Human Biomarker Navigator

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Introduction

Human Biomarker Navigation System: Integrating multi-omics and technological innovations to advance precision medicine

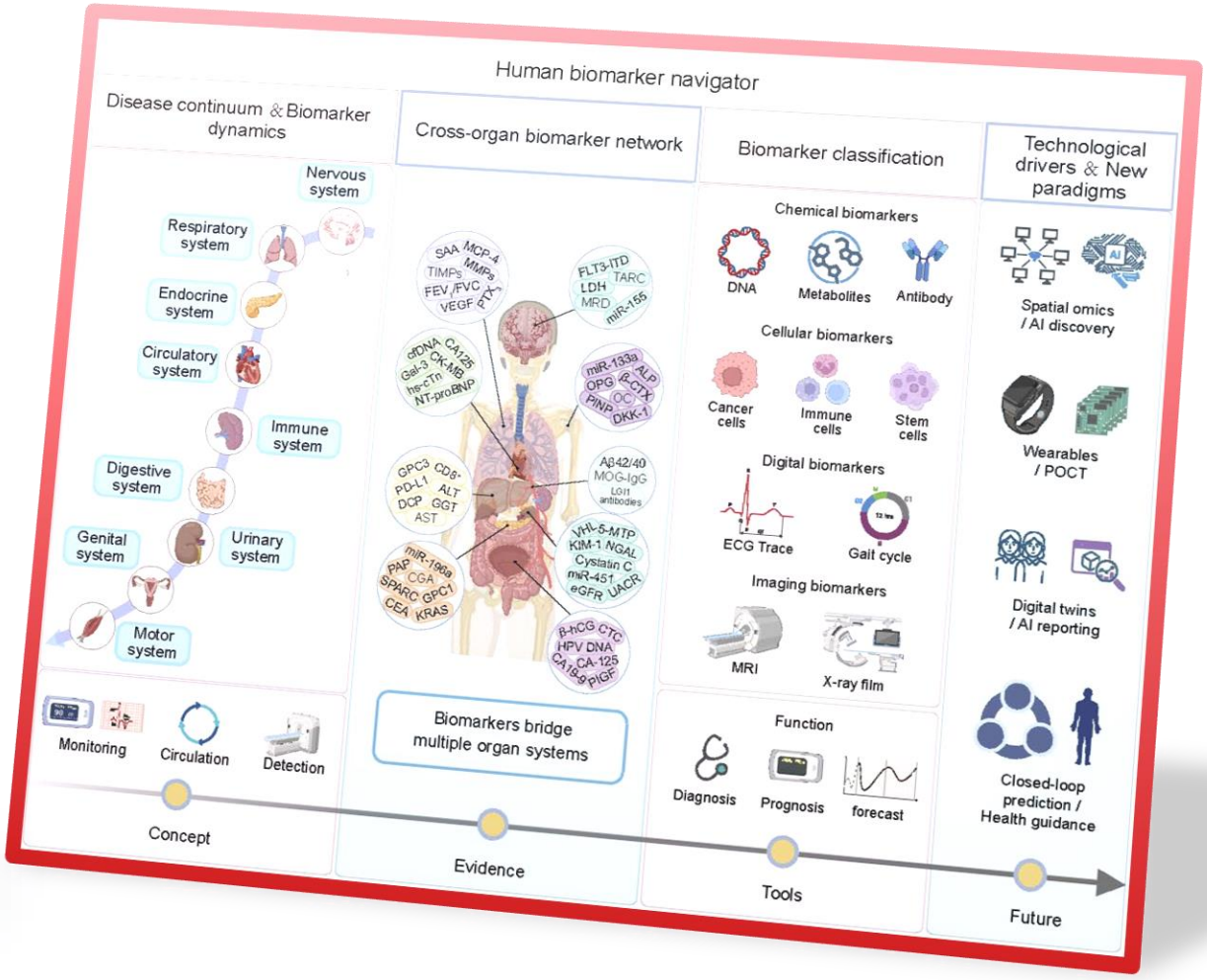
This figure illustrates the core concept of the human biomarker navigation system.

Covers the entire process of the disease

The Human Biomarker Navigator integrates the disease continuum, biomarker dynamics, cross-organ biomarker networks, biomarker classification, and technology-driven paradigms.

The diagram provides a detailed explanation of how biomarkers connect multiple human systems.

the nervous, respiratory, endocrine, circulatory, immune, digestive, urinary, reproductive, and musculoskeletal systems.



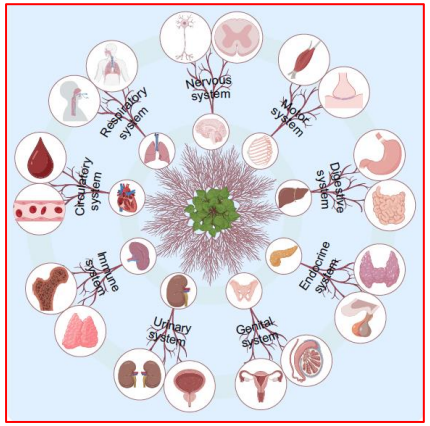
Highlights

- A comprehensive biomarker atlas encompassing nine human physiological systems was developed for the first time, transitioning from localized to holistic perspectives.
- An innovative framework for a “biomarker navigation system” was introduced, evolving it from a static knowledge base to a dynamic clinical decision support tool.
- The intricate networks of biomarkers across different systems, organs, and diseases, along with their regulatory mechanisms, were systematically detailed.
- A web platform termed “Human Biomarker Navigator” (http://www.hbiomarker.com) was launched to offer tools for streamlined retrieval and thorough analysis of biomarker–disease associations.

