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SUPER HIGH-FREQUENCY MULTI-OMICS IN ACUTE ISCHEMIC STROKE

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Background and aims: Stroke biology changes hour-by-hour, but biomarker studies typically sample blood daily at best - missing time-ordered signals. We tested whether hourly plasma multi-omics can uncover molecular trajectories aligned with clinical evolution and identify single-timepoint biomarkers.

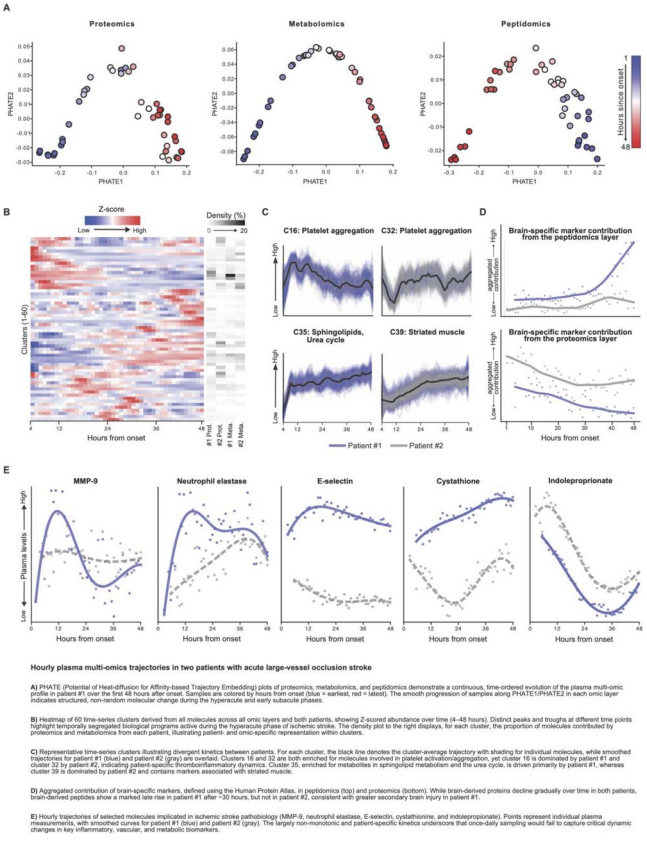
Methods: We performed hourly plasma sampling from 1-48 hours after onset in two patients with acute large-vessel occlusion stroke for proteomics, metabolomics, and peptidomics. We used dimensionality reduction to capture temporal structure and an autoencoder to derive trajectory clusters with pathway enrichment. We quantified tissue contributions by mapping proteins/peptides to the Human Protein Atlas. Validation was conducted in an independent cohort (N=502, PROMISE).

Results: Hourly plasma multi-omics revealed time-ordered change and non-monotonic trajectory clusters (Fig. A-B), underscoring the need for hourly sampling for biomarkers with unknown kinetics. Despite similar baseline severity and reperfusion treatment, patient #1 exhibited molecular changes indicative of rising platelet/NETosis-related thromboinflammation and catabolic stress, whereas patient #2 displayed attenuated responses (Fig. C-E). These differences coincided with greater infarct-progression (final-infarct-volume: 146 vs 17ml), hemorrhagic transformation, and worse 90-day outcome in patient #1 (mRS 5 vs 3). Cystathionine (an intermediate to glutathione redox buffering) rose steadily in patient #1 but declined early in patient #2. In PROMISE (N=502), cystathionine correlated with infarct volume (ρ=0.19, p=2.3$\times$10^{-5}) and predicted worse 90-day mRS (OR=1.70 per SD, p=1.5$\times$10^{-12}).

Conclusions: Hourly plasma multi-omics maps clinically aligned, time-resolved stroke biology and nominates single-timepoint biomarkers. Scaling to larger cohorts will link trajectory clusters to tissue injury and outcomes, enabling early molecular stratification.

Conflict of interest: Ali Rezaei: nothing to disclose

Figure 1 - belongs to Conclusions



Hourly plasma multi-omics trajectories in two patients with acute large-vessel occlusion stroke

A) PHATE (Potential of Heat-diffusion for Affinity-based Trajectory Embedding) plots of proteomics, metabolomics, and peptidomics demonstrate a continuous, time-ordered evolution of the plasma multi-omic profile in patient #1 over the first 48 hours after onset. Samples are colored by hours from onset (blue = earliest, red = latest). The smooth progression of samples along PHATE1/PHATE2 in each omic layer indicates structured, non-random molecular change during the hyperacute and early subacute phases.

B) Heatmap of 60 time-series clusters derived from all molecules across all omic layers and both patients, showing Z-scored abundance over time (4–48 hours). Distinct peaks and troughs at different time points highlight temporally segregated biological programs active during the hyperacute phase of ischemic stroke. The density plot to the right displays, for each cluster, the proportion of molecules contributed by proteomics and metabolomics from each patient, illustrating patient- and omic-specific representation within clusters.

C) Representative time-series clusters illustrating divergent kinetics between patients. For each cluster, the black line denotes the cluster-average trajectory with shading for individual molecules, while smoothed trajectories for patient #1 (blue) and patient #2 (gray) are overlaid. Clusters 16 and 32 are both enriched for molecules involved in platelet activation/aggregation, yet cluster 16 is dominated by patient #1 and cluster 32 by patient #2, indicating patient-specific thromboinflammatory dynamics. Cluster 35, enriched for metabolites in sphingolipid metabolism and the urea cycle, is driven primarily by patient #1, whereas cluster 39 is dominated by patient #2 and contains markers associated with striated muscle.

D) Aggregated contribution of brain-specific markers, defined using the Human Protein Atlas, in peptidomics (top) and proteomics (bottom). While brain-derived proteins decline gradually over time in both patients, brain-derived peptides show a marked late rise in patient #1 after ~30 hours, but not in patient #2, consistent with greater secondary brain injury in patient #1.

E) Hourly trajectories of selected molecules implicated in ischemic stroke pathobiology (MMP-9, neutrophil elastase, E-selectin, cystathionine, and indolepropionate). Points represent individual plasma measurements, with smoothed curves for patient #1 (blue) and patient #2 (gray). The largely non-monotonic and patient-specific kinetics underscore that once-daily sampling would fail to capture critical dynamic changes in key inflammatory, vascular, and metabolic biomarkers.