DIA-based Proteomics Identifies IDH2 as a Targetable Regulator of Acquired Drug Resistance in Chronic Myeloid Leukemia

基于DIA的蛋白质组学发现IDH2是调节慢性粒细胞白血病获得性耐药性的靶点

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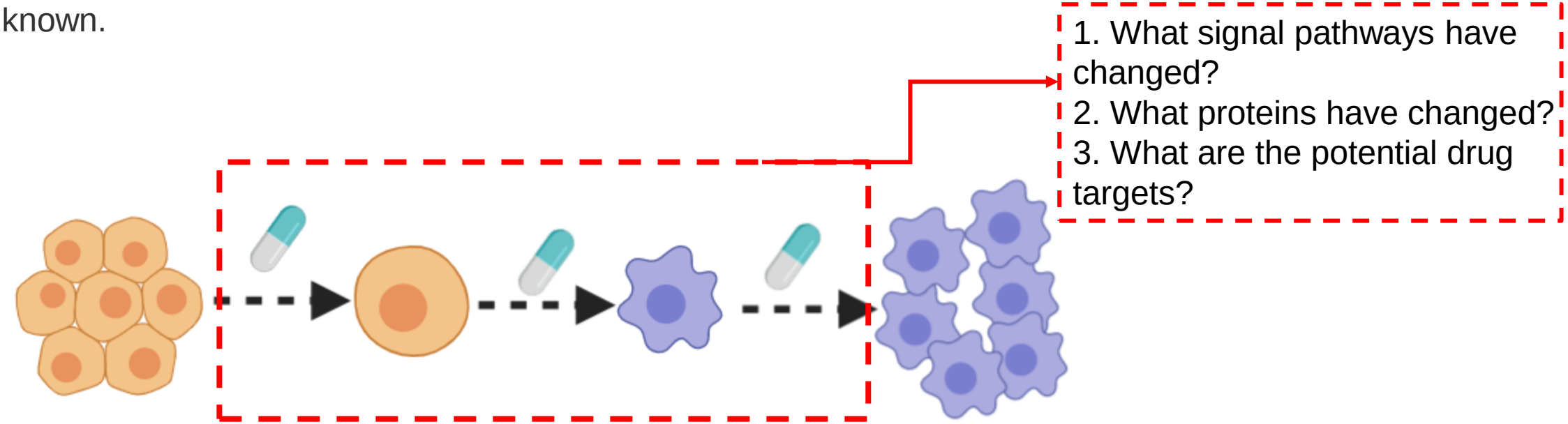
Background of drug resistance in CML

Drug resistance leads to failed chemotherapy treatment in 90% patients[1].

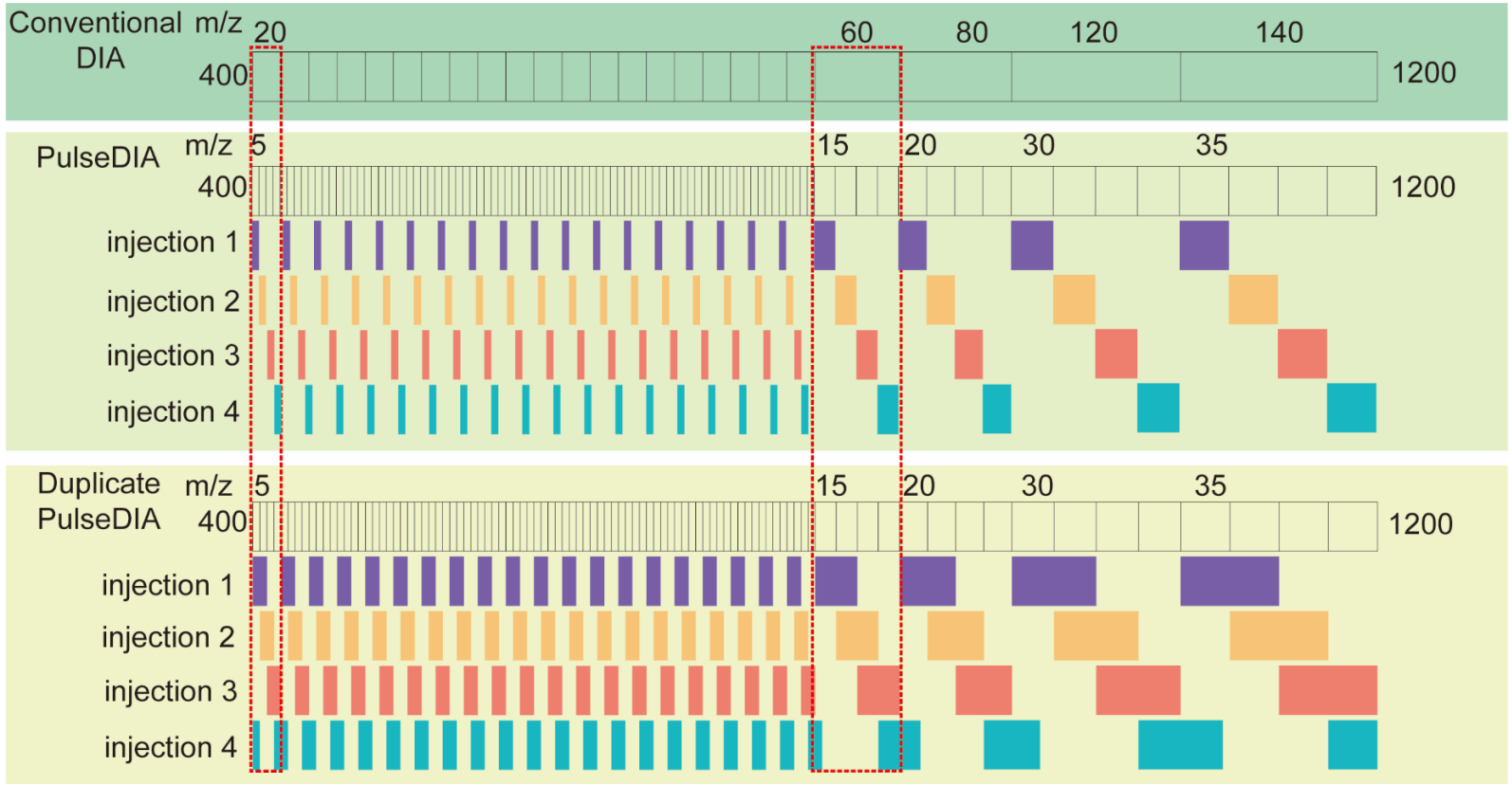
About 20 to 25% of CML patients showed a suboptimal response to imatinib, who have likely developed drug resistance[2].