Figure 1 Precision health and disease monitoring

Elucidated the relationships between physiological systems and their associated biomarkers in the context of disease detection and monitoring

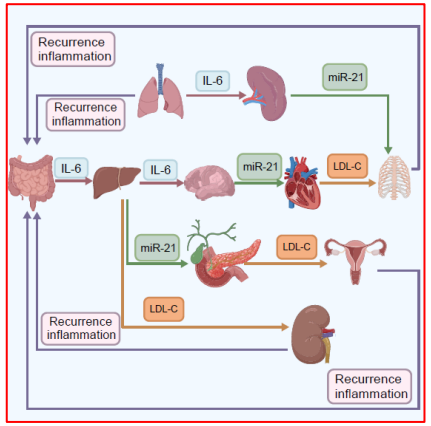
Radial diagram



Integrated major physiological systems, such as the nervous, cardiovascular, and immune systems, with core biomarker networks.

Panel A

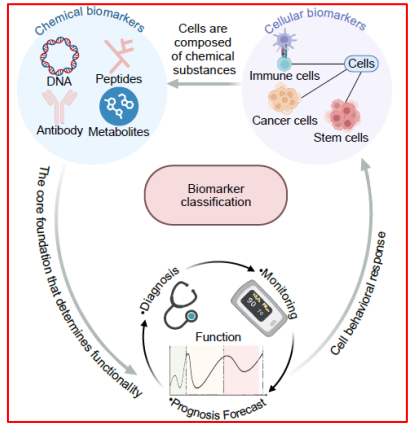
Pathways of inflammation recurrence



Affected multiple organs, including the lung, heart, and pancreas, highlighting IL-6 (interleukin-6), miR-21 (microRNA-21), and LDL-C (low-density lipoprotein cholesterol) as key mediators.

Panel B

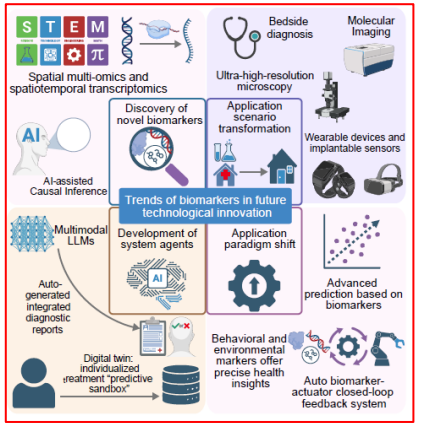
Categorizes biomarkers



Classified biomarkers into two major categories, chemical and cellular biomarkers, and redefined their compositional and functional significance in cellular behaviors and responses.

Panel C

Future of biomarker research



Highlighted technological advances, including spatial multi-omics, AI-assisted causal inference, and the development of system-based interventions for personalized health management

Panel D

Figure 2 Communication and systems biology effects

The systemic biological mechanism by which local organ lesions affect distant organs and lead to “comorbidity” through the blood circulation system as the core medium.

Four classic dialogue axes are taken as examples to intuitively show the systematic interaction.

- **Gut-liver**: Metabolites of gut microbiota TMA and endotoxin LPS enter the liver through the portal vein, driving or aggravating MASLD and liver fibrosis.
- **Gut-brain**: Gut microbiota and its metabolites (TMA, LPS) affect brain function through circulatory system and neural pathways, and are associated with anxiety, depression and cognitive decline.
- **Fat-organ**: Adipose tissue affects systemic insulin sensitivity, cardiovascular function and multiple organ metabolism by releasing signal molecules such as leptin, free fatty acids and inflammatory factors to the circulatory system. Insulin sensitivity can also reversely affect the function and metabolic state of adipose tissue.
- **Heart-kidney**: Heart failure leads to insufficient renal perfusion and activates the RAAS; on the contrary, water and sodium retention and uremic toxins accumulation caused by renal failure will aggravate cardiac load and form a vicious circle.

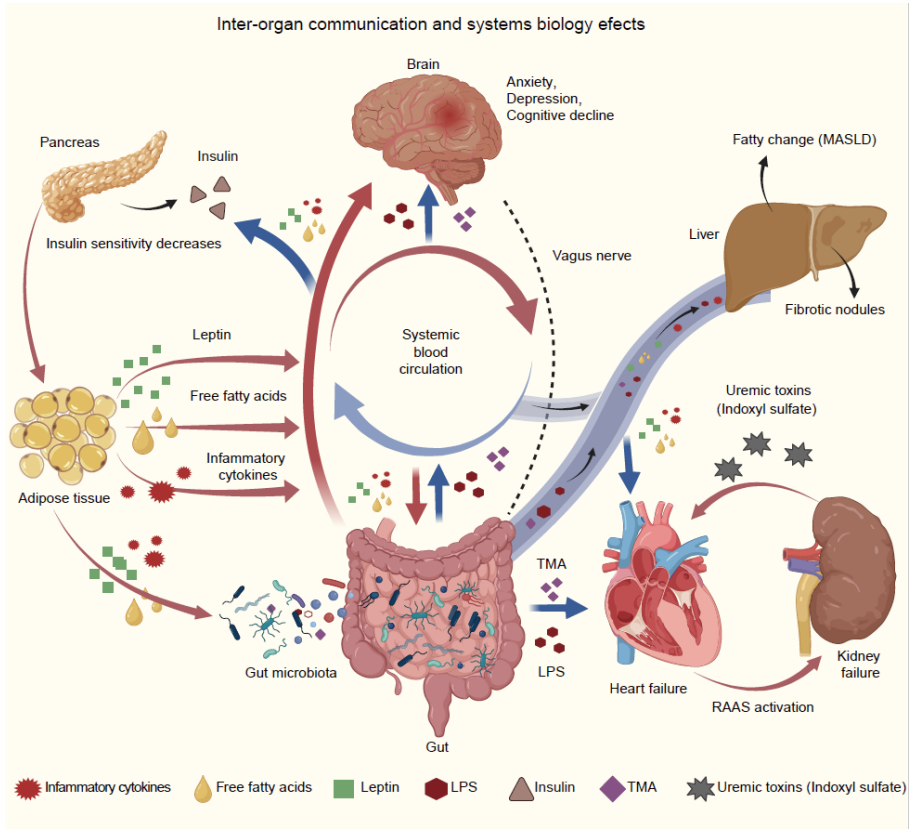


Figure 3 Gut microbiota, host metabolism and distant organ

This schematic illustrates the interactions between the gut microbiota and the host, as well as their effects on host metabolism and distal organs.

