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Review paper

Immunology Under Gravito–Thermal Constraint Regimes

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ABSTRACT

Modern immunology has traditionally interpreted immune function through molecular signalling networks, genetic regulation, cellular interactions, and host-pathogen dynamics. However, immune processes operate within complex physical environments characterized by fluid transport, hydrostatic gradients, thermodynamic regulation, tissue mechanics, and mass-dependent biological organization. The present article introduces a conceptual framework termed Gravito-Thermal Immunodynamics (GTI), in which immunity is examined as a dynamic biological system emerging from interactions between molecular regulation and physical organization across multiple levels of biological complexity. Within this framework, blood circulation, lymphatic transport, hematopoietic organization, cerebrospinal fluid dynamics, inflammatory responses, oedema formation, leukocyte trafficking, and immune surveillance are interpreted as processes influenced by coupled hydrostatic, thermal, osmotic, biomechanical, and gravitational conditions. Immune tissues are viewed not solely as biochemical organs but as active fluid-mediated and poroelastic architectures operating within continuously evolving physical microenvironments. The framework integrates concepts from immunology, fluid mechanics, thermodynamics, mechanobiology, vascular physiology, neurobiology, and systems biology. Inflammation, fever, neuroimmune regulation, cancer-associated immune remodelling, embryonic immune development, immune aging, and immune adaptation under microgravity are reconsidered within broader gravito-thermal and hydro-mechanical contexts. Observations from spaceflight research, glymphatic physiology, tumour biomechanics, lymphatic biology, and developmental systems further support the importance of physical organization in immune function. Gravito-Thermal Immunodynamics does not seek to replace established molecular immunology. Rather, it proposes a complementary physical layer through which immune organization may be interpreted and investigated. By integrating biological signalling with fluid transport, thermodynamic processes, tissue mechanics, and gravity-dependent physiological organization, the framework offers a systems-level perspective that may stimulate interdisciplinary research into the physical foundations of immunity under both terrestrial and extraterrestrial conditions.

1. Introduction

Modern immunology has undergone extraordinary development over the past century, progressing from descriptive studies of infection and host defence to a sophisticated understanding of antigen recognition, cellular signalling, immune memory, differentiation, and gene regulation. Advances in immunogenetics, systems biology, immunometabolism, and RNA-mediated regulation have revealed the remarkable complexity of immune organization and have transformed both biomedical science and clinical

medicine (Abbas et al., 2024; Murphy and Weaver, 2022). Contemporary immunology now recognizes the immune system as a highly dynamic network of cells, tissues, signalling molecules, and regulatory pathways operating across multiple levels of biological organization.

Despite these advances, immune processes do not occur within a physically neutral environment. Every immune response unfolds within tissues characterized by fluid movement, hydrostatic gradients, vascular pressures, osmotic fluxes, thermal exchanges, and biomechanical constraints. Immune cells migrate through blood vessels, lymphatic channels, extracellular matrices, and interstitial compartments; inflammatory mediators diffuse through fluid-filled microenvironments; and immune organs function within continuously evolving mechanical and thermodynamic conditions. Consequently, immune behaviour emerges not solely from molecular signalling but also from the physical environments within which such signalling occurs.

Increasing evidence from vascular biology, mechanobiology, neuroimmunology, lymphatic physiology, developmental biology, and space medicine demonstrates that physical forces contribute significantly to biological organization and physiological regulation. Hydrostatic pressure influences vascular filtration and lymphatic drainage; thermogenesis modulates inflammatory activity and immune kinetics; tissue mechanics affect cellular migration, differentiation, and tissue remodelling; and fluid transport governs the movement of nutrients, signalling molecules, immune cells, and metabolic products throughout the body. Yet these physical dimensions are often investigated independently and are rarely integrated into a unified framework of immune organization.

The influence of gravity provides a particularly important but frequently overlooked dimension of biological regulation. Life on Earth has evolved under persistent gravitational conditions that shape fluid distribution, hydrostatic pressures, vascular dynamics, lymphatic transport, tissue loading, and biomechanical organization. Evidence from spaceflight and microgravity research has demonstrated that alterations in gravitational conditions influence immune-cell function, inflammatory regulation, hematopoiesis, neuroimmune physiology, and host defence, suggesting that immune homeostasis is partly embedded within gravity-dependent physiological architectures (Crucian et al., 2018; Garrett-Bakelman et al., 2019).

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The lymphatic system provides a particularly illustrative example of the interaction between biological organization and physical transport processes. Although embryologically derived from mesodermal vascular structures, the mature lymphatic network functions as a specialized low-pressure regulatory compartment linking tissue interstitial spaces with the venous circulation. Through fluid recovery, molecular transport, immune surveillance, and tissue homeostasis, the lymphatic system demonstrates how immune function depends upon coordinated hydrostatic, biomechanical, and transport mechanisms extending beyond purely molecular regulation.

The present work proposes a broader physical-biological perspective termed Gravito-Thermal Immunodynamics (GTI). The framework extends earlier concepts of intrinsic gravitation and gravito-thermal biological organization developed in relation to embryogenesis, genetic expression, microbial systems, plant biology, cancer progression, neurobiology, and systems-level biological organization (Bhattacharjee, 1988, 2025, 2026a, b, c, d). Within this perspective, immunity is examined as a dynamic gravito-thermal system arising from coupled interactions among molecular signalling, fluid transport, hydrostatic organization, thermogenesis, tissue mechanics, and mass-dependent biological architecture. Rather than viewing immune cells as isolated molecular entities, the proposed framework interprets immunity as a distributed adaptive process operating within interconnected vascular, lymphatic, stromal, neural, and interstitial environments.

The central hypothesis is that immune organization emerges through continuous interactions between biological information and physical structure across multiple scales, extending from cellular and tissue microenvironments to whole-organism physiology and environmental influences. Accordingly, this article explores how gravity-dependent fluid behaviour, thermodynamic regulation, vascular transport, tissue biomechanics, and environmental loading may contribute to immune organization during inflammation, fever, neuroimmune regulation, hematopoiesis, cancer progression, embryonic development, aging, and adaptation to microgravity. The objective is not to replace established molecular immunology but to

propose an additional physical layer through which immune processes may be interpreted within a unified systems-level framework.

2. Gravity, Microgravity, and Biological Organization

Gravity is a universal physical condition under which life on Earth has evolved. Although biology and immunology are commonly interpreted through molecular, genetic, biochemical, and cellular mechanisms, all living systems operate within gravitational fields that influence mass distribution, fluid movement, tissue loading, pressure gradients, thermodynamic behaviour, and structural organization. Consequently, gravity should not be regarded merely as a background environmental factor but as a continuous physical determinant of biological form and function.

At the most fundamental level, mass represents a central organizing variable in biological systems. Mass determines gravitational interactions, contributes to hydrostatic pressure generation, influences tissue density and mechanical loading, stores thermal energy, and provides the physical substrate through which metabolism occurs. Larger biological structures generally contain greater quantities of fluid, charged particles, metabolic machinery, and thermogenic capacity. Through these interconnected effects, mass contributes to fluid organization, heat generation, biomechanical stress, and physiological regulation across multiple levels of biological organization.

In terrestrial organisms, Earth's gravitational field establishes persistent hydrostatic gradients that influence circulation, venous return, capillary filtration, lymphatic drainage, cerebrospinal fluid dynamics, skeletal loading, and postural physiology (Guyton & Hall, 2021). These effects are particularly relevant to immune organization because immune cells, cytokines, antigens, metabolites, and inflammatory mediators are transported through blood, lymphatic, interstitial, and cerebrospinal fluid compartments. Immune function is therefore inseparable from the fluid architectures established by gravitationally regulated transport systems.