The dynamics and temporal changes in the proteome responding to acquired drug resistance are not known.



[1] Mansoori B. et al. Adv. Pharm. Bull. 2017;7:339–348
[2] Milojkovic D. et al. Clin. Cancer Res. 2009;15:7519–7527

PulseDIA



1.The MS1 scan range is 400-1200 m/z.

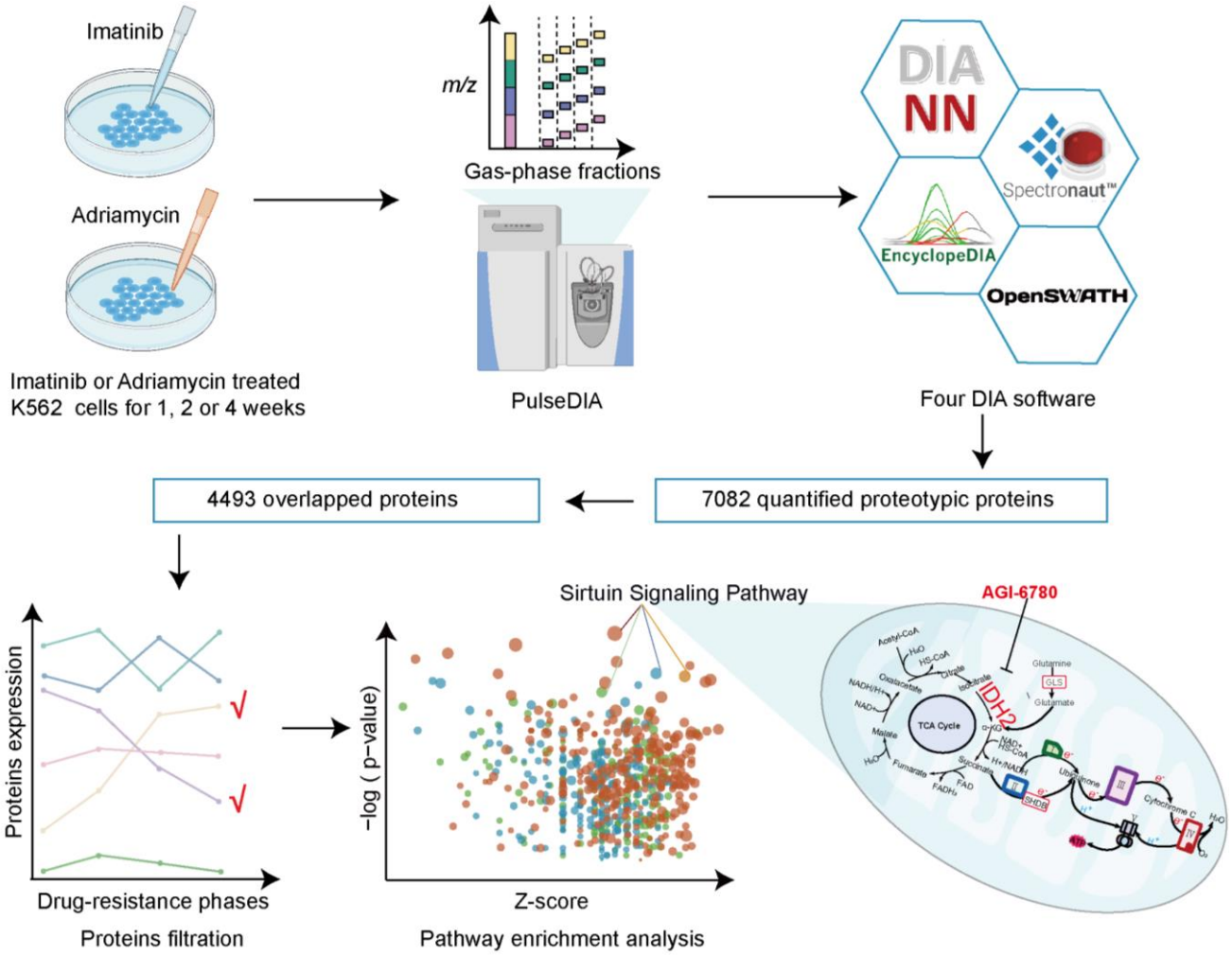
2. PulseDIA contains 24 isolation windows with 1/4window width of the conventional one in each pulse scheme.

Cai X. et al. J. Proteome Res. 2021;20:279–288.

