Gene expression and cellular effects of NVP-BKM120 in lymphoma cell lines

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OBJECTIVES

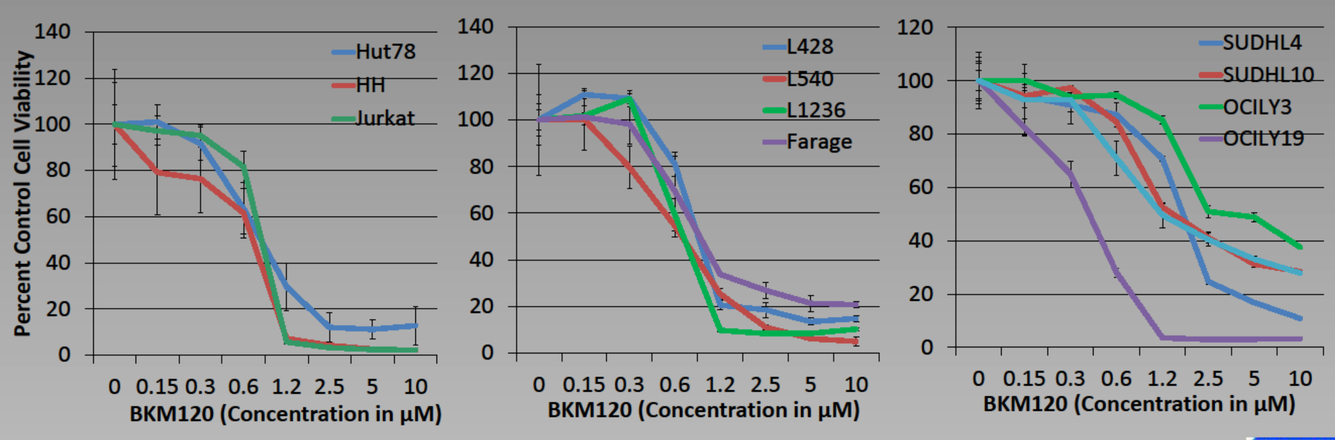
The PI3K pathway plays a significant role in cell cycle, apoptosis and DNA repair and is commonly dysregulated in cancers, making it a potential therapeutic target. NVP-BKM120 (Buparlisib) is a novel oral pan-class I PI3K inhibitor with antitumor activity and efficacy reported in solid tumors. It is in phase I/II clinical trials for treatment of relapsed-refractory NHL. There is a paucity of data on molecular mechanism of action and biological pathways of resistance for BKM120-treated lymphoma.

METHODS

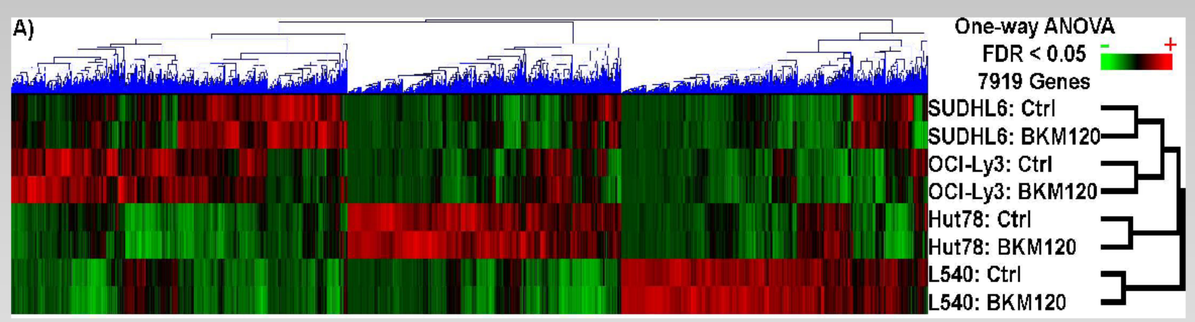
TCL cell lines (Jurkat, Hut78, HH), HL lines (L428, L540) and DLBCL lines (SUDHL4, SUDHL6, SUDHL10, OCILY3, OCILY19) were treated with increasing concentrations of BKM120 (0.16-10 μM) in 96 well plate and cell viability assessed by MTT assay. For gene expression profiling (GEP), SUDHL6, OCILY3, Jurkat, Hut78 and L540 cells were treated at IC_{50} and analyzed on Illumina human HT12 gene chip. Gene Set Enrichment (GSEA) and biological network analysis were done using Ingenuity Pathway Analysis and Cytoscape.