Within the microbiota–host axis, short-chain fatty acids are taken up by epithelial cells, helping maintain the balance between Firmicutes and Bacteroidetes and thereby supporting host health.

01 Under pathological conditions

Reduced gut microbial diversity disrupts tight junctions, leading to increased intestinal permeability and allowing lipopolysaccharides and trimethylamine to enter the portal vein and systemic circulation. Trimethylamine is further oxidized into trimethylamine N-oxide.

02 The effects on distal organs include:

It affects vascular endothelial function by promoting atherosclerosis, inducing neutrophil granule activation, and reducing brain-derived neurotrophic factor; it affects adipose tissue by alleviating insulin resistance and blocking insulin signaling.

03 Dual pathways regulate metabolism

Trimethylamine N-oxide also affects metabolic processes by inhibiting histone deacetylases and activating G protein-coupled receptor 41.

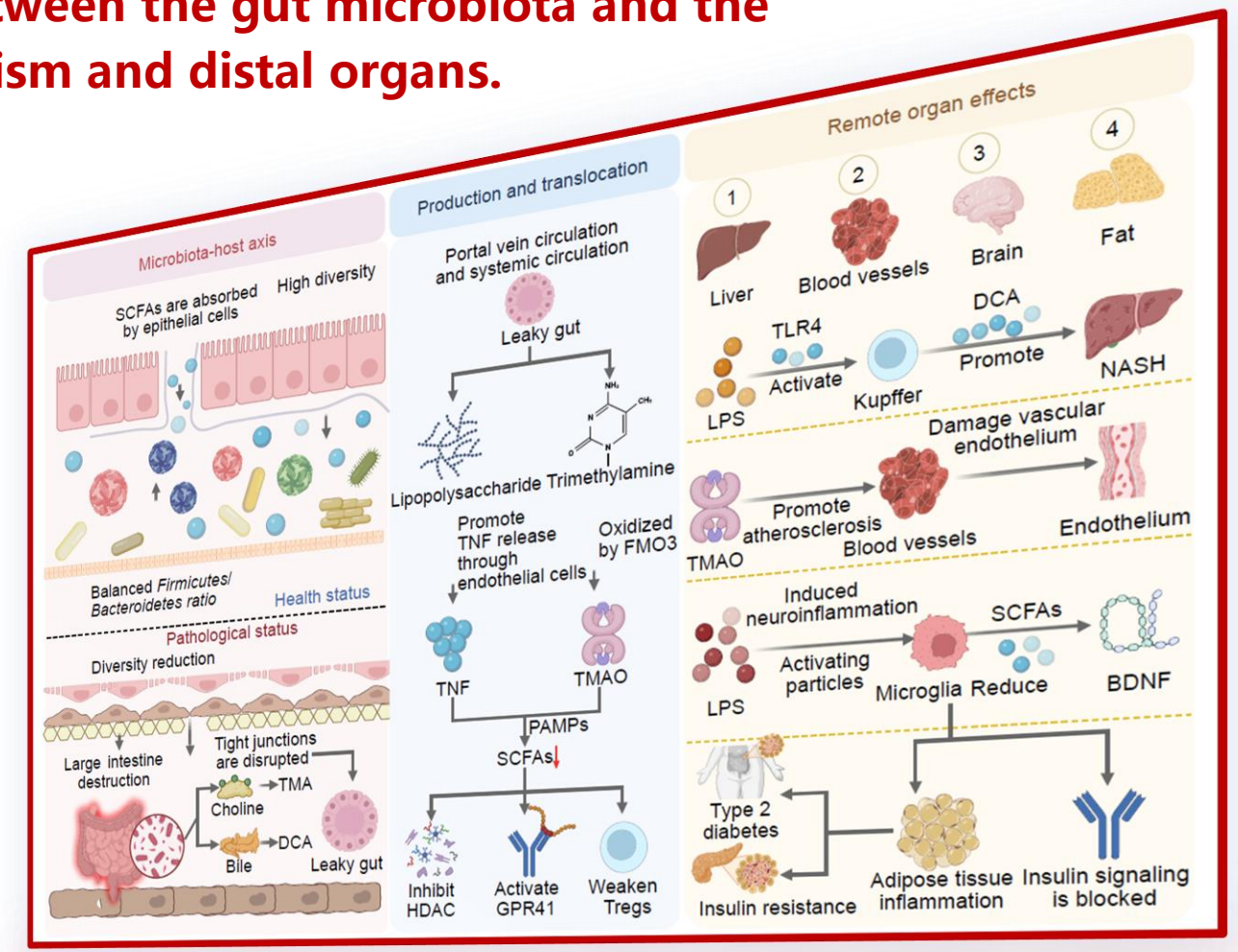


Figure 4 Shared “soil” for chronic diseases

This figure illustrates how multiple chronic stressors converge on inflammatory signaling hubs

- Driving systemic low-grade inflammation and downstream multi-organ dysfunction, thereby contributing to the onset and progression of various chronic diseases, including neurodegenerative disorders, metabolic disorders, cardiovascular diseases, and cancer.
- This mechanistic schematic summarizes key initiating factors, including gut microbiota dysbiosis accompanied by increased lipopolysaccharide translocation, saturated fatty acid-induced lipotoxicity, hyperglycemia, cellular senescence with the release of senescence-associated secretory phenotype (SASP) factors, and tissue hypoxia.

Microenvironmental stressors cooperatively drive immune cell infiltration and phenotypic reprogramming

Macrophages are polarized toward the pro-inflammatory M1 phenotype rather than the anti-inflammatory M2 phenotype, while the Th17/Treg balance is disrupted and shifted toward Th17 dominance. These immune alterations activate core inflammatory pathways, particularly the NF-κB signaling pathway and the NLRP3 inflammasome, which serve as key “engines” for the production and amplification of pro-inflammatory mediators.”

