Ph.D. in Information Technology
Thesis Defense

June 4th, 2024
at 14:30 pm
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Carolina TESTA – XXXVI Cycle

Integration of Genomic Computing and the Nichoid 3D culture system for repurposing and testing Synthetic Lethality-based anti-metastatic drugs

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Abstract:

Conventional cancer treatments often fall short in addressing metastasis, a major cause of cancer-related deaths. The genetic concept of Synthetic Lethality (SL) presents an effective alternative by targeting genetic vulnerabilities in metastatic cancers, where inhibiting two genes simultaneously is lethal. This approach, focused on specific mutations in tumor cells, ensures precise and successful treatment with minimal off-target toxicity. Personalized SL therapy based on individual genetic profiles offers tailored solutions. However, drug development for targeting specific genes is challenging and costly. Drug repurposing, using existing drugs for new therapeutic applications, offers a quicker and cost-effective alternative, allowing to speed up the creation of new therapeutic regimes for personalized medicine. Pharmacological tests to assess the efficacy of the repurposed drug would still be necessary, but current 2D substrate tests may not accurately reflect 3D cell conditions, leading to disparities between in vitro and clinical results.
This interdisciplinary investigation sought to integrate these fundamental aspects of drug development and testing, using both computational and experimental methods. The major aim is to identify potential candidates that could be repurposed for treating metastatic cancer, leveraging the genetic interaction of SL for the discovery process.
The first step of the research passed through a data-driven approach to select the best repurposable drugs that target genes in SL pairs with deleted genes in metastases. This was performed by exploring and integrating several databases with freely accessible data. Interestingly, within the findings of this data analysis, statins, medications primarily used to lower cholesterol levels, emerged as a class of drugs with repurposing potential. A robust support to this hypothesis came from retrospective meta-analyses and experiments showcasing enhanced responses to anticancer treatments in individuals who were already prescribed statins for cardiovascular issues.
A subsequent step involved utilizing a machine learning algorithm to predict both novel SL pairs and new interactions between drugs and targets. This was achieved through the application of Non-Negative Matrix Tri-Factorization (NMTF), a technique based on decomposing an input association matrix into three matrices of non-negative elements and then reconstructing it. The standalone use of NMTF yielded excellent performance, and this was further enhanced when NMTF was employed as an embedding generator in conjunction with other predictors. The algorithm's versatility enabled the prediction of compelling new SL pairs (e.g. TP53 - MTOR or KRAS - STAT3) and novel drug-target combinations (e.g. antidepressants such as Mirtazapine targeting DRD2, Medroxyprogesterone acetate targeting NR3C1, or Olsalazine targeting PTSG1).
The last phase involved the practical assessment of the anti-cancer impact of statins through in vitro f experimentation. The Nichoid was selected as substrate for 3D cell culture in drug testing, based

on preliminary findings indicating its capability to more accurately replicate the physiological cell conditions. This experimental validation demonstrated that statins have an impactful anti-tumor effect as they exploit the principle of SL.
These results underscored the effectiveness of this combined approach, thus offering a holistic method for developing robust anti-tumor therapies that is strong both in computational prediction and experimental validation. This enhances the importance of the findings, diminishing both experimental expenses and timelines, while elevating the likelihood of approval. Future personalized cancer therapies with high efficacy and low toxicity may rely on novel treatments utilizing repurposed anti-metastatic drugs that exploit SL. This holds the promise of providing a higher assurance of survival.

PhD Committee

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