the response to anticancer therapies [5]. In our preliminary experimental results from cell culture, the PARP-inhibitor Olaparib demonstrated a greater anti-proliferative effect on cells cultured on flat substrates, compared to those cultured on the Nichoid, as shown in Figure 1.

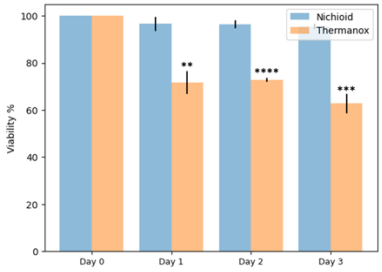

Figure 1: Comparison between OVPA8 cells treated with 3nM Olaparib for 72 hours on Nichoid and Thermanox.

Discussion

The exploitation of SL strategies for assessing new drug targeting cell migration represents an important frontier in anti-metastatic cancer therapy, since it could help to overcome problems related to both drug resistance and side effects of chemotherapeutics. In our study, computer-based approaches have proven to possess the potential to accelerate the identification of the new therapeutic targets to be tested, which is a fundamental aspect in the field of anticancer research. Here, however, we also highlighted how equally important is to screen the new therapies in culture models in which cells can give a response as realistic as possible to the drug treatment.

References

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