The resulting cytokines and chemokines:

IL-1β, IL-6, TNF-α, MCP-1, and other mediators enter the circulation, exerting systemic effects on multiple organs, including insulin resistance, endothelial cell activation, and hepatic acute-phase responses/CRP production. Key biomarkers, including IL-6, TNF-α, CRP, IL-1β, NLRP3, and MCP-1, are annotated with their cellular origins and mechanistic nodes.

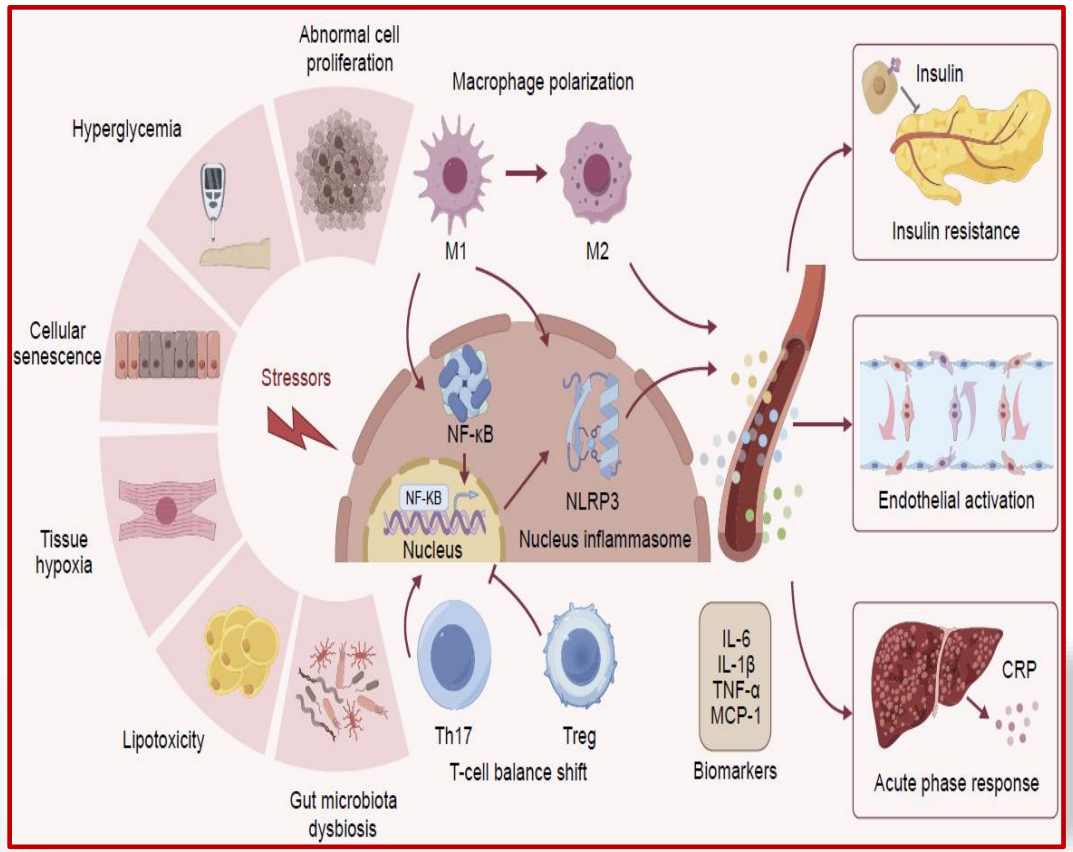
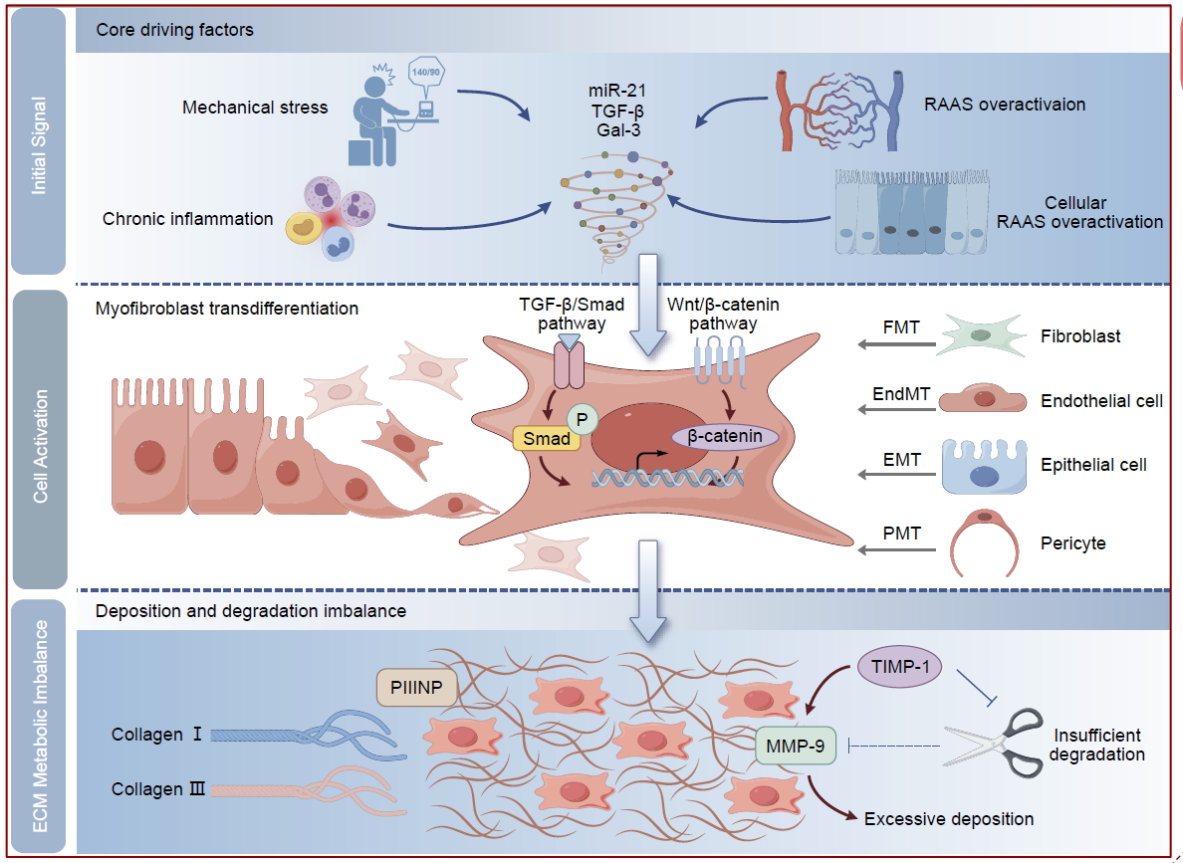


