Target Mining and Drug Repurposing for Hepatocellular Carcinoma via Bioinformatic and Computational Approaches

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INTRODUCTION

- Sorafenib is the only panacea to treat Hepatocellular Carcinoma (HCC), yet, offers limited survival benefits due to drug resistance.
- Advanced oncotherapeutic research demands a thorough insight into pathological cascades involved in the progression of preneoplastic lesions to HCC.
- Hence, target mining to unearth key genetic players of HCC followed by screening drug databases against the identified targets will be a rational way out.
- The integrative approach of bioinformatics and in silico pharmacology offers a gateway to hypothesize novel therapeutic indication of approved drugs i.e., “drug repurposing”

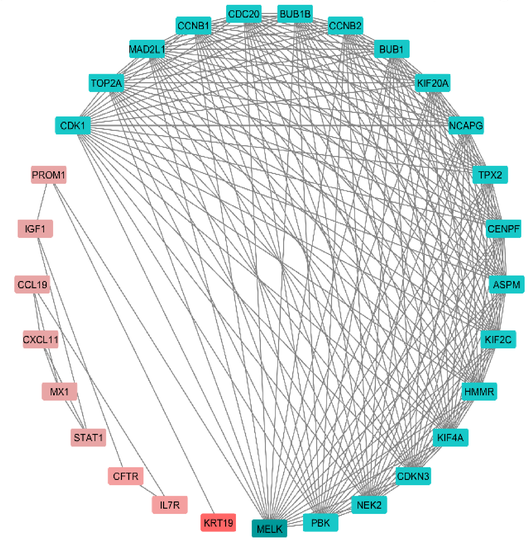
METHODS

- Gene expression profile ‘GSE6764’ encompassing microarray data of 10 Normal, 10 Cirrhosis, 17 Dysplastic nodules, 18 Early and 17 Advanced HCC was analyzed using GEO2R.
- Subsequently, to reveal the cross-talk genes a protein-protein interaction network was constructed using the Search Tool for the Retrieval of Interacting Genes and visualized through Cytoscape.
- Crucial targets were identified based on the overall survival (OS) and Hazard ratio (HR > 1) of hub genes from the Kaplan-Meier plotter.
- The identified targets were screened against all FDA-approved drugs by molecular docking studies through extra precision mode (XP) in the Schrodinger drug design suite.
- Further, the free energy of binding of shortlisted drugs was evaluated by MM/GBSA analysis.

RESULT

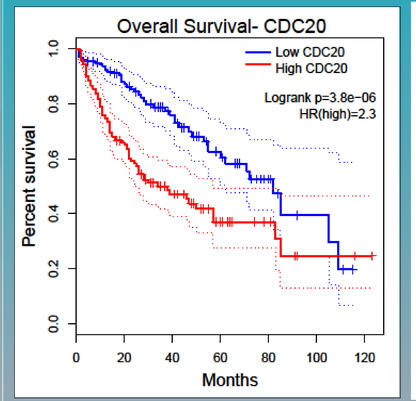
- STAT1 and MX1 are substantially overexpressed in cirrhosis while, CCL19 and IL7R are significantly downregulated between dysplastic nodule and cirrhosis.
- HMMR overexpression is linked with poor prognosis in the evolution of dysplastic nodule to early HCC.
- Furthermore, overexpression of pathological hallmarks of poor prognosis such as CDK1, CDC20, BUB1, MAD2L1, CCNB2, CENPF, TPX2, TOP2A and PBK was identified in the furtherance from early and advanced HCC.
- Based on OS with significant HR, CDC20 was shortlisted and subjected to molecular docking and MM-GBSA analysis.
- Labetalol, a beta-blocker was spotlighted as a hit due to its highest docking score of -7.075, ΔG value -54.08 kcal/mol alongside its stable and stronger ligand-protein complex.

Fig 1: Interactions of cross talk genes underpinning HCC



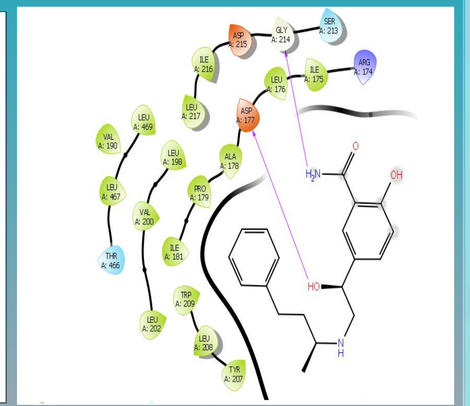
Orange colour nodes represents cross talk genes involved in preneoplastic lesion and blue colour nodes represents cross talk genes in HCC

Fig 2: Kaplan Meier plotter – Overall survival



Overall survival validation of HCC patients with high and low expression of CDC20-

Fig 3: Interactions of Labetalol



2D image of Labetalol exhibiting interactions with CDC20

CONCLUSION

- This study reveals a series of key cross-talk genetic underpinnings related to crucial transition from pre-neoplastic lesions to HCC.
- Our result suggests the pertinence of labetalol as a potential repurposable drug in the treatment for HCC.

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