The physical basis of many of these processes may be represented by the hydrostatic relationship:

$$P = \rho g h$$

where P represents hydrostatic pressure, ρ is fluid density, g denotes gravitational acceleration, and h represents the height of the fluid column. This relationship contributes to blood pressure gradients, capillary filtration, lymphatic return, pulmonary perfusion, oedema formation, and cerebrospinal fluid distribution. Through its influence on fluid transport and tissue hydration, gravity indirectly affects leukocyte trafficking, antigen transport, inflammatory compartmentalization, and immune-cell communication (Levick & Michel, 2010).

Within the present framework, a distinction is made between extrinsic gravity and intrinsic gravitation. Extrinsic gravity refers to the external gravitational environment, including terrestrial gravity and the altered gravitational conditions encountered during spaceflight or planetary exploration. Intrinsic gravitation refers to the mass-dependent physical organization of biological structures themselves, whereby tissue mass, density, fluid content, and architectural arrangement influence local pressure distributions, thermal inertia, mechanical loading, and structural stability. Although intrinsic gravitational forces are extremely small in the classical Newtonian sense, mass organization remains biologically significant because it contributes to the physical environments within which physiological and immunological processes occur.

Microgravity provides a unique experimental setting for examining the biological significance of gravity. During spaceflight, normal terrestrial hydrostatic gradients are reduced or reorganized, producing cephalad fluid shifts, altered cardiovascular regulation, reduced mechanical loading, modifications in lymphatic transport, and measurable immune dysregulation. Astronauts exposed to prolonged microgravity exhibit altered T-cell activation, cytokine regulation, leukocyte behaviour, hematopoietic adaptation, and reactivation of latent viral infections (Crucian et al., 2018; Garrett-Bakelman et al., 2019). Such observations indicate that biological systems are not gravity-neutral and that immune homeostasis has evolved within the persistent gravito–hydraulic environment of Earth.

The implications extend beyond terrestrial physiology. In astrobiological contexts, life may emerge or persist under gravitational conditions substantially different from those of Earth, including microgravity, lunar gravity, Martian gravity, artificial gravity, or higher-gravity planetary environments. Such conditions may alter fluid distribution, tissue morphogenesis, microbial ecology, developmental pathways, metabolic organization, and immune regulation. Consequently, investigations of life beyond Earth must consider not only molecular adaptation but also the influence of gravito–thermal boundary conditions on biological organization.

An illustrative example of fluid-mediated organization is provided by the lymphatic system. Although embryologically derived from mesodermal vascular structures, the mature lymphatic network functions as a specialized low-pressure regulatory compartment linking tissue interstitial spaces with the venous circulation. Through fluid recovery, molecular transport, immune surveillance, and maintenance of tissue homeostasis, the lymphatic system demonstrates how biological function depends upon coordinated hydrostatic, biomechanical, and transport mechanisms extending beyond purely molecular regulation.

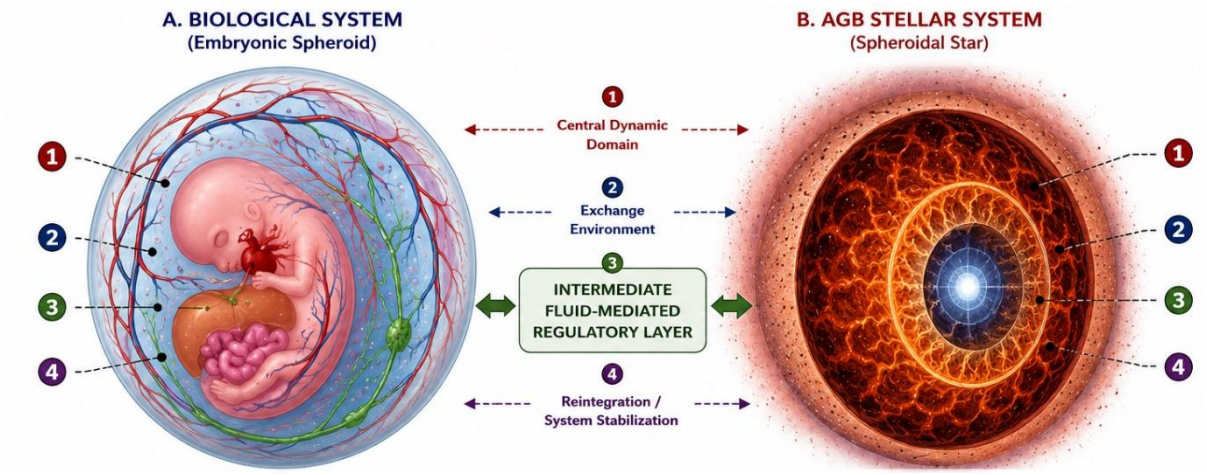

Fig. 1 Intermediate Fluid-Mediated Regulatory Layers: A Systems-Level Analogy Between Immunobiology and AGB Stellar Organization

Figure 1 presents a conceptual systems-level analogy comparing the blood–interstitium–lymph–venous continuum with the core–envelope–circumstellar organization of an asymptotic giant branch (AGB) star. The purpose of the comparison is not to suggest structural or evolutionary homology but to highlight a recurring organizational motif in which an intermediate fluid-mediated regulatory compartment occupies a position between a central dynamic domain and a peripheral exchange environment. In biological systems, this role is performed by the lymphatic network; in evolved stellar systems, a comparable systems-level role may be represented by the circumstellar envelope. Both may be viewed as transport-regulatory layers contributing to redistribution, buffering, communication, and system stabilization across very different scales of natural organization.

Within the Gravito–Thermal Immunodynamics framework, gravity is therefore interpreted as a foundational physical determinant linking mass organization, hydrostatic pressure, fluid transport, thermogenesis, tissue mechanics, and immune regulation. This perspective provides a bridge between classical immunology, physiology, space biology, and astrobiology, and establishes the physical context within which immune processes operate. The following sections examine how these principles manifest within immune tissues and their associated physiological functions.

3. Immune Tissues as Active Poroelastic Architectures

Traditionally, immune organs have been regarded primarily as sites of hematopoiesis, immune-cell maturation, antigen presentation, and immunological surveillance. However, advances in mechanobiology, tissue engineering, and systems physiology increasingly indicate that immune tissues function as dynamic fluid–solid systems whose behaviour emerges from interactions among cells, extracellular matrices, vascular networks, lymphatic pathways, and interstitial fluids (Ingber, 2006; Cowin & Doty, 2007). Such tissues exhibit many characteristics of active poroelastic materials in which deformable solid frameworks coexist with fluid-filled compartments through which cells, nutrients, cytokines, metabolites, and signalling molecules continuously circulate.

From this perspective, immune organs are not static anatomical structures but mechanically adaptive architectures that continuously respond to fluid flow, pressure gradients, tissue deformation, and cellular migration. Their functional behaviour reflects the coupling of stromal matrices, vascular and lymphatic networks, interstitial fluid dynamics, and immune-cell trafficking. Consequently, immune organization emerges not solely from molecular signalling but also from the physical microenvironments within which these signals operate. Bone marrow, lymphoid tissues, and lymphatic networks exemplify such fluid-mediated architectures. Their internal microenvironments are shaped by hydrostatic forces, fluid exchange, matrix stiffness, oxygen availability, metabolic activity, and thermal conditions, all of which influence immune-cell production, maturation, migration, and activation. Within the Gravito–Thermal Immunodynamics framework, immune tissues may therefore be interpreted as active gravito–thermo–poroelastic systems in which fluid mechanics, tissue mechanics, thermodynamics, and cellular behaviour are tightly integrated.

