

Plasma proteomics reveals systemic immune-metabolic dysregulation in Alzheimer's disease

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INTRODUCTION

Plasma proteomics has emerged as a powerful approach for characterizing systemic molecular changes in Alzheimer's disease (AD). However, the biological interpretation of large protein lists remains challenging, as conventional enrichment methods are sensitive to gene-set size, pathway overlap, and analytic choices, and often fail to distinguish structured disease biology from diffuse signal inflation. To address these limitations, we developed xEnrich, a statistical enrichment framework designed to quantify coordinated biological structure across pathways, tissues, and cell types while explicitly controlling for confounding and instability inherent to high-dimensional omics data.

METHOD

We applied xEnrich to harmonized plasma proteomic profiles from 4,217 individuals with AD and 8,372 non-impaired controls from the Global Neurodegeneration Proteomics Consortium, using an age- and sex-matched case-control design. Differential protein abundance was estimated using complementary pooled and site-stratified meta-analytic models. xEnrich integrates direction-aware enrichment, adaptive permutation testing, conditional null models, and information-theoretic metrics to assess enrichment strength, specificity, and robustness beyond simple over-representation. Enrichment analyses were conducted across curated biological pathways, organs, and cell types, with sensitivity analyses evaluating cross-site reproducibility, gene-set size effects, and stability across analytical strategies.

RESULTS

xEnrich identified an AD-specific plasma proteomic signature marked by coordinated enrichment of innate immune, metabolic, vascular, and tissue-remodelling pathways, including complement and coagulation, bioenergetic regulation, angiogenesis, and extracellular matrix organization (Fig. 1a-c).

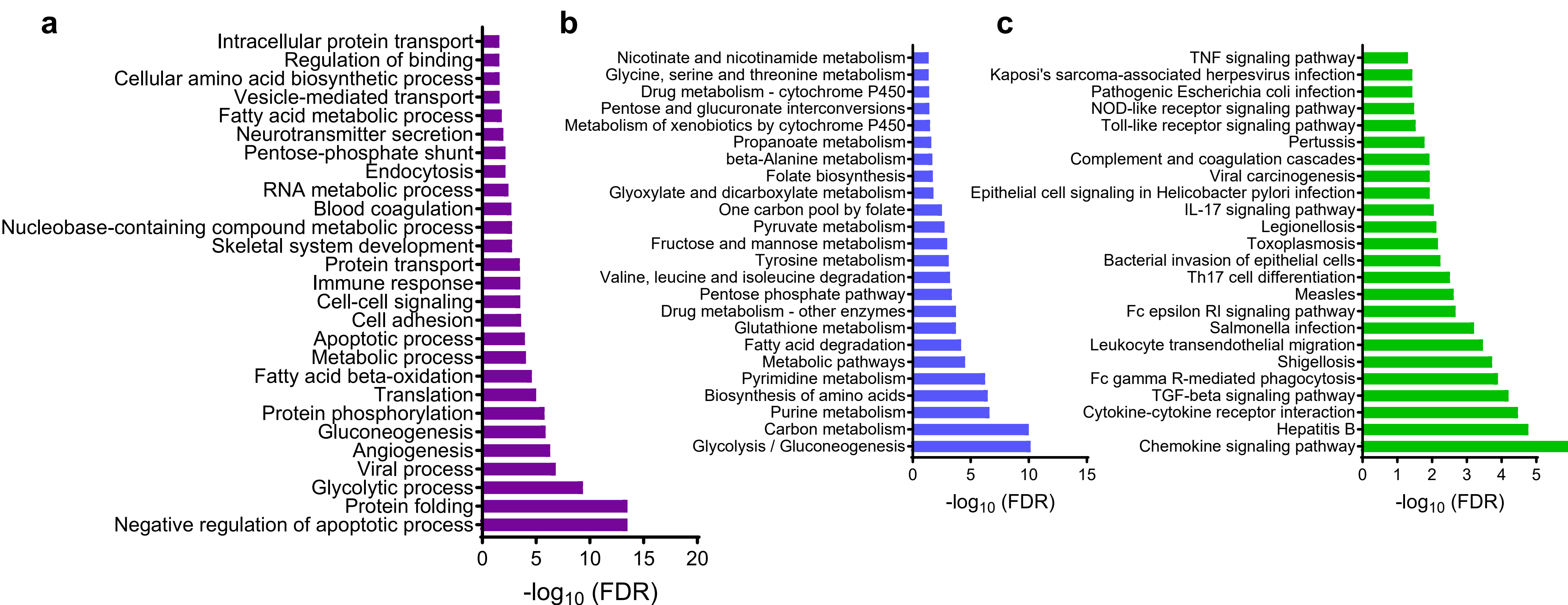


Fig. 1. Plasma proteomic enrichment for (a) PANTHER biological processes, (b) KEGG metabolic pathways, and (c) KEGG immune pathways.