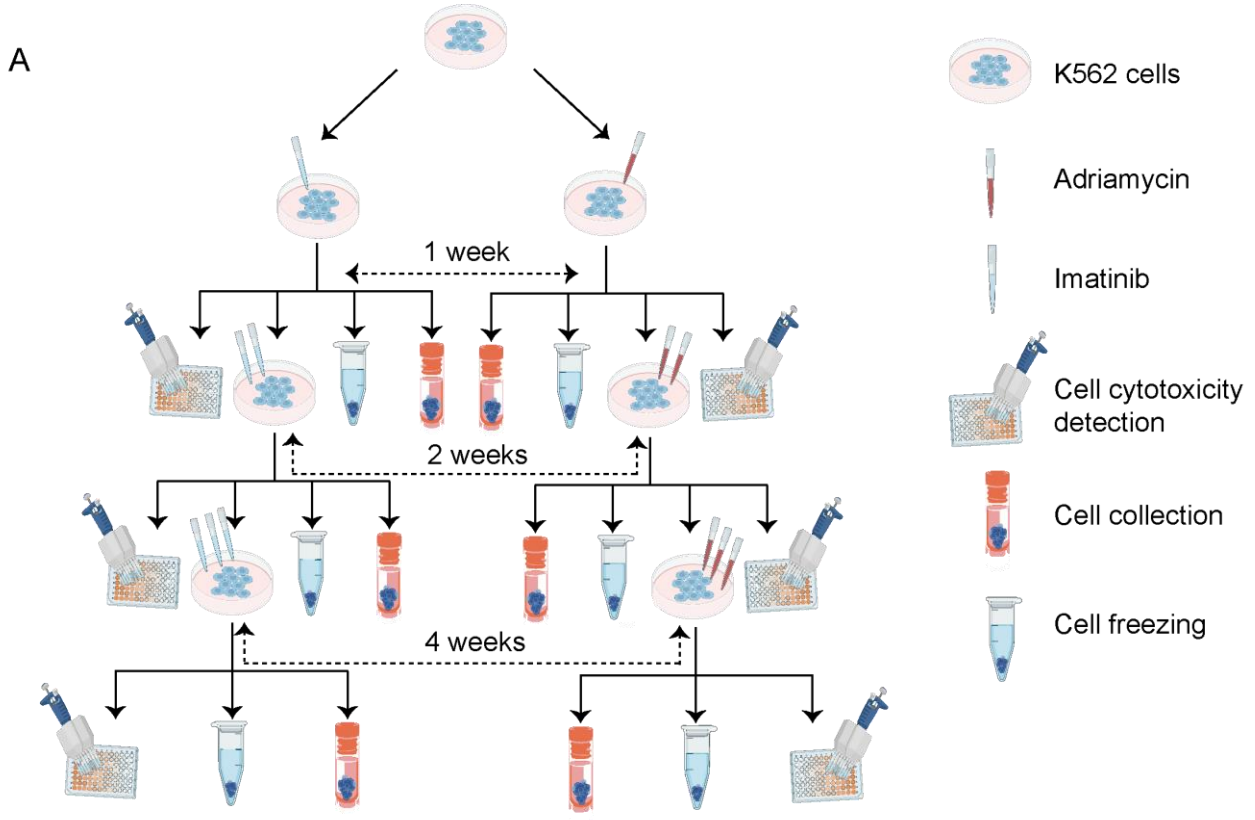
Objectives

- Exploring dynamic process of imatinib and adriamycin induced drug-resistance development.
- Exploring potential target for reversing drug resistance in K562 cells.

Study Design

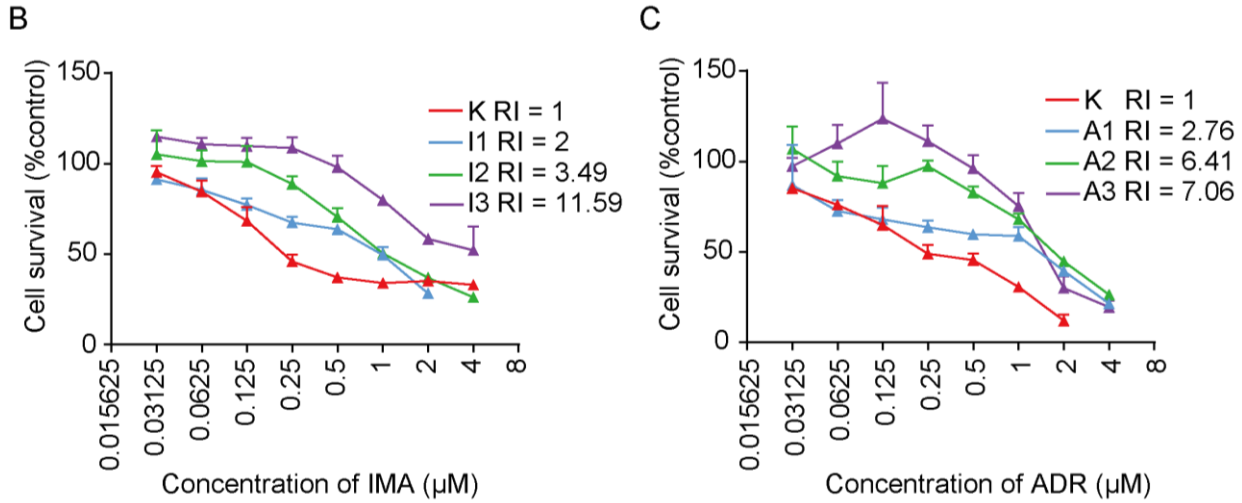


Establishment of drug-resistance cell models



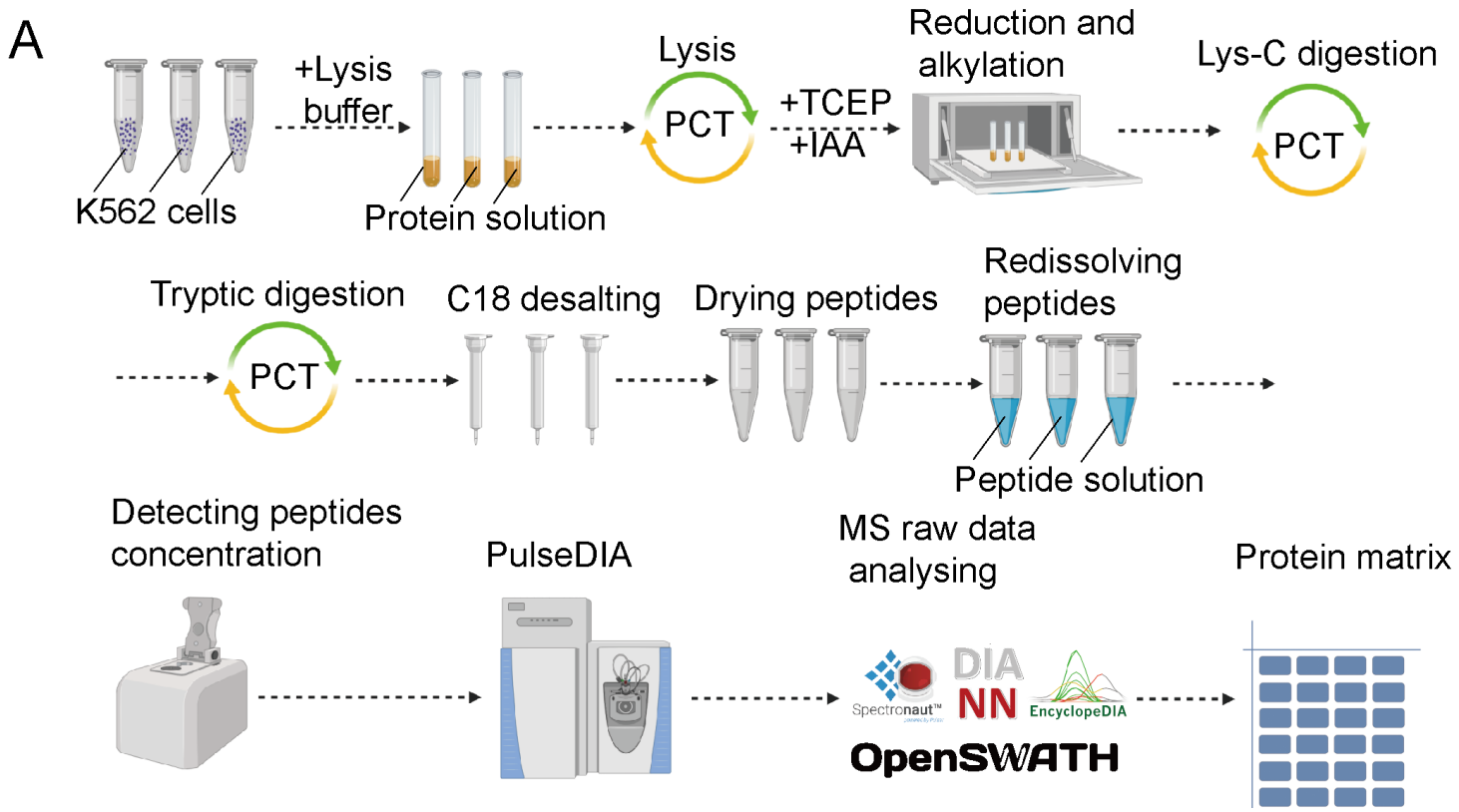
Establish derivative K562 cells with mild, intermediate and severe resistance to Adriamycin(ADR) and Imatinib (IMA).