3.1 Bone Marrow

A Gravito–Thermal Hematopoietic Reservoir Bone marrow serves as the principal site of adult hematopoiesis and provides a specialized microenvironment for the generation, maintenance, and release of blood and immune cells. Rather than functioning merely as a cellular production site,

marrow behaves as a highly organized fluid–cellular matrix in which hematopoietic stem cells, stromal elements, vascular sinusoids, extracellular matrices, and interstitial fluids interact within a continuously regulated microenvironment (Morrison & Scadden, 2014; Méndez-Ferrer et al., 2020). Hematopoietic stem cells reside within specialized niches where vascular supply, oxygen tension, mechanical forces, and metabolic conditions influence self-renewal and lineage commitment. Sinusoidal blood vessels regulate cellular egress into the circulation, while matrix stiffness, interstitial fluid flow, and stromal-cell tension contribute to niche architecture and cellular behaviour. These interactions indicate that hematopoiesis occurs within a coupled hydro-mechanical and thermodynamic environment rather than within a purely biochemical compartment. From the perspective of Gravito–Thermal Immunodynamics, bone marrow may be viewed as a gravity-sensitive hematopoietic reservoir in which mass distribution, fluid dynamics, vascular pressures, oxygen gradients, and metabolic heat generation collectively influence immune-cell production. The biological significance of these physical factors becomes particularly evident under altered loading conditions, including aging, prolonged immobilization, bed rest, and microgravity exposure, where hematopoietic alterations and immune dysregulation have been documented (Crucian et al., 2018). Bone marrow therefore represents an important interface between tissue mechanics, fluid organization, thermodynamic regulation, and immune-cell generation.

3.2 The Lymphatic System

3.2.1 Gravity, Fluid Transport, and Immune Surveillance

The lymphatic system occupies a central position in immune organization by simultaneously regulating fluid homeostasis, antigen transport, and immune-cell trafficking. Unlike the cardiovascular system, lymphatic circulation lacks a central pump and therefore depends upon distributed mechanical forces generated by skeletal muscle contraction, respiratory pressure fluctuations, tissue compression, intrinsic lymphatic contractility, and valve-mediated unidirectional flow (Swartz, 2001). Because lymphatic transport occurs against gravitational influences, its efficiency is closely linked to hydrostatic conditions and tissue mechanics. Under normal physiological conditions, lymphatic vessels continuously return interstitial fluid, proteins, antigens, and immune cells to the circulation, thereby maintaining tissue homeostasis and supporting immune surveillance. Impairment of lymphatic drainage, whether through immobility, vascular dysfunction, obstruction, or inflammation, frequently results in oedema, altered antigen transport, impaired inflammatory resolution, and disruption of immune-cell trafficking. The lymphatic network may therefore be regarded as a distributed gravito–hydraulic system linking peripheral tissues with central lymphoid organs. Through its regulation of fluid balance and immune transport, it establishes the physical pathways through which antigen presentation, dendritic-cell migration, lymphocyte recirculation, and inflammatory clearance occur (Swartz & Lund, 2012). Observations from spaceflight further support this concept. Microgravity-induced fluid redistribution has been associated with altered lymphatic behaviour, immune dysregulation, cytokine imbalance, and viral reactivation (Crucian et al., 2018; Garrett-Bakelman et al., 2019), suggesting that normal immune function is partly dependent upon terrestrial gravito–hydraulic organization. Within the Gravito–Thermal Immunodynamics framework, the lymphatic system represents a distributed fluid-mechanical network through which gravity, hydrostatic pressure, tissue mechanics, and immune surveillance become integrated. By regulating both fluid transport and immune communication, lymphatic circulation forms a critical component of the gravito–thermal continuum underlying immune organization.

3.2.2 Immune Tissues as Gravito–Thermal Poroelastic Systems

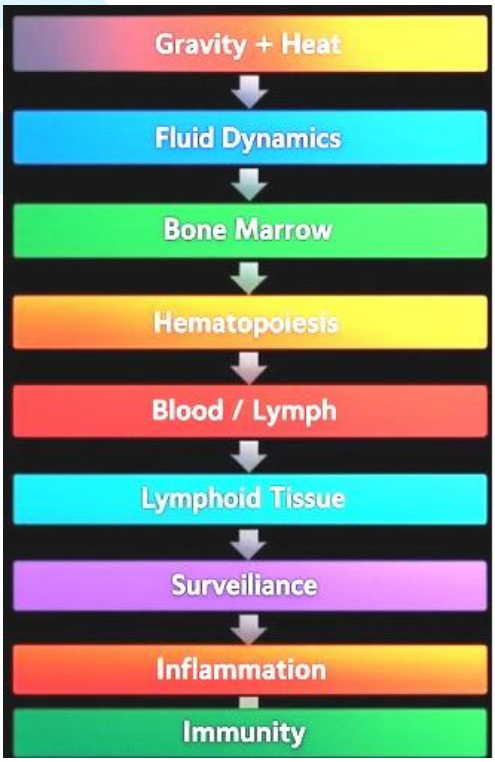

Fig. 2 Conceptual representation of immune organization across interconnected fluid-mediated levels. Gravity-dependent fluid redistribution and thermal gradients influence bone arrow function, hematopoiesis, blood and lymphatic transport, lymphoid tissue organization, immune surveillance, inflammation, and the resulting immune response

4. Inflammation as Gravito-Thermal Reorganization

Inflammation is a fundamental protective response to infection, tissue injury, toxic exposure, and other forms of cellular stress. While contemporary immunology has extensively characterized the molecular pathways governing inflammatory activation, including cytokine signalling, leukocyte recruitment, and vascular responses, inflammation also involves substantial alterations in fluid transport, tissue mechanics, hydrostatic pressures, osmotic gradients, and heat production. Consequently, inflammatory processes may be viewed not only as biochemical events but also as localized gravito-thermal reorganizations of tissue microenvironments. Following pathogen recognition or tissue injury, inflammatory mediators such as histamine, prostaglandins, bradykinin, tumour necrosis factor-alpha (TNF-alpha), and interleukins induce vasodilation, increased vascular permeability, and enhanced blood flow. These responses promote redistribution of fluids, plasma proteins, and immune cells into affected tissues while simultaneously increasing metabolic activity and local heat production (Medzhitov, 2008; Nathan, 2022). The inflammatory focus therefore becomes a dynamic region of coupled hydrostatic, osmotic, thermal, and cellular reorganization. Within the Gravito-Thermal Immunodynamics framework, inflammation may be interpreted as a process of localized gravito-thermal restructuring characterized by increased vascular permeability, fluid redistribution, osmotic influx, thermogenic activation, and immune-cell accumulation. Together, these processes modify tissue architecture and establish a specialized microenvironment that supports pathogen elimination, debris clearance, and tissue repair. The classical cardinal signs of inflammation provide a useful illustration of this physical-biological integration. Redness (rubor) reflects vasodilation and increased local perfusion. Heat (calor) arises from enhanced blood flow and elevated metabolic activity. Swelling (tumor) results from fluid accumulation within the interstitial compartment. Pain (dolor) develops through tissue distortion, nociceptor activation, and inflammatory mediators. Loss of function (functio laesa) represents the combined consequences of tissue oedema, structural disruption, altered mechanics, and protective physiological responses. Thus, the classical manifestations of inflammation emerge from the interaction of immune signalling with hydro-mechanical and thermodynamic processes operating within tissues. Inflammatory microenvironments are further characterized by changes in extracellular fluid transport. Increased vascular permeability facilitates the movement of plasma proteins, complement components, cytokines, and leukocytes into the interstitial space, altering tissue hydration, interstitial pressure, diffusion pathways, and matrix organization. These changes support immune-cell recruitment and host defence while simultaneously imposing biomechanical stresses upon affected tissues. From a systems perspective, inflammation represents an adaptive state in which molecular signalling, cellular behaviour, vascular physiology, fluid dynamics, and thermogenesis become integrated. Within this framework, gravito-thermal influences act indirectly through their effects on hydrostatic pressures, fluid distribution, tissue loading, and lymphatic drainage. The resulting inflammatory landscape therefore reflects both biological regulation and physical reorganization operating across multiple spatial scales.