Figure 5 Tissue fibrosis as a shared terminal pathway of organ failure

The core mechanism of tissue fibrosis represents a common terminal process underlying functional decline in multiple organs (e.g., heart, liver, kidneys, lungs) and systemic autoimmune diseases.



01

Upper section: the start signal

- Chronic inflammation serves as the primary driving force, interacting synergistically with mechanical stress, excessive activation of the renin-angiotensin-aldosterone system, and cellular senescence.
- Upstream signals converge on fibrogenic mediators and regulatory factors, including TGF-β, Gal-3, and miR-21, collectively amplifying fibrotic signaling and microenvironmental remodeling.

02

The middle section: cellular events

- The sources of activated muscle fibroblasts are diverse.
- The study highlights the core signaling axis, wherein the TGF-β/Smad pathway serves as the predominant driver of fibrosis promotion, while the Wnt/β-catenin pathway acts as a supplementary mechanism for maintaining fibroblast activation and matrix gene transcription.

03

Lower section: Imbalance in extracellular matrix metabolism

- The balance between MMPs and their tissue inhibitors is disrupted, leading to excessive deposition of the extracellular matrix and insufficient degradation.
- This imbalance promotes the accumulation of collagen (particularly type I and type III), as well as progressive tissue sclerosis and scar formation. Key biomarkers are identified at critical mechanistic nodes, including TGF-β, type III procollagen N-terminal peptide, TIMP-1, MMP-9, Gal-3, and miR-21.

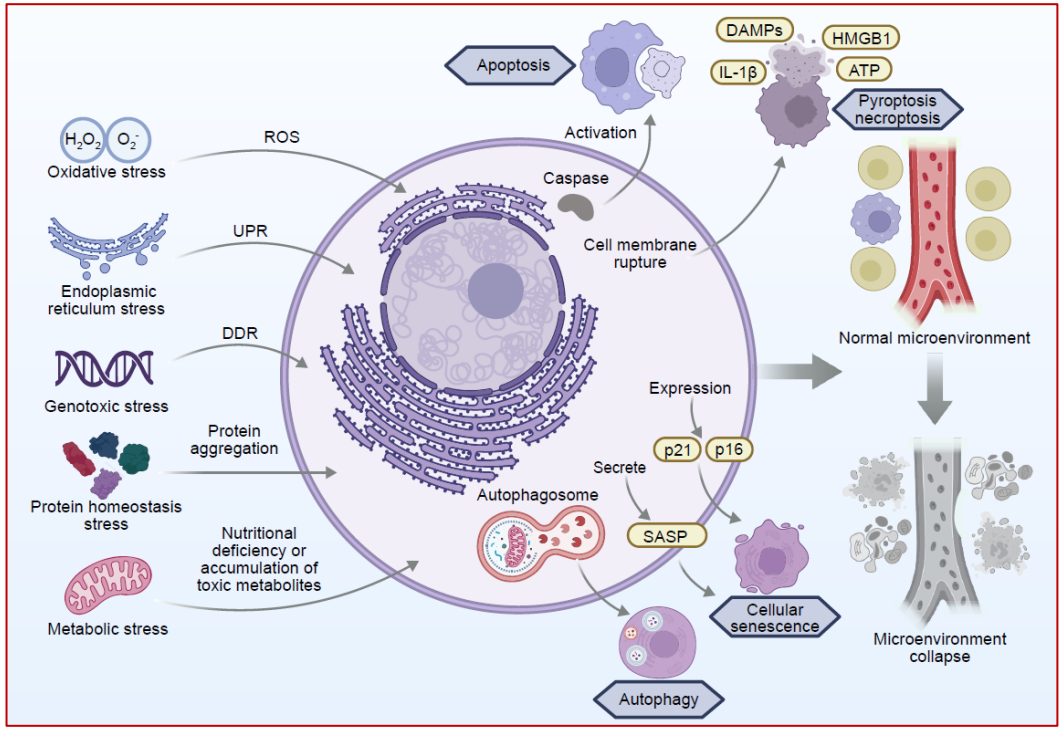
Figure 6 Microenvironment collapse due to cellular stress and imbalance

Imbalance in cell fate determination under stress conditions leads to microenvironmental collapse

Map of various stress-stimulated pathways mediating cell fate selection

The left half illustrates stress input signals, including oxidative stress (reactive oxygen species), endoplasmic reticulum stress (unfolded protein response), genotoxic stress (DNA damage response), proteostasis stress (protein aggregation), and metabolic stress (nutrient deficiency or accumulation of toxic metabolites). The middle section depicts the cell fate pathways: apoptosis (cysteine protease activation), inflammatory cell death (cell membrane rupture releasing injury-associated molecular patterns such as IL-1β, HMGB1, and ATP), cellular senescence (secretion of senescence-related secretory phenotypes), and autophagy (autosome formation).