Drug sensitivity of derivative K562 cells



Model	IC_{50} (μM, 95% confidence interval)[a]		Resistance index[b]
	IMA	ADR	
Native K562 cells	0.37 (0.26–0.54)	0.29 (0.24–0.35)	1
Model IMA phase 1	0.74 (0.61–0.90)	—	2
Model IMA phase 2	1.29 (1.06–1.58)	—	3.49
Model IMA phase 3	4.29 (3.03–6.36)	—	11.59
Model ADR phase 1	—	0.80 (0.51–1.24)	2.76
Model ADR phase 2	—	1.86 (1.5–2.30)	6.41
Model ADR phase 3	—	2.05 (1.32–3.32)	7.06

Peptide and protein identification

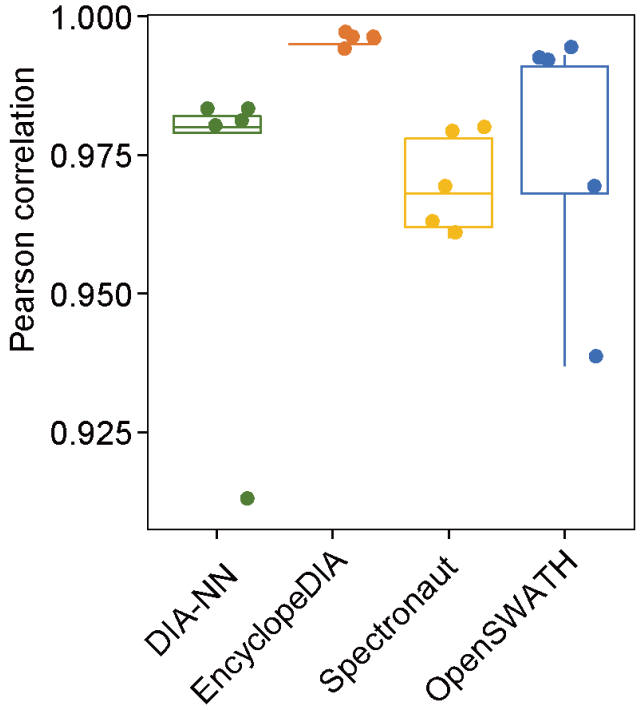


PCT-assisted peptide preparation and PulseDIA-MS were carried out to analyze the parental and the derivative resistant K562 cells.

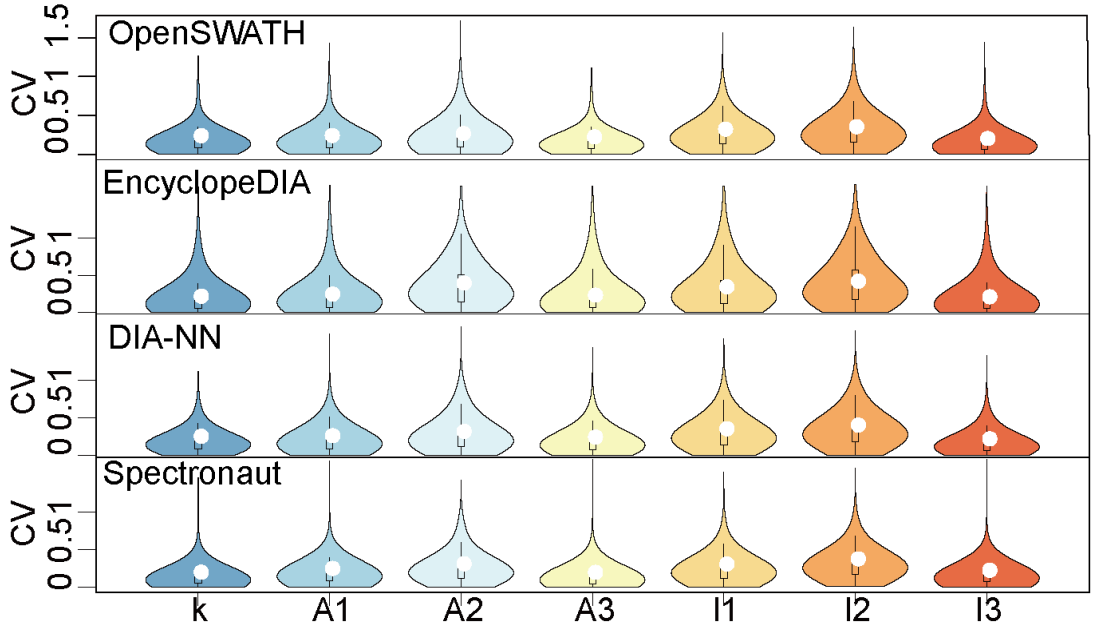
[1]PHL: Rosenberger G, et al (2014). Sci Data 1, 140031
[2] DPHL: Zhu T, et al. (2020). Genomics Proteomics Bioinformatics 18, 104-119

