

Ovarian Cancer Lipidome Dynamics in a Dicer-Pten Double-Knockout Mouse Model

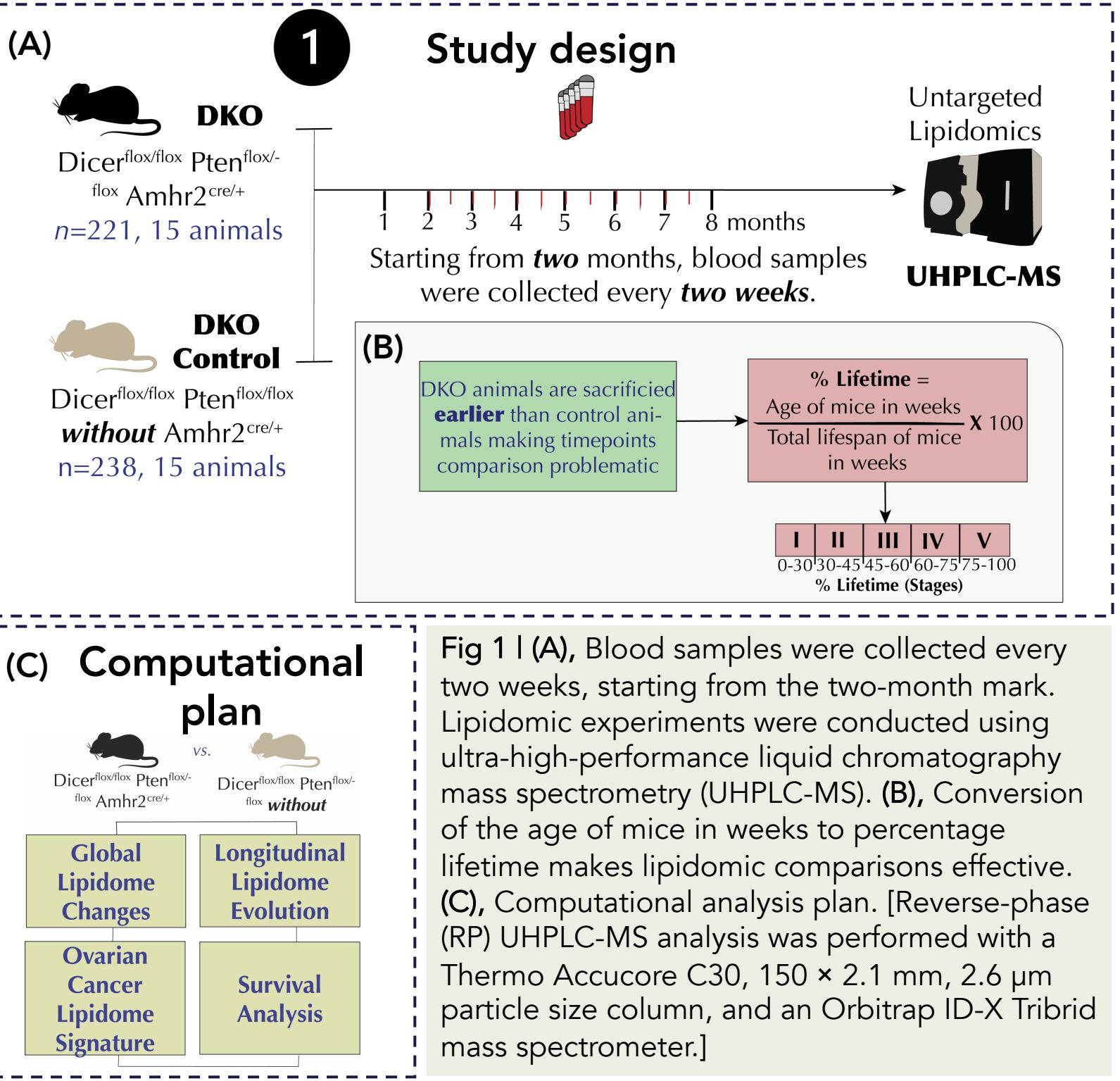
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Background