4.1 Oedema Formation

Gravito-Osmotic Imbalance and Fluid Accumulation Oedema is one of the most visible manifestations of inflammation and provides a direct example of the interaction between immune activity and fluid mechanics. It develops when fluid movement from the vascular compartment into the interstitial space exceeds the capacity of lymphatic drainage and tissue reabsorption mechanisms. The resulting accumulation of interstitial fluid alters tissue architecture, increases mechanical stress, and modifies local immune microenvironments. Under normal physiological conditions, fluid exchange across capillary walls is regulated by interactions among hydrostatic pressures, oncotic forces, lymphatic drainage, and tissue compliance. Inflammatory mediators disrupt this balance by increasing vascular permeability and promoting the leakage of plasma proteins into the interstitial compartment, thereby enhancing local fluid retention (Levick and Michel, 2010). The conceptual basis of transvascular fluid exchange is commonly described by the Starling relation:

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where Jv denotes net fluid movement, *Kf* is the filtration coefficient, *Pc* and *Pi* represent capillary and interstitial hydrostatic pressures, pi c and pi i represent capillary and interstitial oncotic pressures, respectively, and sigma is the reflection coefficient. Although contemporary models incorporate endothelial glycocalyx function and revised Starling principles, the equation remains useful for conceptualizing inflammatory fluid exchange (Levick and Michel, 2010). During inflammation, increased vascular permeability, elevated local hydrostatic pressure, and altered lymphatic clearance favour fluid accumulation within tissues. The resulting swelling increases tissue tension and modifies the diffusion of oxygen, nutrients, cytokines, and immune cells, thereby

influencing both inflammatory and reparative processes. Within the Gravito-Thermal Immunodynamics framework, oedema may be interpreted as a manifestation of gravito-osmotic imbalance arising from interactions among hydrostatic forces, gravitational loading, vascular permeability, osmotic gradients, and lymphatic transport. The tendency for dependent oedema to occur in the lower extremities during heart failure, venous insufficiency, prolonged standing, or reduced mobility illustrates the continuing influence of gravity on fluid distribution. Conversely, microgravity produces substantial redistribution of body fluids and altered tissue hydration patterns. Inflammatory swelling therefore represents more than passive fluid accumulation. It reflects a dynamic reorganization of tissue hydrostatics, osmotic forces, lymphatic function, and biomechanical properties occurring within a gravity-conditioned biological environment. Oedema thus provides a clear example of how immune regulation and physical transport processes become integrated during inflammatory responses.

Inflammation as Gravito-Thermal Reorganization

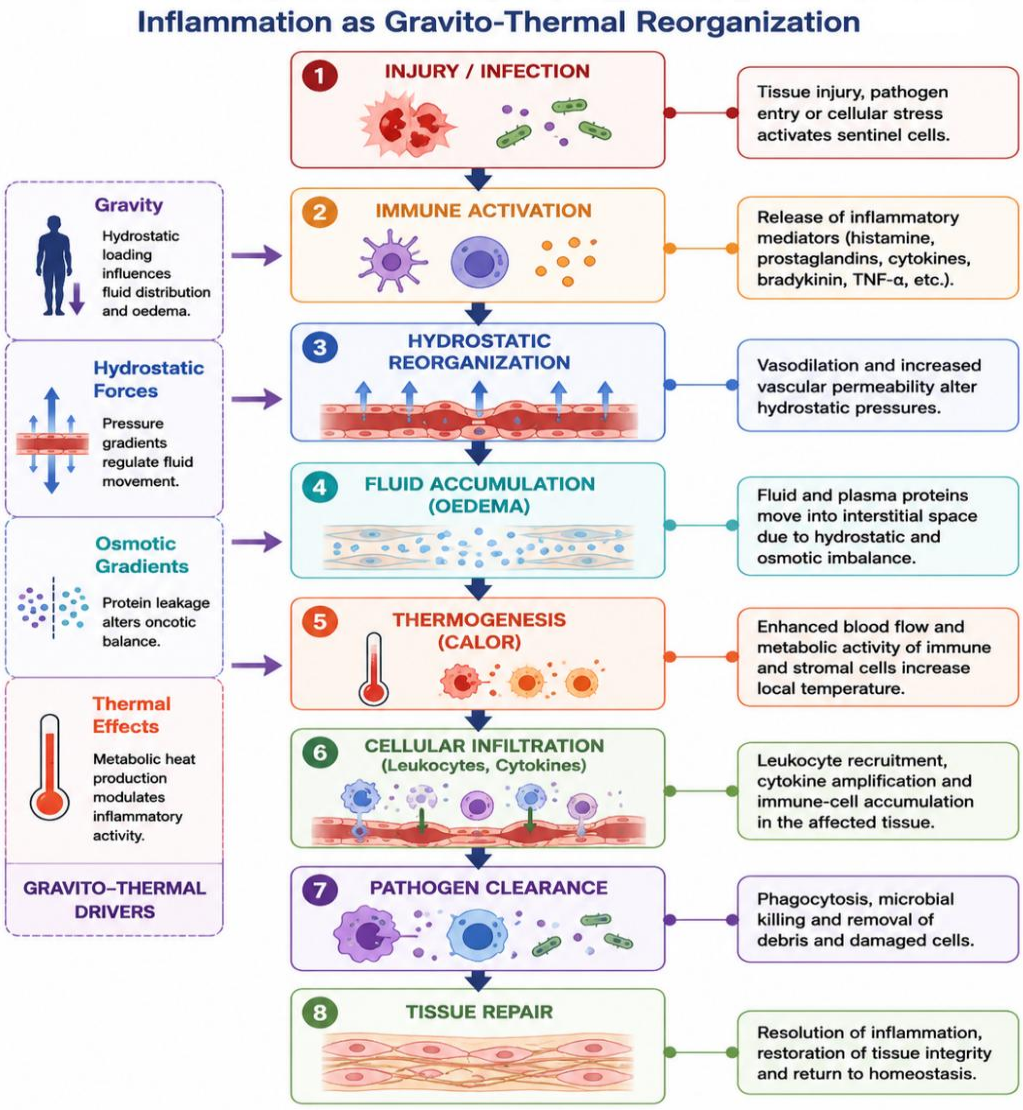

Fig. 3 Inflammatory activation induces coordinated changes in vascular permeability, fluid transport, thermogenesis, immune-cell recruitment, and tissue mechanics. The figure illustrates how hydrostatic, osmotic, thermal, and cellular processes interact to produce inflammation, oedema formation, and tissue repair within a gravito-thermal framework