Quality Control of PulseDIA Proteome Dataset

Technical duplicates

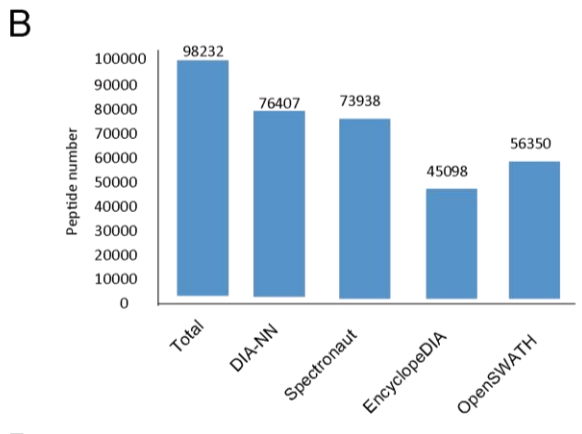


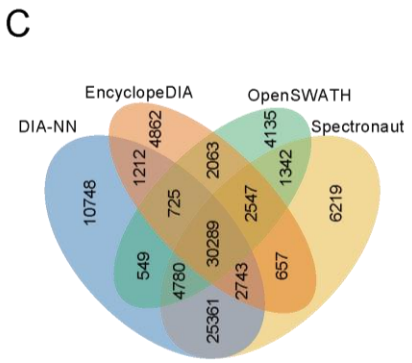
Biological triplicates

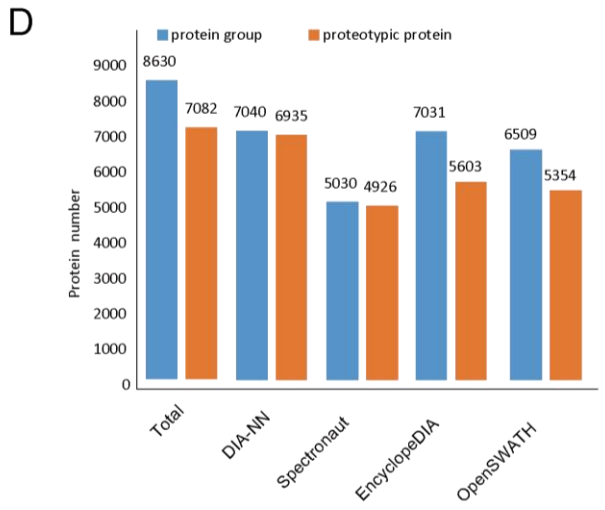


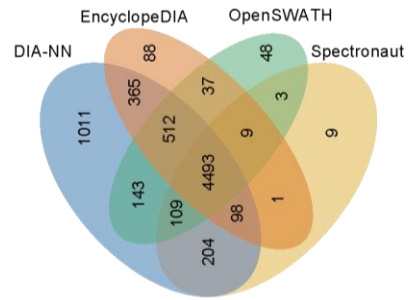
Technical duplicates showed a strong correlation (r>0.9), biological triplicates showed low CV (~20%) of proteins intensity

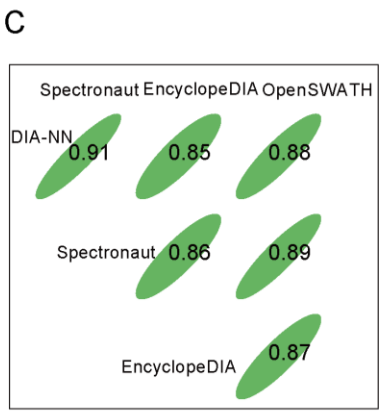
Comparison of qualitative and quantitative results of four DIA tools

