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The Nichoid Micro Scaffold as a Tool for Repurposing "Migrastatic" Drugs Exploiting Synthetic Lethality

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INTRODUCTION: Since the normal process of developing new drugs is long and expensive, in recent years the use of biological and medical big data for computer-based approaches has gained increasing attention to investigate new therapeutic possibilities for already approved drugs [1]. Of great interest is the exploitation of this approach in the field of therapeutic cancer research, and particularly the investigation of "migrastatic" agents able to contrast cell invasion and migration to prevent metastases formation [2]. Moreover, the use of synthetic lethality (SL) for developing drug targets could help to overcome resistance and side effects, leading to death only malignant cells carrying a specific mutation [3]. Here, we combined the computational integration of these three concepts with experimental drug testing on an innovative bioengineered micro-scaffold named Nichoid [4], able to mimic the structural niche of cancer cells adhering in 3D culture.
METHODS: We retrieved and integrated different data from several databases: DisGeNET for gene-disease association, SynLethDB for SL couples and DrugBank for drugs. We then selected two PARP-inhibitors and two statins to test on BRCA1-mutated ovarian and breast cancer cell lines. We expanded the cells on the Nichoid, a micro-structured substrate fabricated by two-photon laser polymerization in a biocompatible photoresin, and we compared the response of cells expanded o the Nichoid to cells cultured on conventional flat substrates.
RESULTS: Through a specific filtering scoring schema, we extrapolated a set of genes associated with metastases, the SL couples in which the sets are contained and we identified the drugs targeting SL partner genes. Among the repurposed drugs, we addressed statins, normally administered to lower lipid levels but with an ability to improve the response to anticancer therapies, according to retrospective studies.
Moreover, preliminary experimental results showed a marked difference in the effect of the PARP-inhibitor Olaparib on cells cultured on the Nichoid, compared to cells cultured on flat.
DISCUSSION & CONCLUSIONS: SL is an important frontier in cancer therapy of chemotherapy-resistant cancers. Computer-based approaches can help in the identification of potential new therapeutic couples to be tested in the context of SL strategies. Here, we show how crucial is to screen the new candidate drugs in realistic culture models, in which cells can respond to the drug as similarly as possible as in vivo.
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