5. Neuroimmunology and Cerebrospinal Fluid Dynamics

The central nervous system (CNS) was traditionally regarded as an immune-privileged organ isolated from peripheral immunity by specialized anatomical barriers. Contemporary neuroimmunology, however, has demonstrated extensive communication among neural, vascular, lymphatic, and immune systems. Immune surveillance, inflammatory signalling, waste clearance, and tissue homeostasis are now recognized as highly dynamic processes involving continuous interactions among neurons, glial cells, cerebrospinal fluid (CSF), vascular networks, and meningeal lymphatic pathways (Louveau et al., 2015; Kipnis, 2016). The CNS operates within a buoyancy-mediated cerebrospinal fluid environment that provides

mechanical support, regulates intracranial pressure, facilitates nutrient transport, and promotes metabolic waste clearance. Consequently, neuroimmune activity occurs within a continuously regulated fluid architecture shaped by CSF circulation, vascular perfusion, hydrostatic gradients, glymphatic transport, and thermal regulation. Beyond its classical mechanical role, CSF functions as an important transport medium linking neural activity, vascular physiology, and immune regulation (Iliff et al., 2012).

A major advance in neuroimmunology has been the recognition of the glymphatic system, a perivascular transport network that facilitates the clearance of metabolic waste products and inflammatory mediators from the brain. Glymphatic function depends upon CSF movement, arterial pulsations, aquaporin-4 water channels, sleep-dependent physiological states, and hydrostatic pressure gradients (Iliff et al., 2012; Nedergaard and Goldman, 2020). Efficient glymphatic transport promotes the removal of potentially neurotoxic proteins, including amyloid-beta and tau, thereby contributing to neural homeostasis and immune regulation.

Microglia, the principal resident immune cells of the CNS, continuously monitor the neural microenvironment and respond to infection, injury, and metabolic stress. Their activation is influenced not only by molecular signals but also by alterations in extracellular fluid composition, tissue swelling, oxygen availability, vascular integrity, and intracranial pressure (Kipnis, 2016). Neuroinflammatory responses therefore emerge from the interaction of immune signalling with fluid dynamics, pressure regulation, and metabolic conditions operating within the brain.

Within the Gravito-Thermal Immunodynamics framework, neuroinflammation may be interpreted as a localized gravito-hydraulic and thermodynamic reorganization of neural tissues. Inflammatory activation is frequently accompanied by altered vascular permeability, interstitial fluid accumulation, changes in intracranial pressure, local heat production, and modifications in glymphatic transport. These processes influence immune-cell communication, metabolite clearance, neuronal function, and tissue repair.

The importance of fluid-mediated regulation is particularly evident in cerebral oedema, where excess accumulation of fluid within neural tissues alters intracranial compliance and elevates intracranial pressure. Because the cranial cavity has limited capacity for expansion, relatively small increases in tissue fluid volume may generate substantial physiological consequences. Traumatic brain injury, stroke, infection, neuroinflammatory disorders, and neurodegenerative diseases frequently involve such disturbances of intracranial fluid balance (Guyton and Hall, 2021). Age-related changes further highlight the importance of neuro-fluidic regulation. Aging is associated with reduced CSF turnover, altered intracranial compliance, ventricular enlargement, diminished glymphatic efficiency, and impaired lymphatic drainage. These changes may compromise the clearance of inflammatory mediators and neurotoxic metabolites, thereby contributing to chronic neuroinflammation and neurodegeneration (Nedergaard and Goldman, 2020).

Evidence from spaceflight studies provides additional support for the role of fluid dynamics in neuroimmune regulation. Prolonged exposure to microgravity produces cephalad fluid shifts, altered CSF distribution, changes in intracranial pressure dynamics, structural brain adaptations, and measurable immune alterations (Roberts et al., 2017; Garrett-Bakelman et al., 2019). These findings suggest that neuroimmune homeostasis has evolved within the hydrostatic environment established by terrestrial gravity and may be sensitive to altered gravito-hydraulic conditions.

Within the present framework, the CNS may therefore be viewed as an active neuro-fluidic immune environment in which immune regulation emerges from interactions among neural tissues, CSF circulation, glymphatic transport, vascular physiology, hydrostatic forces, and thermodynamic processes. This perspective complements established molecular models of neuroimmunology by emphasizing the importance of fluid transport, pressure regulation, and buoyancy-mediated tissue organization in shaping neuroimmune behaviour.

Gravito-Hydraulic Organization of Neuroimmune Function

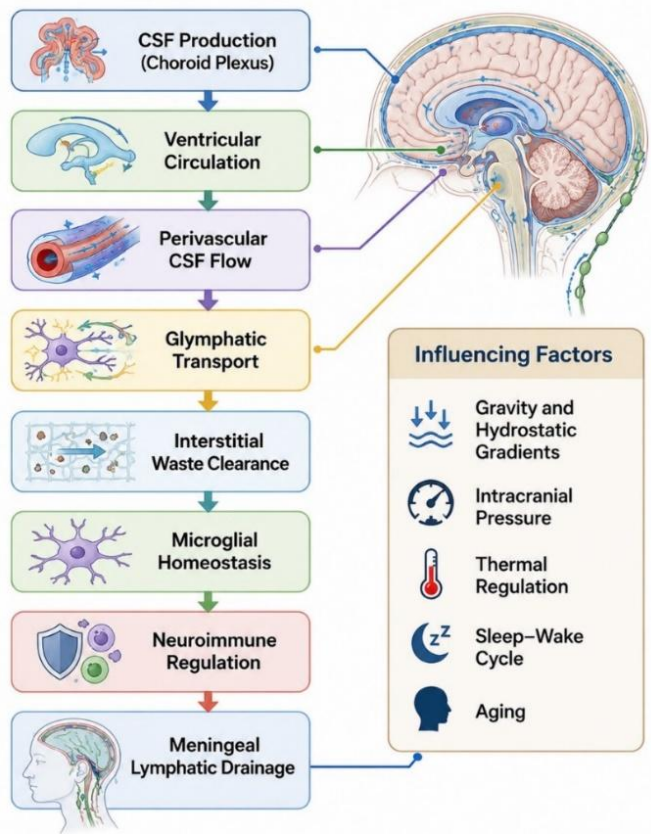

Fig. 4 CSF circulation, glymphatic transport, waste clearance, microglial homeostasis, and neuroimmune regulation operate within a fluid-mediated environment influenced by hydrostatic gradients, intracranial pressure, thermal regulation, aging, and gravity-dependent fluid dynamics. The figure illustrates the proposed coupling of neural, immune, and fluid-transport processes within a gravito-hydraulic framework