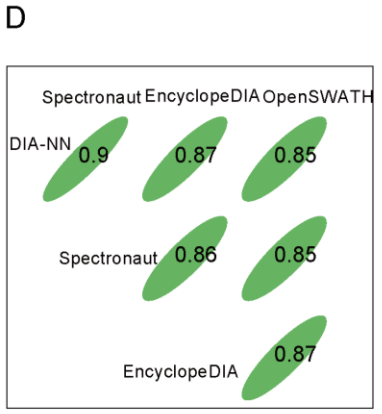


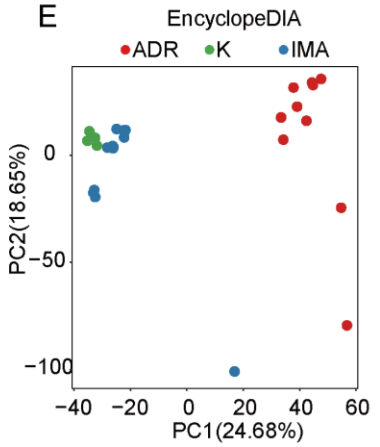


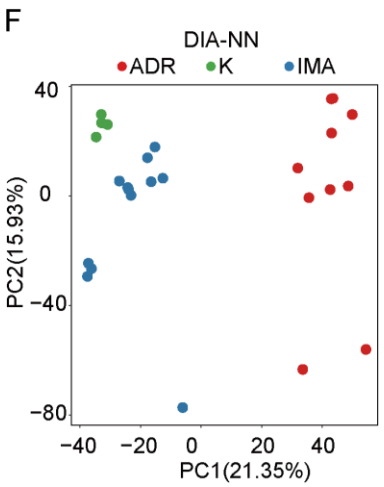


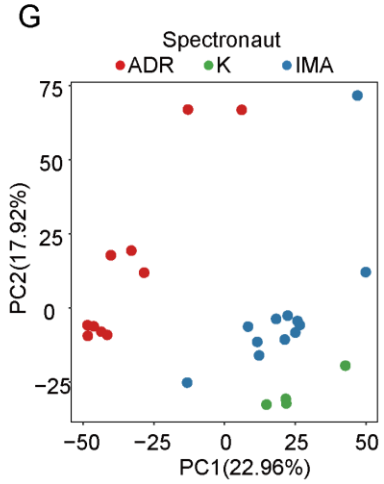


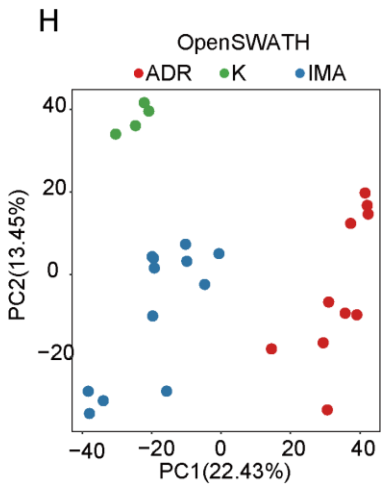




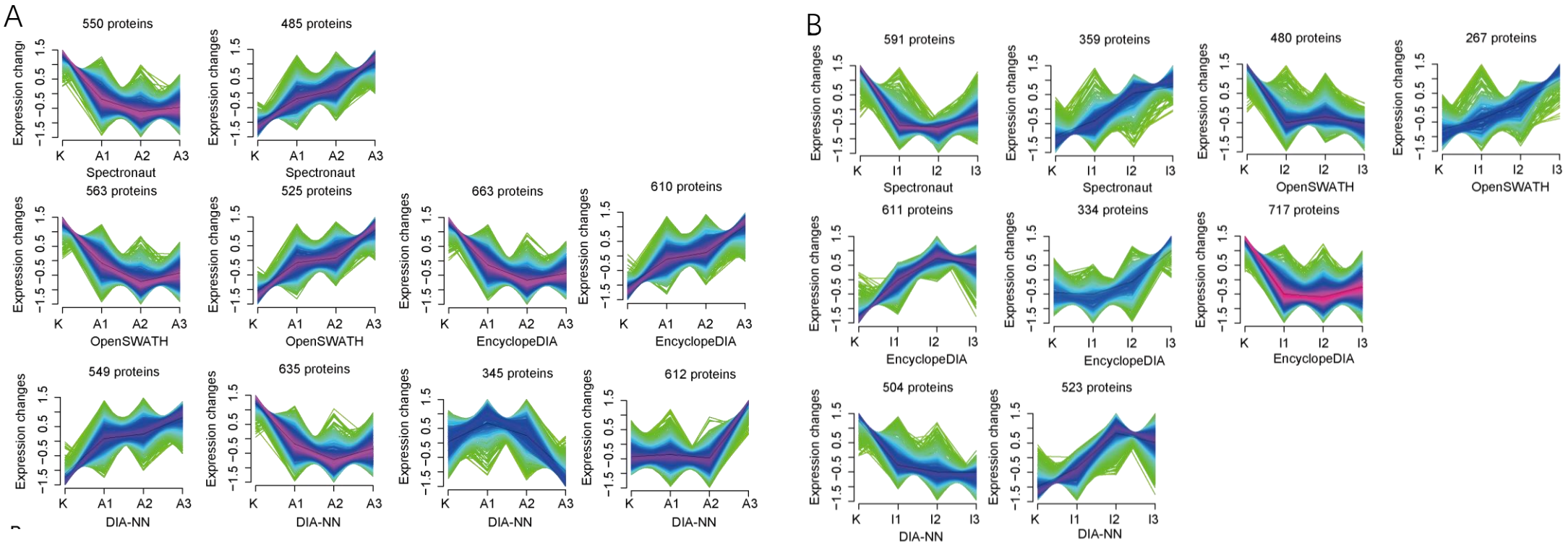






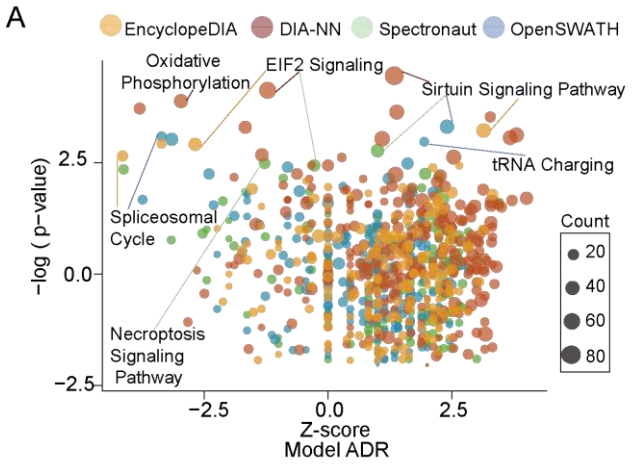


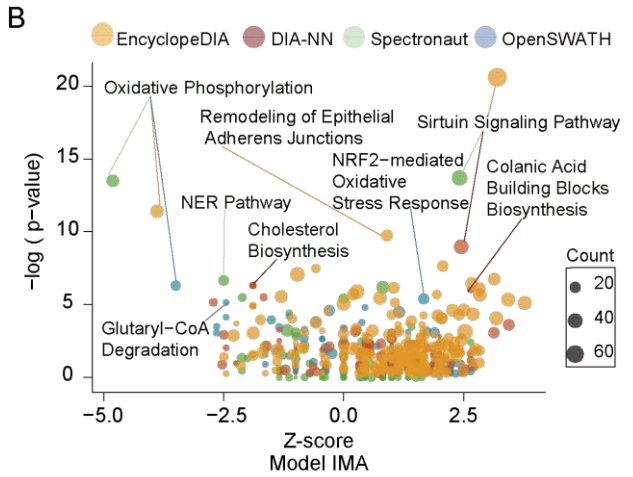
Dynamic Proteomic Changes During Acquisition of Drug Resistance