Ovarian cancer (OC) is one of the deadliest cancers affecting the female reproductive system [1]. It presents little or no symptoms at the early stages, and typically unspecific symptoms at later stages [2]. Of the OC subtypes, high-grade serous carcinoma (HGSC) is responsible for most OC deaths [3]. However, very little is known about the metabolic course of this disease. In this longitudinal study, using a Dicer-Pten Double-Knockout (DKO) HGSC mouse model [4], we investigated the temporal course of lipidome changes using machine and statistical learning approaches.

Methods



Abbreviations

DG: Diacylglycerols, TG: Triacylglycerols, FA: Fatty acids, HexCer: Hexosylceramides, LPC: Lysophosphatidylcholines, LPE: Lysophosphatidylethanolamines, PC: Phosphatidylcholines, PC-O: Ether phosphatidylcholines, PE: Phosphatidylethanolamines, PE-O: Ether phosphatidylethanolamines, PI: Phosphatidylinositols, Cer: Ceramides, SM: Sphingomyelins, RF: Random Forests, SVM: Support Vector Machine, Voting: Voting Classifier. ROC-AUC: Receiver Operator Characteristic – Area Under the Curve. ΔRMST: differences in restricted mean survival times.

References

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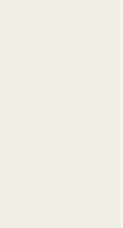
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Results