The right half of the figure illustrates the transition from a normal microenvironment to a collapsed state, characterized by tissue loss, chronic inflammation, and functional failure. Key biomarkers are labeled as follows: p21, p16 (cellular senescence), SA-β-Gal (β-galactosidase), LC3 (autophagy-associated protein), p62 (autophagy substrate), and cfDNA (free DNA).



Various diseases disrupt the microenvironmental homeostasis through shared pathways of cellular fate dysregulation.

Figure 7 Cellular metabolic reprogramming and energy crisis

Cellular metabolic reprogramming forms the foundation for distinct functional states of cancer cells, activated immune cells, and fibrotic effector cells, thereby serving as a mechanistic bridge linking cancer, metabolic disorders, and immune dysregulation.

01. Left half: Metabolic characteristics of normal cells under physiological conditions

Metabolic homeostasis primarily relies on mitochondrial oxidative phosphorylation to efficiently produce ATP. Glucose and glutamine maintain equilibrium among glycolysis, the tricarboxylic acid cycle, and glutamine metabolism, supporting normal bi osynthetic demands and adaptive cellular responses.

02. Right half: Cell metabolic reprogramming under disease conditions

Under adequate oxygen supply, cells still prioritize aerobic glycolysis (the Warburg effect), leading to enhanced glycolysis and increased lactate production, with upregulation of key enzymes PKM2 and LDHA. Concurrently, glutamine metabolism is intensified to provide carbon and nitrogen sources, while the pentose phosphate pathway is strengthened to support nucleotide synthesis and redox homeostasis. Additionally, lipid metabolism undergoes remodeling, characterized by increased de novo fatty acid synthesis and suppressed oxidation, driven by enzymes such as ACC and FASN.

03. Propagative advantages and potential risks

These coordinated metabolic transitions enable cells to rapidly produce the biosynthetic precursors required for proliferation and effector functions, albeit at the cost of reduced energy efficiency. The imbalance between energy demand and ATP production leads to an energy crisis, accompanied by the accumulation of metabolic byproducts such as lactate, which acidifies the microenvironment and impairs cellular stress response capacity.

04. The systemic imprint of metabolic reprogramming

The figure highlights key metabolic biomarkers at the cellular or tissue level associated with this reprogramming state: elevated lactate levels, altered ketone body concentrations, changes in serum or plasma amino acid profiles (particularly branched-chain amino acids), and increased FGF-21 levels—all collectively reflecting systemic metabolic stress and adaptation.

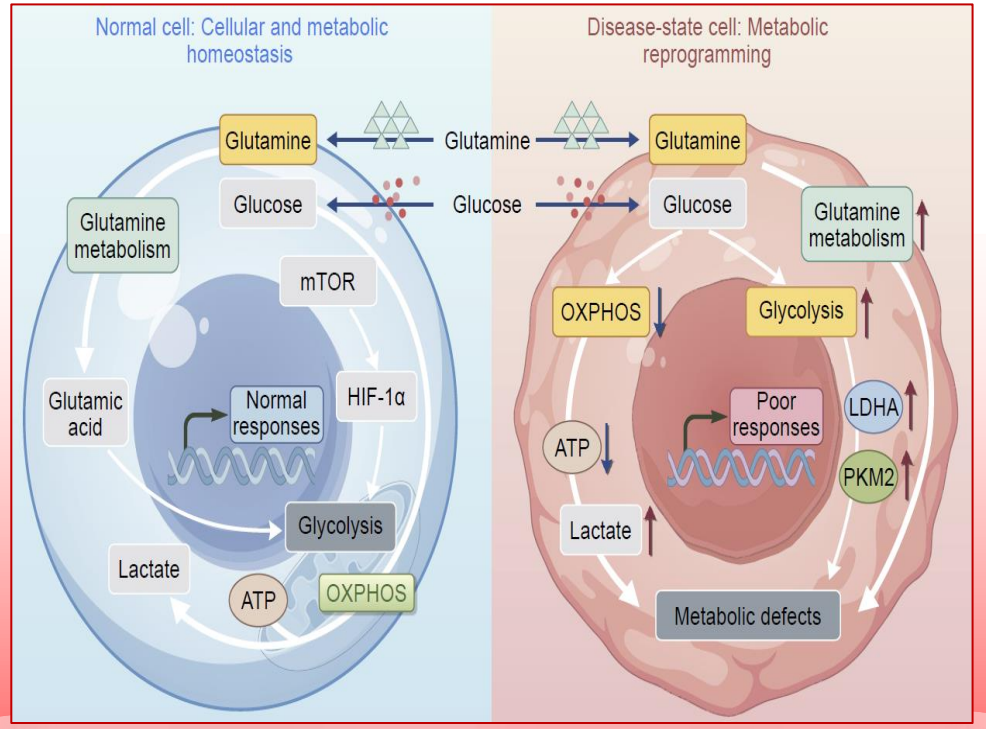
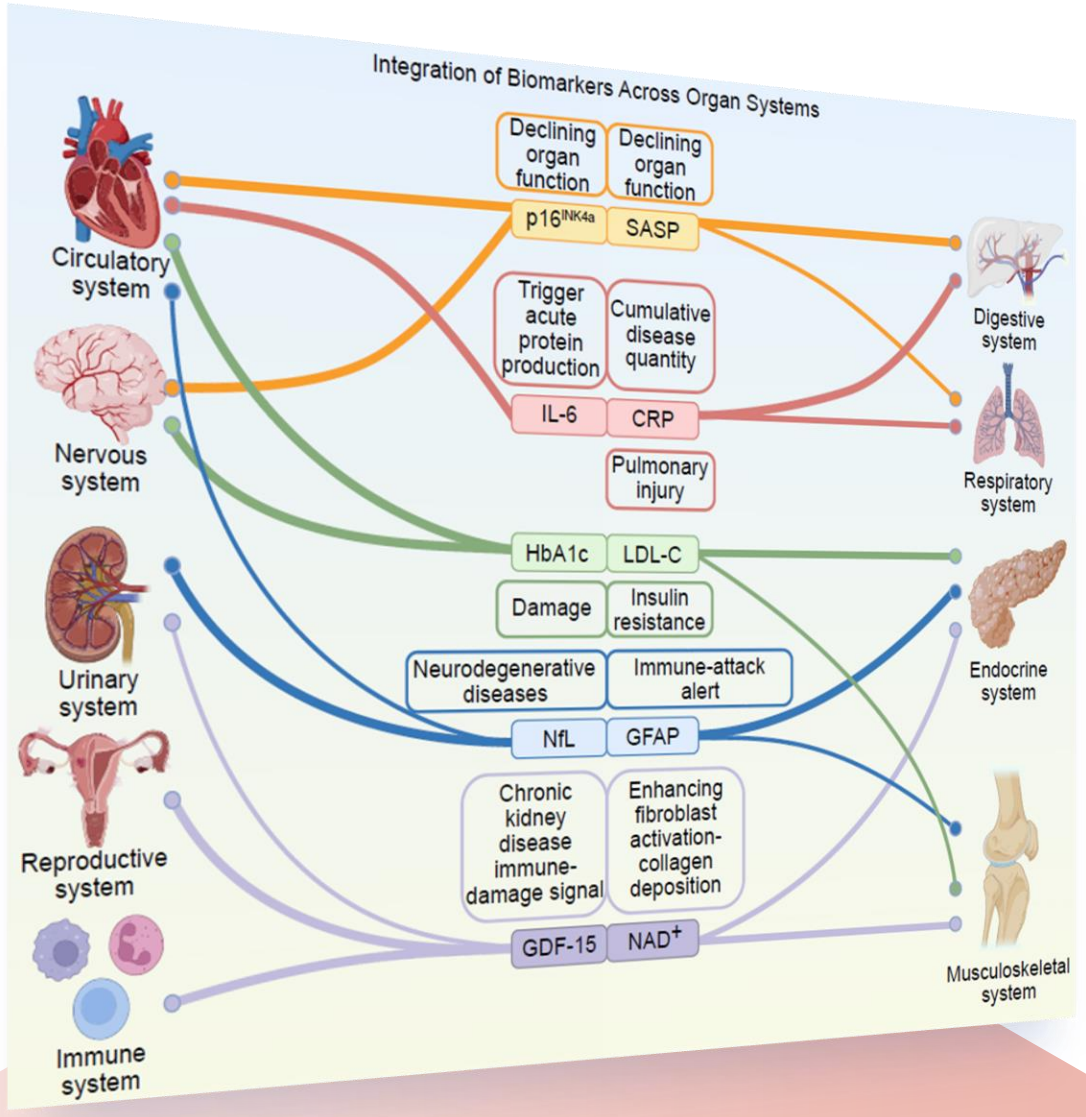