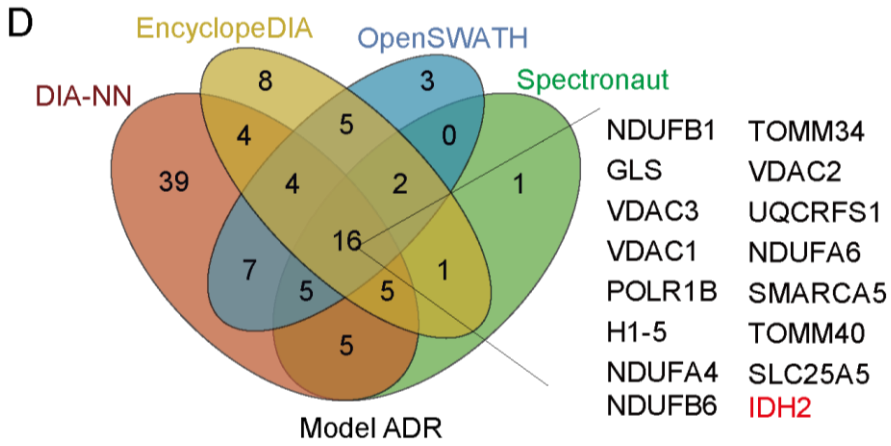


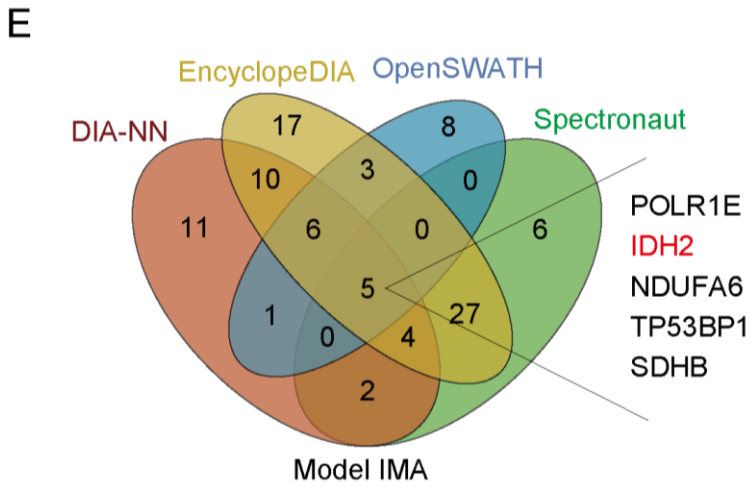
The cluster for proteins that were continuously upregulated and downregulated from K562 cells resistant to ADR (A) and IMA (B)

Activated sirtuin signaling pathway



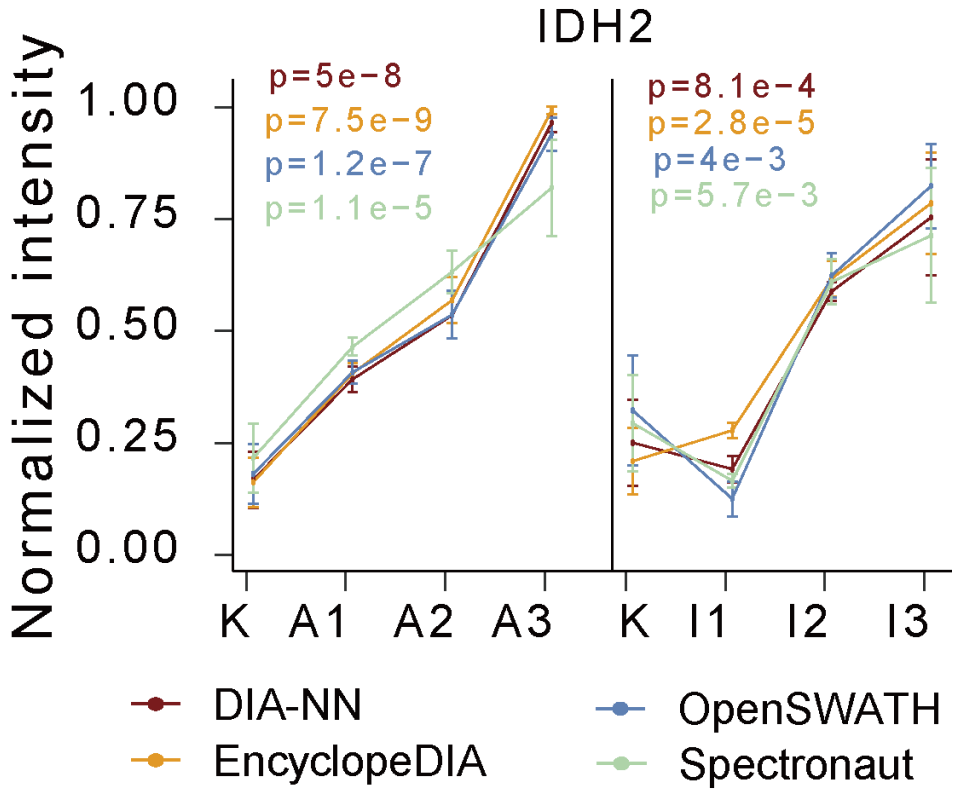


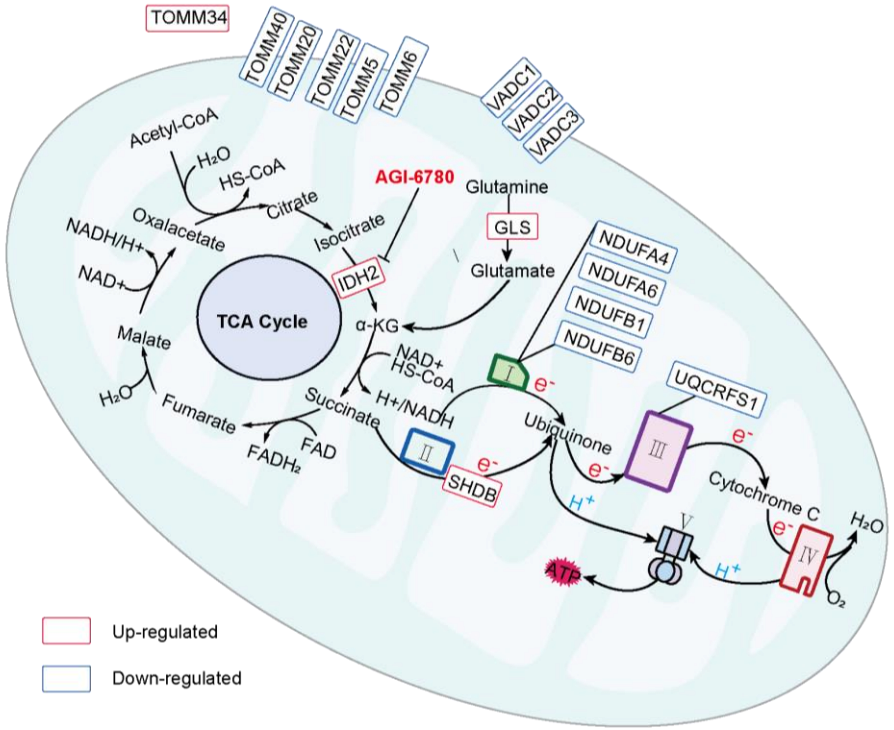




A,B Pathway annotation of continuously up- and down-regulated proteins revealed activated sirtuin signaling pathway; D, E Venn diagram shows the overlapped proteins involved in the sirtuin signaling pathway

