Here is a concise, editor-facing explanation of how the chosen algorithms—and their comparison—let AI refine pathway roles across immunity, metabolism, and plasticity, with references.

What we integrate. We assemble four data layers—innate immune states (monocytes/macrophages), metabolic context (oxLDL, β-HB, SCFAs; glycolysis/OXPHOS proxies), epigenetic marks (e.g., H3K4me3, H3 acetylation), and vascular phenotypes (endothelial adhesion, VSMC state, plaque readouts). These heterogeneous signals are harmonized in a heterogeneous knowledge graph and in matrices suitable for pathway activity scoring.[1]

How models work together.

1. Graph models (KG/GNN) propose missing but plausible links among metabolites, pathways, and cell types—useful for cross-domain assimilation[1].
2. Multimodal factor analysis (MOFA/MOFA+) compresses all signals into a few latent factors that track "trained-immunity intensity," enabling direct comparison across modalities[2].
3. We quantify pathway activity from expression using PROGENy (perturbation-derived footprints) and GSVA (sample-level gene-set variation), so outputs are pathway-level and biologically interpretable[3, 4].
4. Interpretable prediction (regularized models) then evaluates which features best predict plaque-related outcomes, with SHAP attributing importance to specific pathways/axes. Where temporal/interventional priors exist, NOTEARS helps propose causal directions.

How comparison refines pathways. We retain only pathways that (i) are highly ranked by ≥2 independent model families (graph + factor + predictor), and (ii) show stable attributions across resampling. This consensus avoids model-specific bias and yields a short, testable list.

What emerges (with biological anchors). The pipeline consistently prioritizes:
AMPK–SIRT1–HDAC axis**:** higher AMPK/SIRT1 with lower HDAC activity aligns with increased H3 acetylation in innate cells and lower NLRP3 readiness—consistent with β-HB acting as an endogenous class-I HDAC inhibitor[5].
β-HB–GPR109A–NLRP3 axis: graph and predictive models converge on ketone-receptor signaling that dampens inflammasome activity; this matches human ex vivo suppression of NLRP3-dependent IL-1β/IL-18 and ApoE$^{-/-}$ in-vivo plaque mitigation by oral 3-HB[6, 7].
These AI-refined axes sit on an atherosclerosis-specific trained-immunity backdrop (e.g., oxLDL-induced H3K4me3 memory in monocytes; Western diet–driven, NLRP3-dependent training in Ldlr$^{-/-}$ mice), closing the loop from computation to mechanism[8, 9].

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