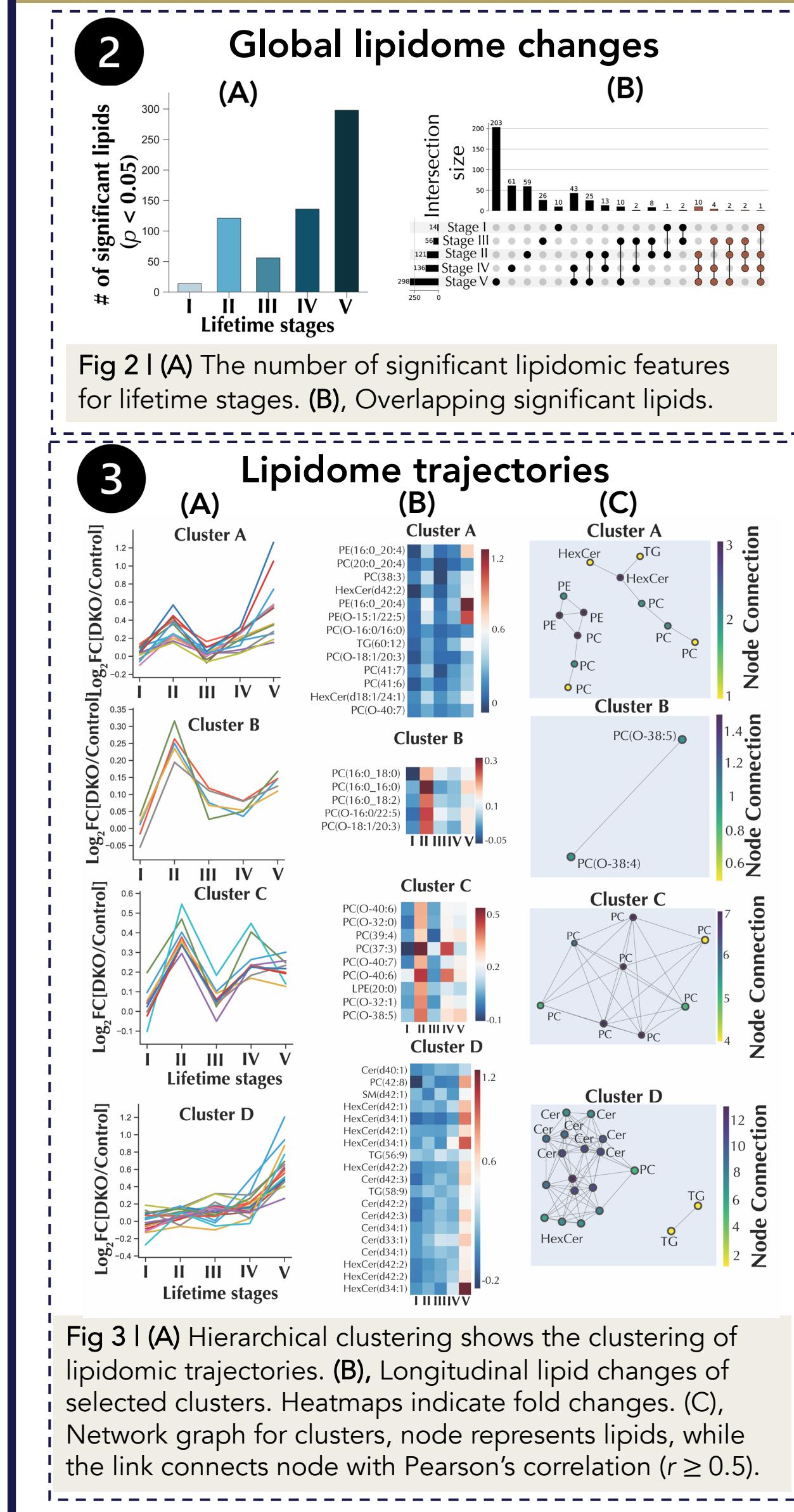


Fig 2 | (A) The number of significant lipidomic features for lifetime stages. (B), Overlapping significant lipids.

Fig 3 | (A) Hierarchical clustering shows the clustering of lipidomic trajectories. (B), Longitudinal lipid changes of selected clusters. Heatmaps indicate fold changes. (C), Network graph for clusters, node represents lipids, while the link connects node with Pearson's correlation ($r \geq 0.5$).

Fig 4 | (A), Machine learning pipeline. (B), The best ROC-AUC scores for each lifetime stages.

Fig 5 | Discriminative lipidomic features for the five lifetime stages. Lifetime stages (A) I (B) II (C) III (D) IV (E) V

Fig 6 | Volcano plots comparing DKO lifetime stages (A) - (D). (E), Upset plot showing the intersection of the significant lipids from the volcano plots. Kaplan-Meier survival curves of (F), PC(39:4) (G), PC(37:2). (H), PC(40:7). P -values were computed with the Log rank test. (I), Selected prognostic circulating lipids.

Summary

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The longitudinal RP UHPLC-MS lipidomic dataset was used to identify global lipidome alterations between DKO and DKO control mice, investigate lipidome changes in response to ovarian cancer (OC) progression, identify discriminative lipids for the five lifetime stages, and identify prognostic circulating lipid candidates.

A total of 19 lipid features were found to be significantly differentiated in at least three of the five lifetime stages (Fig 2B), where ~70% of lipids are phosphatidylcholines (PC O-), making it the most-upregulated lipid classes in this univariate time-resolved analysis.

Significant metabolic rewiring of the serum lipidome are apparent with disease progression as presented in our clustering analysis with mostly PC and PC O- being perturbed at early stages and HexCer and Cer at later stages.

ML results shows that early progression of OC is marked by increased levels of phospholipids, notably PC and PC-O, while in contrast, later stages were marked by more diverse lipids alterations including sphingolipids, fatty acyls, glycerolipids, steroid lipids, and phospholipids.

Of about 30 lipid candidates tested as circulating prognostic lipids, three lipid species have a statistically significant different Kaplan Meier (KM) curve via the log rank test. This include PC(39:4), PC(37:2), and PC(40:7) (Fig 6F-H).

The alterations provided evidence of perturbations in cell membrane stability, cellular proliferation, and survival, as our study provides the first in-depth, longitudinal lipidome dynamics study of ovarian cancer in the DKO mouse model. Future direction on our work will involve in-depth biological interpretations of lipid species in the context of OC.