Figure 8 Integration of biomarkers across organ systems.



The complex network of connections between biomarkers and various organ systems in the human body

Biomarkers and Human Health

This figure aids in understanding how different biomarkers serve as indicators of human health status or disease progression.
The key biomarkers and their associations depicted in the figure include: p16INK4a and SASP, associated with organ function decline; IL-6, which triggers acute-phase protein production and is linked to cumulative disease burden and lung injury; CRP, associated with cumulative disease burden; HbA1c, indicating damage and related to insulin resistance; LDL-C, associated with insulin resistance; NfL, associated with neurodegenerative diseases; GFAP, signaling immune attack responses; GDF-15, associated with chronic kidney disease and immune injury signals; and NAD+, enhancing fibroblast activation and collagen deposition.

Interactions between organ systems

The involved organ systems encompass the circulatory, digestive, respiratory, nervous, urinary, endocrine, reproductive, immune, and musculoskeletal systems. Solid lines in the diagram represent the direct effects of biomarkers on each system, while dashed lines indicate indirect or chronic influences, highlighting the complexity and multifaceted nature of these interactions. This visual atlas helps underscore the broad significance of biomarkers in clinical practice and research, providing insights into potential diagnostic and therapeutic targets.

Figure 9 Biomarker stratification network and navigation pathways

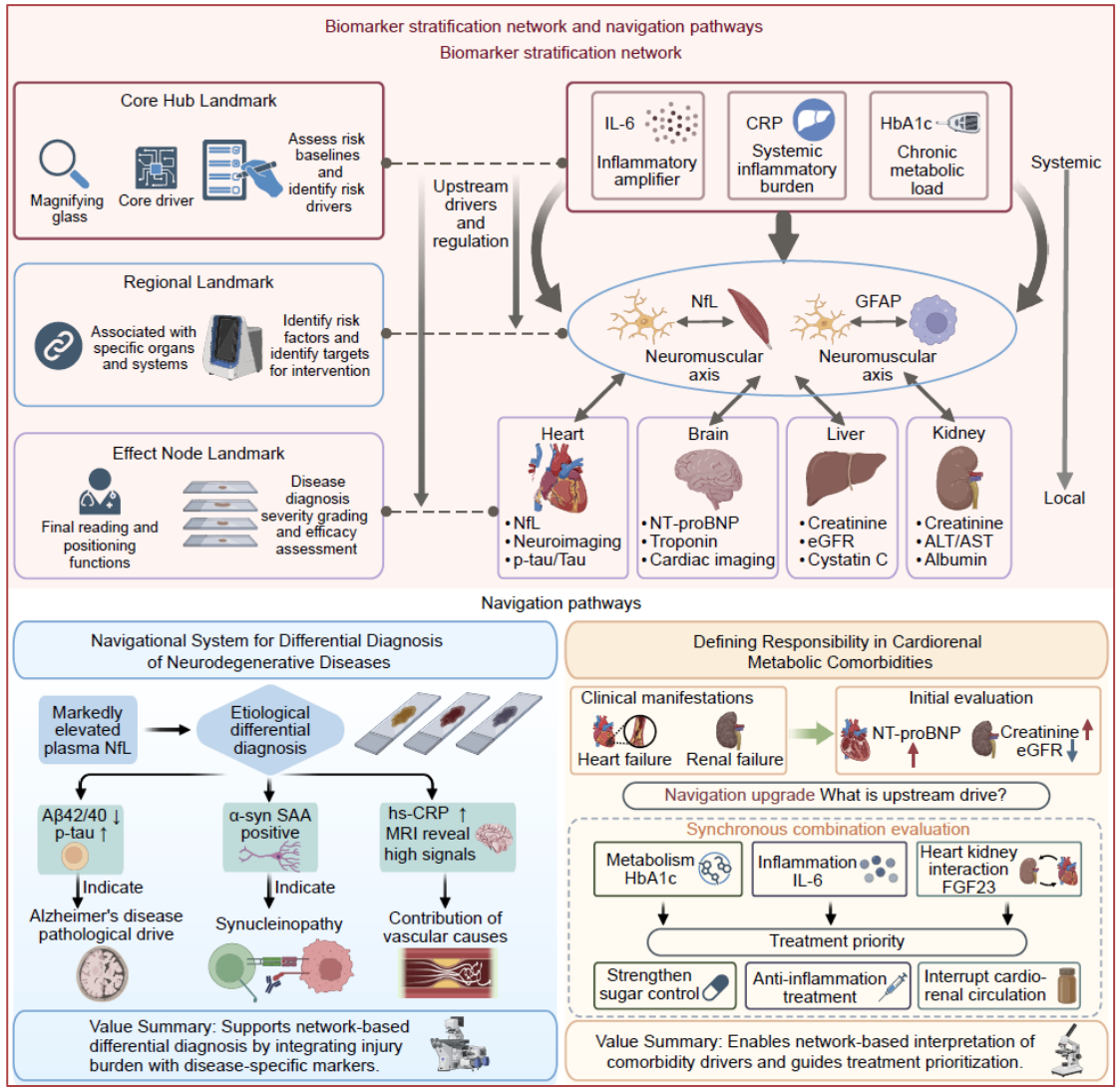
A network-based hierarchical biomarker framework for disease interpretation and clinical decision-making

Biomarker Stratification Network