Enrichment localized predominantly to peripheral immune and metabolic tissues (spleen, bone marrow, lymphoid organs, liver, pancreas, and reproductive tissues), with minimal brain-derived signal (Fig. 2a). Cell type-specific analyses implicated monocytes, dendritic cells, erythroid lineages, and stromal populations across multiple organs, and leading-edge integration revealed coherent biological processes of immune-hemostatic activation, proliferative regulation, and translational-metabolic efficiency (Fig. 2b). These patterns were reproducible across analytical strategies and robust to gene-set size and site-specific confounding.

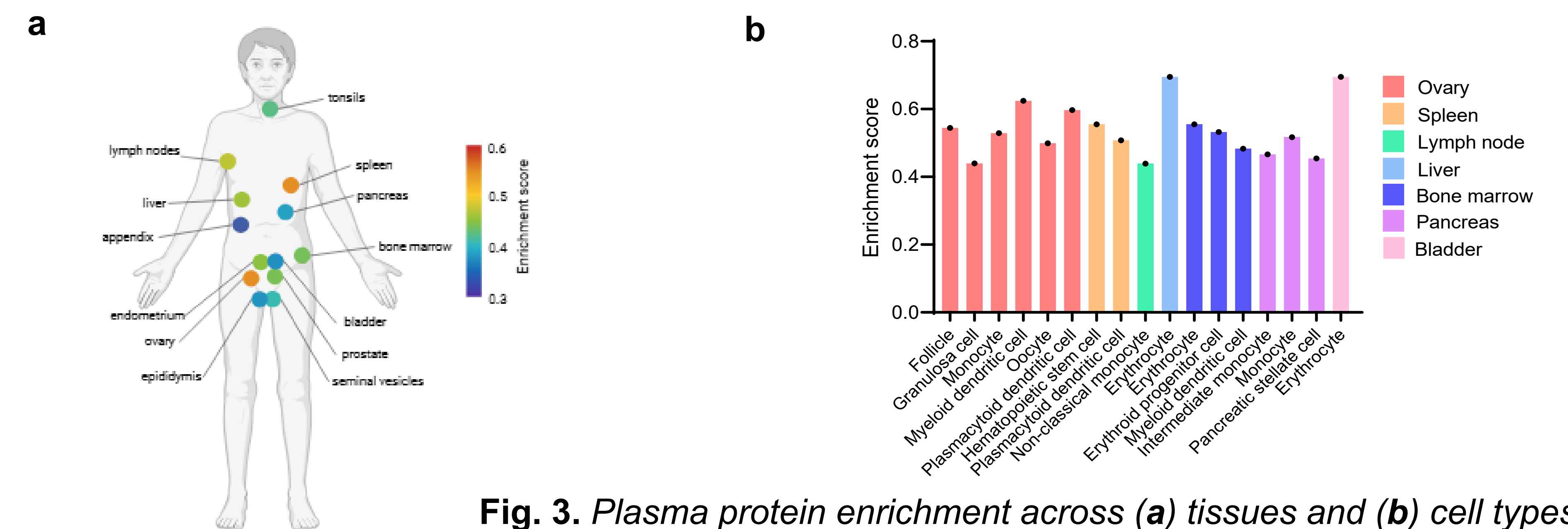


Fig. 3. Plasma protein enrichment across (a) tissues and (b) cell types.