6. Fever as Systemic Thermal Coordination

Fever is one of the most conserved physiological responses to infection and inflammation and represents a highly regulated adaptive mechanism rather than a passive consequence of disease. Contemporary research has shown that fever involves coordinated interactions among the immune, nervous, endocrine, vascular, and metabolic systems, resulting in a temporary elevation of body temperature that enhances host defence and supports pathogen control (Evans et al., 2015; Kluger, 2015). The febrile response is initiated when endogenous pyrogens, particularly interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and prostaglandin E2 (PGE2), act upon hypothalamic thermoregulatory centres. These signals elevate the hypothalamic thermal set point and trigger coordinated physiological responses including vasomotor adjustments, shivering thermogenesis, metabolic activation, and behavioural adaptations (Dinarello and Gelfand, 2001). The resulting increase in body temperature establishes a temporary thermodynamic state optimized for immune activity. Within the Gravito-Thermal Immunodynamics framework, fever may be interpreted as a systemic thermal coordination mechanism that reorganizes the physical environment in which immune responses occur. Elevated temperature increases molecular mobility, accelerates enzymatic reactions, modifies fluid properties, and enhances cellular metabolism. These changes influence the transport of cytokines, antibodies, complement proteins, nutrients, and metabolites throughout vascular and interstitial compartments, thereby improving the efficiency of immune communication and host defence. Fever also exerts direct effects on immune-cell behaviour. Moderate elevations in temperature have been shown to enhance leukocyte trafficking, strengthen lymphocyte-endothelial interactions, improve dendritic-cell function, and facilitate antigen presentation (Mace et al., 2011). Consequently, fever acts not merely as a marker of inflammation but as a systemic coordinator of immune kinetics that promotes interactions between innate and adaptive immune responses. Temperature-dependent changes additionally influence vascular physiology and fluid transport. Increased temperature alters vascular tone, reduces fluid viscosity, and enhances tissue perfusion, thereby facilitating the delivery of immune cells and soluble defence factors to sites of infection. Such changes demonstrate the close relationship among thermoregulation, circulation, and immune function. The antimicrobial benefits of fever are equally important. Many viruses, bacteria, and other pathogens replicate optimally within narrow temperature ranges and exhibit reduced growth efficiency under febrile conditions. Simultaneously, elevated temperatures enhance multiple host-defence mechanisms, creating a physiological environment that favours immune function over pathogen survival (Kluger, 2015). From a gravito-thermal perspective, fever may also be viewed as a systemic reorganization of fluid transport and energy distribution. Changes in vascular tone, tissue perfusion, hydrostatic relationships, and lymphatic transport influence the movement of heat, immune mediators, and metabolic substrates throughout the body. Consequently, fever represents not only a thermal event but also a coordinated reconfiguration of circulatory and fluid-dynamic processes occurring within a gravity-conditioned biological system. Viewed in this manner, fever emerges as a multiscale adaptive response integrating neuroendocrine regulation, immune signalling, thermodynamics, vascular physiology, and fluid mechanics. Within the Gravito-Thermal Immunodynamics framework, it occupies a central position linking energy metabolism, heat distribution, fluid transport, and immune organization during host defence.

7. Microgravity and Space Immunology

Spaceflight provides a unique natural experiment for examining the relationship between gravity and immune function. Unlike terrestrial physiology, which operates within a relatively constant gravitational field, microgravity profoundly alters fluid distribution, hydrostatic gradients, tissue loading, cardiovascular regulation, and cellular behaviour.

Studies conducted during short- and long-duration missions have consistently demonstrated measurable alterations in immune competence, providing some of the strongest evidence that immune organization is influenced not only by molecular mechanisms but also by gravity-dependent physical environments (Crucian et al., 2018; Garrett-Bakelman et al., 2019). One of the most consistent findings in space immunology is impaired immune-cell function. Astronauts exposed to microgravity exhibit altered T-cell activation, reduced lymphocyte responsiveness, changes in cytokine production, and modifications in inflammatory signalling pathways (Frippiat et al., 2016).

Long-duration missions are also associated with immune dysregulation and increased reactivation of latent viruses, including Epstein-Barr virus, varicella-zoster virus, and cytomegalovirus, suggesting altered immune surveillance under spaceflight conditions (Mehta et al., 2017).

Fever as Systemic Gravito–Thermal Coordination

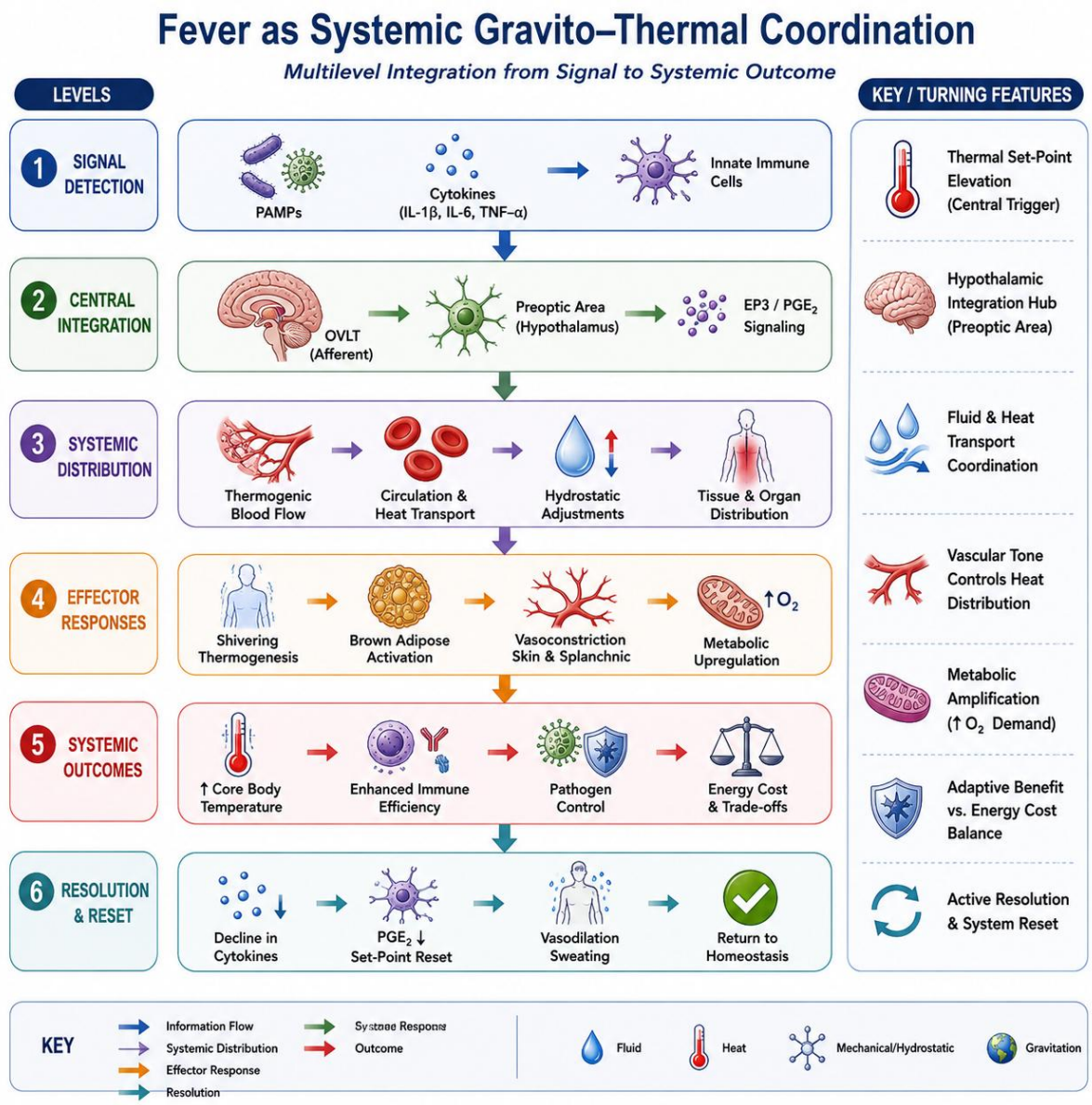

Fig. 5 Fever is depicted as a coordinated adaptive response linking immune activation, hypothalamic thermoregulation, thermogenesis, fluid redistribution, and enhanced immune function. Infection-induced cytokines elevate the hypothalamic thermal set point, producing systemic thermal and circulatory adjustments that improve immune efficiency, pathogen control, and physiological recovery

These immune alterations are accompanied by broader physiological changes. Microgravity induces cephalad fluid shifts and substantially reduces the hydrostatic gradients normally present under terrestrial gravity. As a consequence, vascular pressures, interstitial fluid distribution, lymphatic transport, and tissue hydration are altered throughout the body (Hargens and Vico, 2016). Because immune-cell trafficking, antigen transport, and inflammatory clearance depend upon these fluid-mediated systems, disruption of normal gravito-hydraulic organization may contribute significantly to immune dysfunction during spaceflight. Bone marrow and lymphatic tissues may be particularly affected.