The upper section illustrates that biomarkers are categorized into three tiers: core hub biomarkers for assessing baseline risk and upstream drivers; regional biomarkers for associating biomarkers with specific organs or systems; and effect node biomarkers for diagnosis, severity grading, and efficacy evaluation. The central network links systemic biomarkers (including IL-6, CRP, and HbA1c) with inflammation amplification, systemic inflammatory burden, and chronic metabolic burden. These drivers interact with intermediate neuroimmune biomarkers (such as NfL and GFAP) and extend to organ-specific biomarkers including NT-proBNP, troponin, p-tau/tau, creatinine, eGFR, cystatin C, ALT/AST, and albumin.

Navigation Path

The following panel illustrates two representative diagnostic pathways: differential diagnosis of neurodegenerative diseases based on NfL, Aβ42/40, p-tau, α-synuclein seed amplification, hs-CRP, and MRI findings; and utilization of NT-proBNP, creatinine/eGFR, HbA1c, IL-6, and FGF23 to elucidate cardiorenal metabolic comorbidities, thereby identifying upstream driving factors and guiding therapeutic priorities.



Conclusion

- A comprehensive panoramic biomarker atlas covering nine major human physiological systems was established, enabling systematic characterization of biomarker trajectories across the health–disease continuum.
- A biomarker-centered network framework was developed to uncover complex interactions among physiological systems, organs, and diseases, offering molecular insights into the shared mechanisms driving multimorbidity.
- The newly developed Human Biomarker Navigator website provides an integrated and interactive platform for cross-disease biomarker exploration and the construction of biomarker interaction networks.
- Website: http://www.hbiomarker.com

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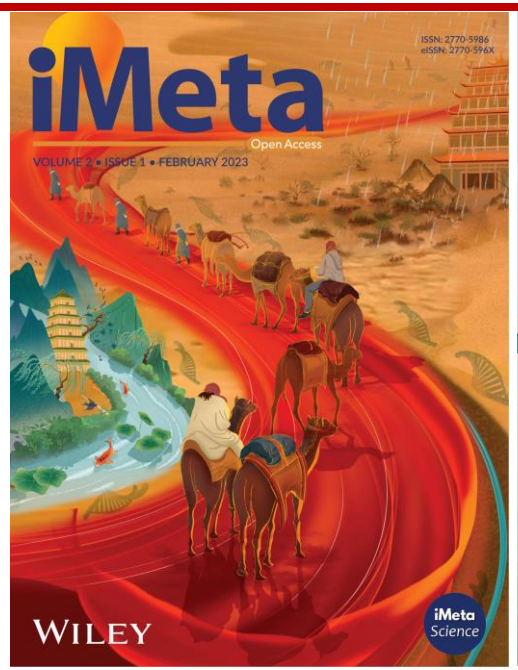

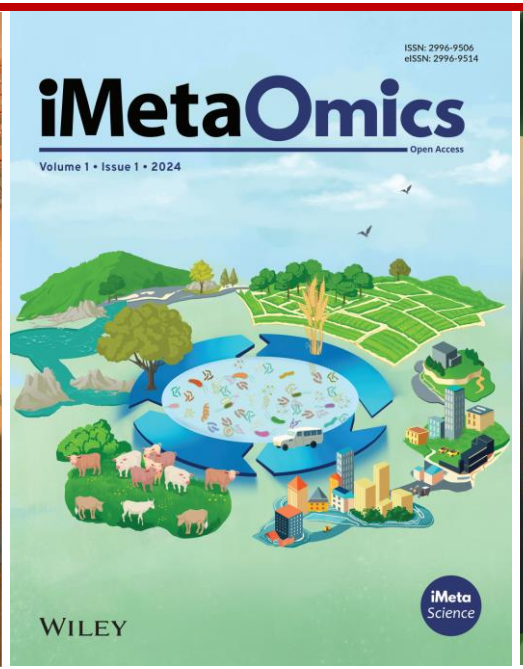

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