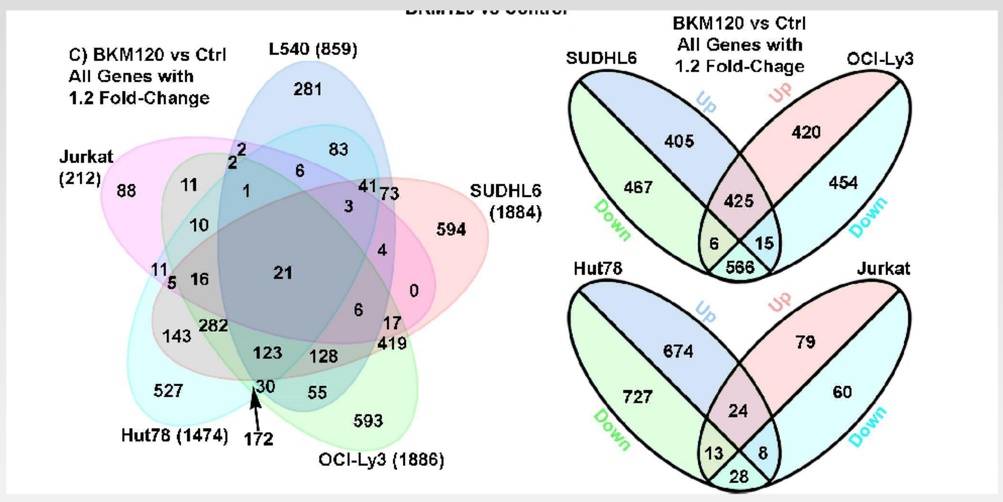
RESULTS

1. Effect of BKM120 on cell survival in the lymphoma cell lines.

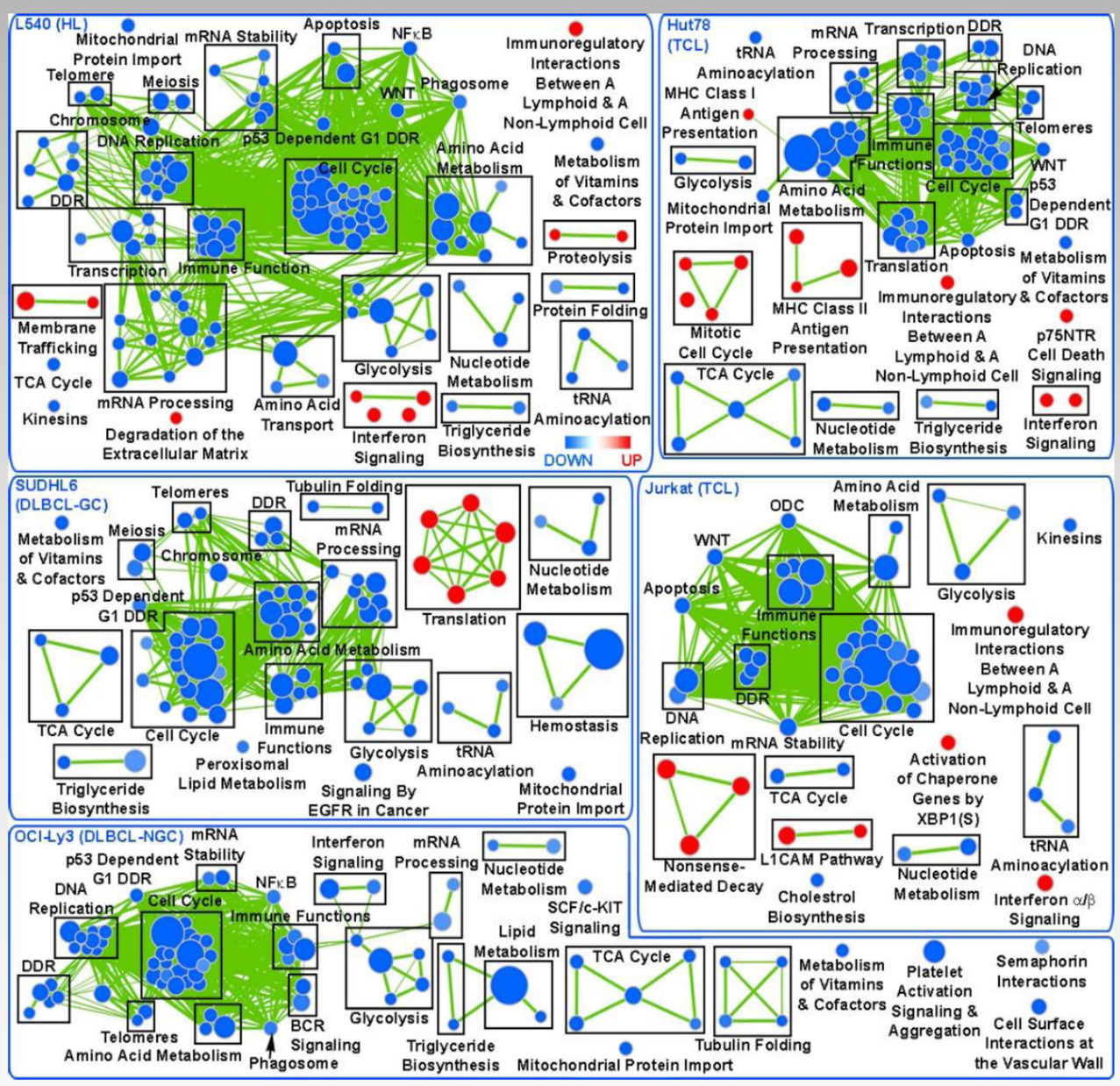


2. Microarray analysis show conserved GEP based on the 'cell of origin' in the lymphoma cell lines, with BKM120 treatment.

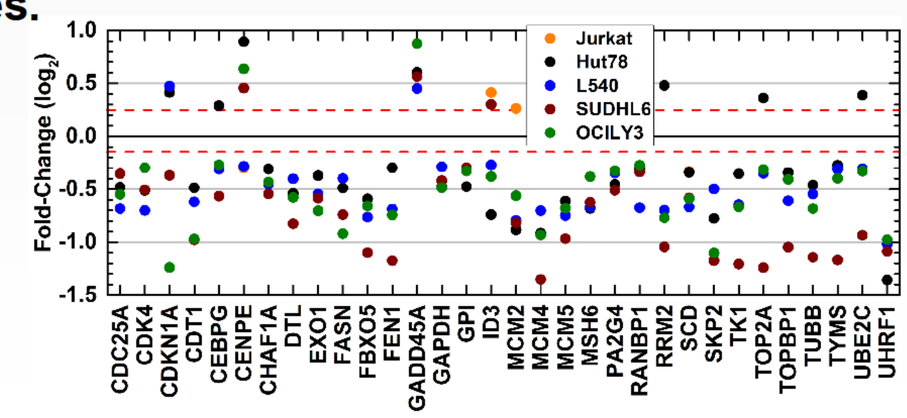




3. Network representation of Gene set enrichment analysis (GSEA) show conserved and non-conserved overlap in the biological pathway responses to BKM120 treatment in the lymphoma cell lines.



4. DAVID functional annotation analysis of the key significant genes show common biological responses enriched in all BKM120 treated lymphoma cell lines.



Annotation Cluster	Functional Annotation	Enrichment Score
1	Cell Cycle, cell cycle phase, cell cycle process, regulation of cell cycle, mitotic cell cycle, microtubule-based process	8.08
2	DNA metabolic process, response to DNA damage stimulus, DNA repair, cellular response to stress, DNA damage, DNA repair	7.86
3	nucleoplasm, nuclear lumen, intracellular organelle lumen, organelle lumen, membrane-enclosed lumen	4.7
4	DNA replication, MCM regulation, replication initiation, Transcription	3.27
5	Nucleus, DNA binding	2.98

CONCLUSIONS

BKM120 induced potent dose-dependent cell death via inhibition of the PI3K pathway. GSEA of treated cells shows decrease of cell cycle function, DNA replication and metabolic function across all cell lines. Western blot confirmations suggests G2/M arrest and induction of apoptosis. We plan further studies with BKM120 in combination with other drugs.

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Pre-clinical studies

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