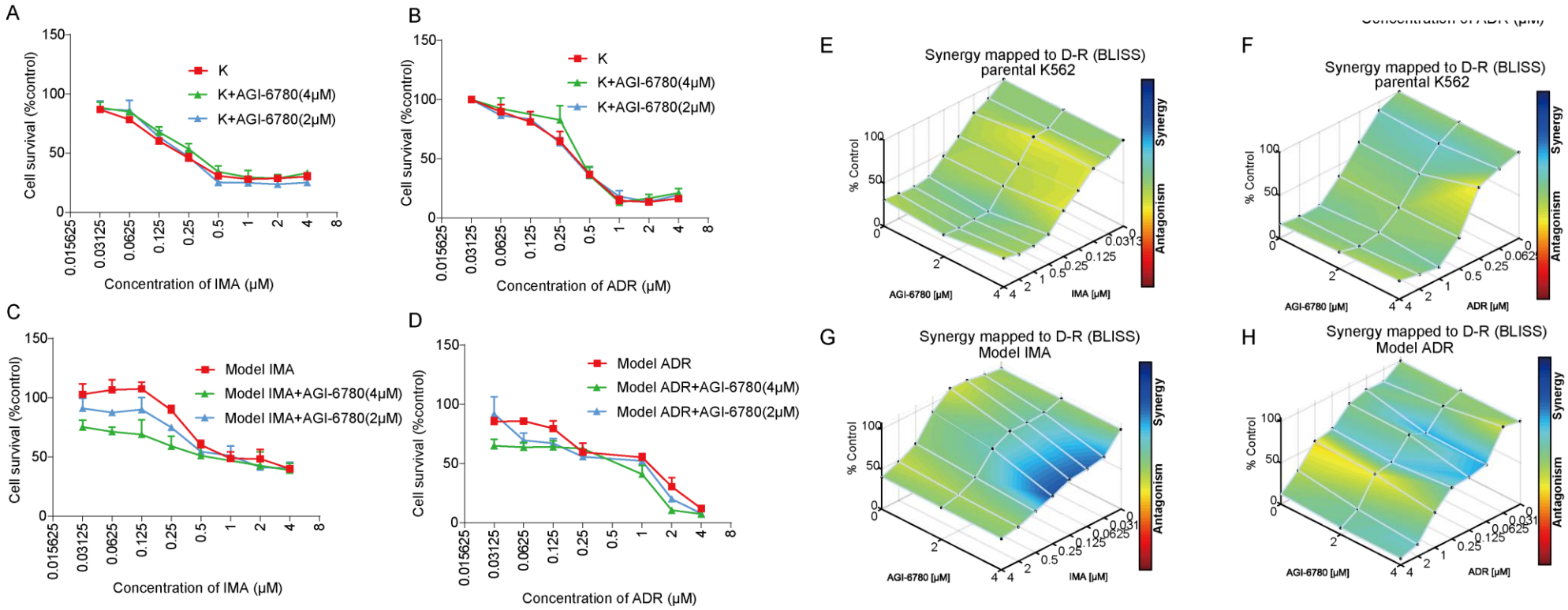
Abnormal Mitochondrial Function in Drug-Resistant K562 Cells





IDH2 is involved in abnormal mitochondrial function and upregulated in both K562 cells resistant models.

IDH2 is a potential target for reversing drug resistance in K562 cells



A-D, AGI-6780, a selective inhibitor of IDH2, increases the sensitivity of derived drug-resistant K562cells(C,D), but not parental K562 cells (A,B), to ADR and IMA. E–H, Bliss independence models show the synergistic or antagonistic effects from the combination of two drugs.

Take-home messages

- Temporal proteomic dynamics in the imatinib or adriamycin-induced drug resistance.
- Comparison of four DIA software tools (OpenSWATH, Spectronaut, DIA-NN, and EncyclopeDIA).
- Sirtuin signaling pathway was significantly regulated in resistant K562 cells.
- IDH2 was identified as a potential drug target correlated for resistant K562 cells.

Publication

MCP RESEARCH

DIA-Based Proteomics Identifies IDH2 as a Targetable Regulator of Acquired Drug Resistance in Chronic Myeloid Leukemia

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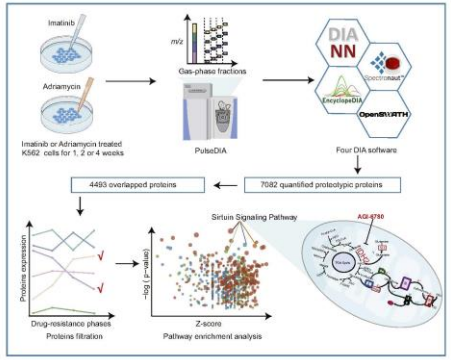
Graphical Abstract



In Brief
To understand the underlying resistance mechanisms in response to imatinib (IMA) and adriamycin (ADR), we explored two unique drug resistance models of K562 cells. We applied an optimized DIA–MS method to quantify 98,232 peptides from 7082 proteotypic proteins from these samples using four DIA software tools including OpenSWATH, Spectronaut, DIA-NN, and EncyclopeDIA. The sirtuin signaling pathway was found significantly regulated in both models, and IDH2 was identified as a druggable regulator of acquired drug resistance.

Highlights

- Temporal proteomic dynamics in the imatinib or adriamycin-induced drug resistance.
- Comparison of four DIA software tools (OpenSWATH, Spectronaut, DIA-NN, and EncyclopeDIA).
- Sirtuin signaling pathway was significantly regulated in resistant K562 cells.
- IDH2 was identified as a potential drug target correlated for resistant K562 cells.

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Acknowledgements

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UOMICS -since 2017

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College of Pharmacy in Dalian Medical University

All labmates in Laboratory of Big Proteomic Data

THANK YOU

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