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Program: PhD, Bioinformatics and Computational Biology

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Title: A Knowledge-guided Fuzzy Logic Mechanistic Model of Synthetic Lethality in the HCT-116 Vorinostat-resistant Colon Cancer Cell line

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Committee Members: Dr. Dmitri Klimov, Dr. Saleet Jafri

ABSTRACT:

With an overall lifetime risk of about 4.3% and 4.0%, in men and women respectively, colorectal cancer remains the third leading cause of cancer-related deaths in the United States. In persons aged 55 and below, its rate increased at 1% per year in the years 2008 to 2017 despite the steady decline associated with improved screening, early diagnosis, and treatment in the general population. Besides standardized therapeutic regimen, many trials seek to evaluate the potential benefits of Vorinostat, either as a single agent or in combination with other anti-neoplastic agents for its treatment. Vorinostat, an FDA approved anti-cancer drug known as suberoylanilide hydroxamic acid (SAHA), a histone deacetylase (HDAC) inhibitor, through many mechanisms, causes cancer cell arrest and death. However, like many other anti-neoplastic agents, resistance and or failures have been observed. In the HCT116 colon cancer cell line xenograft model, exploiting potential lethal molecular interactions by additional gene knockouts restored Vorinostat sensitivity. This phenomenon, known as synthetic lethality, offers a promise to selectively target cancer cells. Although without clearly delineated understanding of underlying molecular processes, h has been demonstrated as an effective cancer-killing mechanism. In this study, we aimed to elucidate mechanistic interactions in multiple perturbations of identified synthetically lethal experiments, particularly in the Vorinostat-resistant HCT116 (colon cancer xenograft model) cell line. Given that previous studies showed that knocking down GLI1, a downstream transcription factor involved in the Sonic Hedgehog pathway – an embryonal gene regulatory process, resulted in restoration of Vorinostat sensitivity in the HCT116 colorectal cancer cell line, we hypothesized that Vorinostat resistance is a result of upregulation of embryonal cellular differentiation processes; that elucidated regulatory mechanism would include cross-talks that regulate this biological process. We employed a knowledge-guided fuzzy logic regulatory inference method to elucidate mechanistic relationships. We validated inferred regulatory models in independent datasets. In addition, we evaluated the biomedical significance of key regulatory network genes in an independent clinically annotated dataset. We found no significant evidence that Vorinostat resistance is due to an upregulation of embryonal gene regulatory pathways. Our observation rather supports a topological rewiring of canonical oncogenic pathways around the PIK3CS, AKT, RAS/BRAF etc. regulatory pathways. Reasoning that significant regulatory network genes are likely implicated in the clinical course of colorectal cancer; we show that the identified key regulatory network genes’ expression profile can predict short-to medium-term survival in colorectal cancer patients – providing a rational basis for prognostication and potentially effective combination of therapeutics that target these genes along with Vorinostat in the treatment of colorectal cancer.