Prolonged microgravity is associated with changes in bone metabolism, marrow physiology, and circulating immune-cell populations. Similarly, altered fluid loading conditions may influence lymphatic transport, antigen delivery, and immune-cell migration. Although the precise mechanisms remain incompletely understood, these observations suggest that immune homeostasis is partly dependent upon the hydro-mechanical and fluid-dynamic conditions established by Earth's gravitational environment (Crucian et al., 2018).

Microgravity also reduces mechanical loading throughout the musculoskeletal system, altering mechanotransductive signalling pathways that influence endothelial cells, stromal cells, extracellular matrices, and immune cells. These biomechanical adaptations may further contribute to altered immune regulation during prolonged missions.

Within the Gravito-Thermal Immunodynamics framework, the physiological changes observed during

spaceflight may be interpreted as consequences of disrupted gravito-hydraulic organization. Reduced gravitational loading alters hydrostatic pressure distributions, fluid transport, tissue mechanics, and vascular-lymphatic interactions that normally support immune homeostasis. Consequently, immune dysregulation under microgravity provides indirect evidence that terrestrial immunity has evolved within a persistent gravito-thermal environment in which fluid dynamics, mechanical forces, and metabolic organization remain tightly coupled. Beyond astronaut health, these findings have broader implications for space biology and astrobiology. By revealing the consequences of altered gravity on fluid organization, tissue function, and immune regulation, spaceflight research offers valuable insight into the physical foundations of immunity and highlights the importance of gravito-hydraulic processes in biological organization.

Microgravity-Induced Alterations in Immune Organization

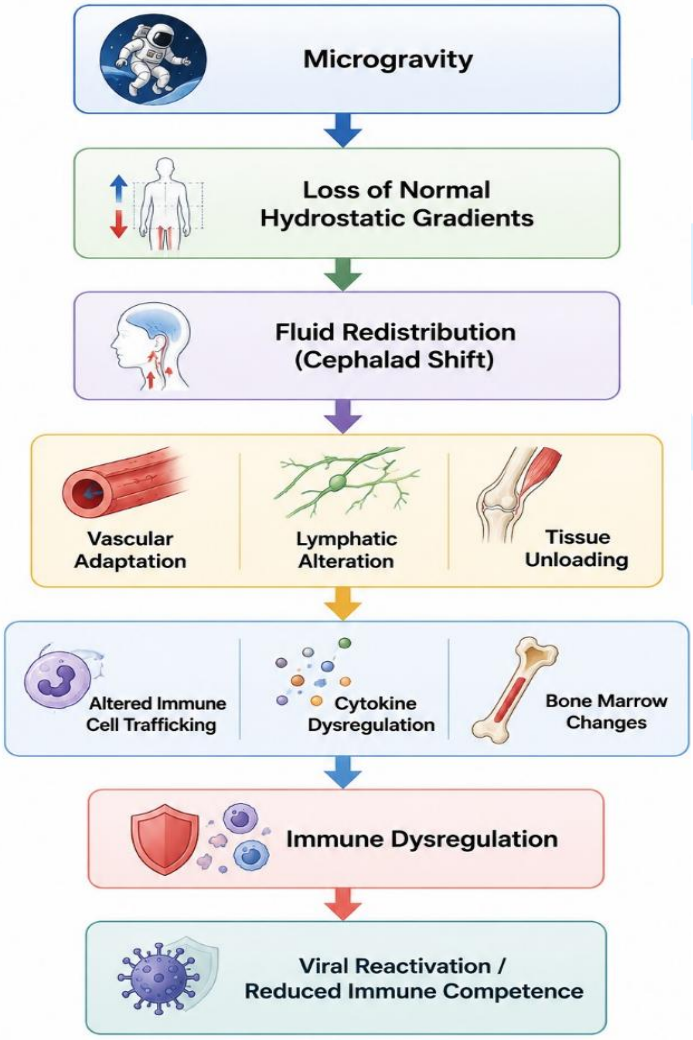

Fig. 6 Microgravity reduces normal hydrostatic gradients and produces cephalad fluid redistribution, vascular adaptation, altered lymphatic transport, tissue unloading, and immune dysregulation. The figure summarizes the proposed gravito-hydraulic pathway linking altered fluid organization with impaired immune competence and viral reactivation during spaceflight

8. Cancer Immunology Under Gravito-Thermal Constraints

Cancer is traditionally understood as a disease driven by genetic mutations, dysregulated signalling pathways, uncontrolled cellular proliferation, and immune evasion. Increasing evidence, however, indicates that tumour progression is also strongly influenced by the physical characteristics of the tumour microenvironment, including vascular architecture, fluid transport, mechanical stress, metabolic reprogramming, and chronic inflammation (Hanahan, 2022; Jain, 2014). Consequently, tumour biology may be viewed as the interaction of molecular, cellular, biomechanical, and thermodynamic processes operating within a continuously evolving tissue ecosystem. A defining feature of malignant tissues is the development of abnormal microenvironments that differ substantially from surrounding healthy tissues. Tumours frequently exhibit heterogeneous perfusion, altered oxygenation, elevated metabolic activity, and localized thermal variation arising from increased glucose consumption, inflammatory activity, and vascular irregularity (Vaupel et al., 2019). These conditions influence cellular metabolism, immune-cell behaviour, and therapeutic response. Tumour-associated vasculature is typically irregular, highly permeable, and inefficiently organized. As a consequence, many solid tumours develop regions of hypoxia, acidosis, and metabolic stress together with elevated interstitial fluid pressure (Jain, 2014). Dysfunctional lymphatic drainage, increased extracellular matrix deposition, and vascular leakage promote fluid accumulation within the tumour microenvironment, creating conditions of interstitial hypertension that impair transport processes and restrict tissue perfusion (Heldin et al., 2004). Within the Gravito-Thermal Immunodynamics framework, the tumour microenvironment may be interpreted as an abnormal gravito-thermo-poroelastic system composed of tumour cells, stromal elements, extracellular matrices, vascular networks, immune cells, and interstitial fluids. Continuous interactions among these components generate localized hydrostatic, thermal, osmotic, and mechanical conditions that influence tumour growth and immune regulation. One consequence of these altered physical conditions is the formation of immune exclusion zones. In many solid tumours, cytotoxic lymphocytes accumulate at the tumour periphery but fail to penetrate deeply into the tumour mass. While molecular mechanisms such as checkpoint signalling and immunosuppressive cytokines contribute to this phenomenon, physical barriers including elevated interstitial pressure, dense extracellular matrices, abnormal fluid flow, and tissue stiffness may also restrict immune-cell infiltration (Joyce and Fearon,