An innate immune-hemostatic activation program operated in pancreatic and ovarian monocytes and stromal/stellate cells, alongside a proliferative-developmental program of cell-cycle and chromatin remodelling most pronounced in granulosa cells, hematopoietic progenitors, oocytes, and plasmacytoid dendritic cells. An anabolic translational module enriched in erythroid lineages reflected elevated ribosomal load, oxidative metabolic demand, and proteostasis burden (Fig. 4)

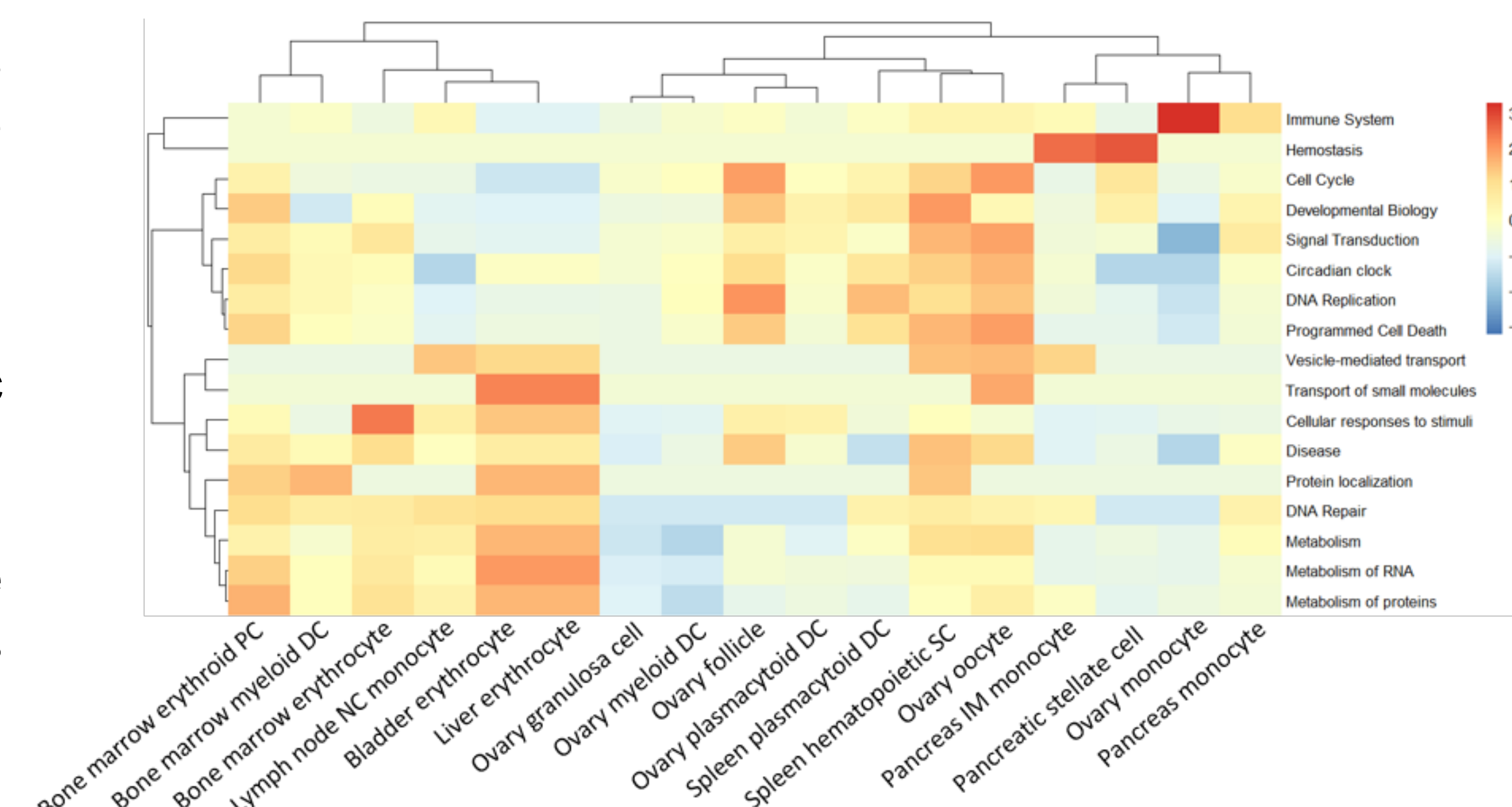


Fig. 4. Reactome pathway enrichment of leading-edge nodes across specific cell types.

CONCLUSION

Using xEnrich, we show that AD plasma proteomics reflects a coherent, multi-organ immune-metabolic signature rather than brain-restricted molecular changes. The peripheral localization and reproducibility of these signals support systemic immune-metabolic dysregulation as a core feature of AD biology. More broadly, this work demonstrates that biologically structured enrichment frameworks can yield reproducible, interpretable insights from large-scale plasma proteomics.

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