2015). These same physical barriers influence therapeutic delivery. Increased tissue pressure, vascular compression, fluid stagnation, and extracellular matrix density reduce the penetration of anticancer drugs, antibodies, nanoparticles, and immune-based therapies, thereby contributing to therapeutic resistance (Jain, 2014). Impaired transport similarly affects the movement of immune cells, inflammatory mediators, oxygen, and metabolic substrates throughout the tumour microenvironment. Chronic inflammation further reinforces these abnormalities. Tumour-associated macrophages, neutrophils, myeloid-derived suppressor cells, and regulatory T cells modify the local environment through cytokine secretion, angiogenesis, extracellular matrix remodelling, and metabolic reprogramming (Hanahan, 2022). These activities establish self-sustaining feedback loops linking inflammation, vascular dysfunction, tissue mechanics, and tumour progression. From a gravito-thermal perspective, cancer may therefore be interpreted as a disorder of both biological regulation and physical organization. Altered thermal gradients, elevated interstitial pressures, disrupted fluid transport, impaired lymphatic clearance, and mechanically distorted tissue architectures collectively influence immune surveillance, inflammatory responses, therapeutic delivery, and metastatic potential. Tumour-associated immune dysfunction thus reflects not only molecular dysregulation but also the emergence of a pathological gravito-thermal state characterized by coupled disturbances in fluid mechanics, thermodynamics, tissue biomechanics, and immune function. This interpretation does not diminish the central role of genetic and molecular mechanisms in oncogenesis. Rather, it emphasizes that tumour evolution occurs within a dynamic physical environment that actively shapes immune responses and disease progression. Integrating cancer immunology with concepts from fluid mechanics, poroelasticity, thermodynamics, and tissue biomechanics may therefore provide a broader framework for understanding tumour behaviour and for improving therapeutic strategies.

The tumour microenvironment may be regarded as a poroelastic fluid–solid system in which interstitial fluid pressure, extracellular matrix mechanics, vascular permeability, and cellular proliferation interact to influence transport, immune-cell infiltration, and therapeutic delivery (Heldin et al., 2004; Jain, 2014; Stylianopoulos & Jain, 2013).

Tumour Microenvironment as a Gravito–Thermo–Poroelastic System

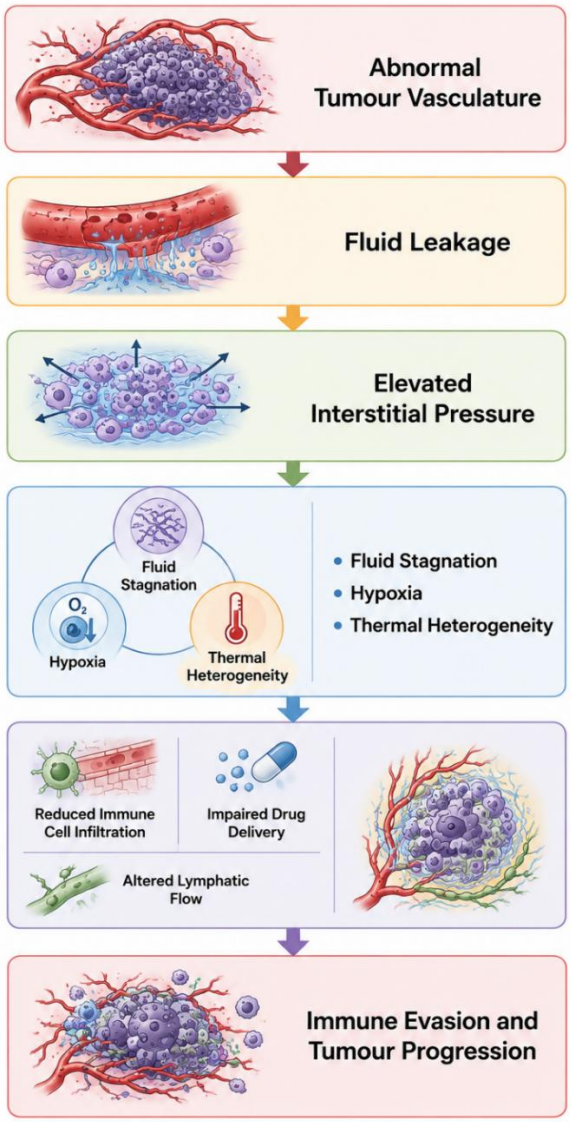

Fig. 7 Abnormal tumour vasculature promotes fluid leakage and elevated interstitial pressure, leading to fluid stagnation, hypoxia, thermal heterogeneity, impaired immune-cell infiltration, altered lymphatic transport, and tumour progression. The figure illustrates the coupling of vascular, mechanical, thermal, and immune processes within the tumour microenvironment

9. Embryogenesis and Developmental Immunodynamics

The immune system originates during embryogenesis within highly regulated fluid environments characterized by buoyancy, osmotic balance, thermal stability, morphogen transport, and hydrostatic organization. Within these environments, cellular differentiation, tissue patterning, vascular development, and immune ontogeny emerge through coordinated interactions among genetic programs, biochemical signalling pathways, and physical developmental processes (Gilbert, 2023; Ginhoux and Guilliams, 2016). Consequently, immune development may be viewed not solely as a molecular phenomenon

but also as a process embedded within evolving fluid-mediated and gravito-thermal architectures.

Early embryonic development occurs within protected aqueous compartments that provide mechanical support, facilitate nutrient exchange, regulate osmotic conditions, and enable the transport of developmental signals. Morphogen gradients, growth factors, ions, and metabolites establish spatial patterns that guide lineage specification and organogenesis. These processes depend fundamentally upon diffusion, fluid transport, and the physical organization of developing tissues (Gilbert, 2023). The emergence of the immune system is closely linked to these developmental fluid environments.

Primitive hematopoiesis first arises within the yolk sac, generating early macrophage and erythroid populations. Definitive hematopoietic stem cells subsequently emerge within the aorta-gonad-mesonephros region before colonizing the fetal liver and later the developing bone marrow (Orkin and Zon, 2008). Throughout these transitions, hematopoietic progenitors migrate through vascular and fluid-mediated environments while progressively establishing the foundations of immune architecture. The development of blood vessels, bone marrow, thymus, and lymphatic networks creates the principal transport and regulatory systems upon which postnatal immunity depends. Hemodynamic forces, vascular flow patterns, and tissue-fluid interactions contribute to vascular maturation, endothelial differentiation, and hematopoietic niche formation. Simultaneously, thymic development and lymphatic differentiation establish specialized microenvironments for immune-cell maturation, trafficking, and surveillance. Recent advances in developmental immunology have demonstrated that several tissue-resident immune populations originate during embryogenesis and persist throughout life. Microglia, Kupffer cells, Langerhans cells, and multiple macrophage populations are established during fetal development and subsequently assume long-term roles in tissue homeostasis and immune regulation (Ginhoux and Guilliams, 2016). Their developmental origins highlight the importance of embryonic environments in shaping lifelong immune function. From a gravito-thermal perspective, embryogenesis represents the earliest stage of immune organization within a fluid-mediated developmental continuum. Hydrostatic forces, fluid transport, thermal regulation, tissue mechanics, and mass-dependent organization contribute to the physical context within which hematopoietic tissues, vascular systems, thymic structures, and lymphatic pathways emerge.

Developmental Immunodynamics within Embryonic Gravito–Thermal Environments

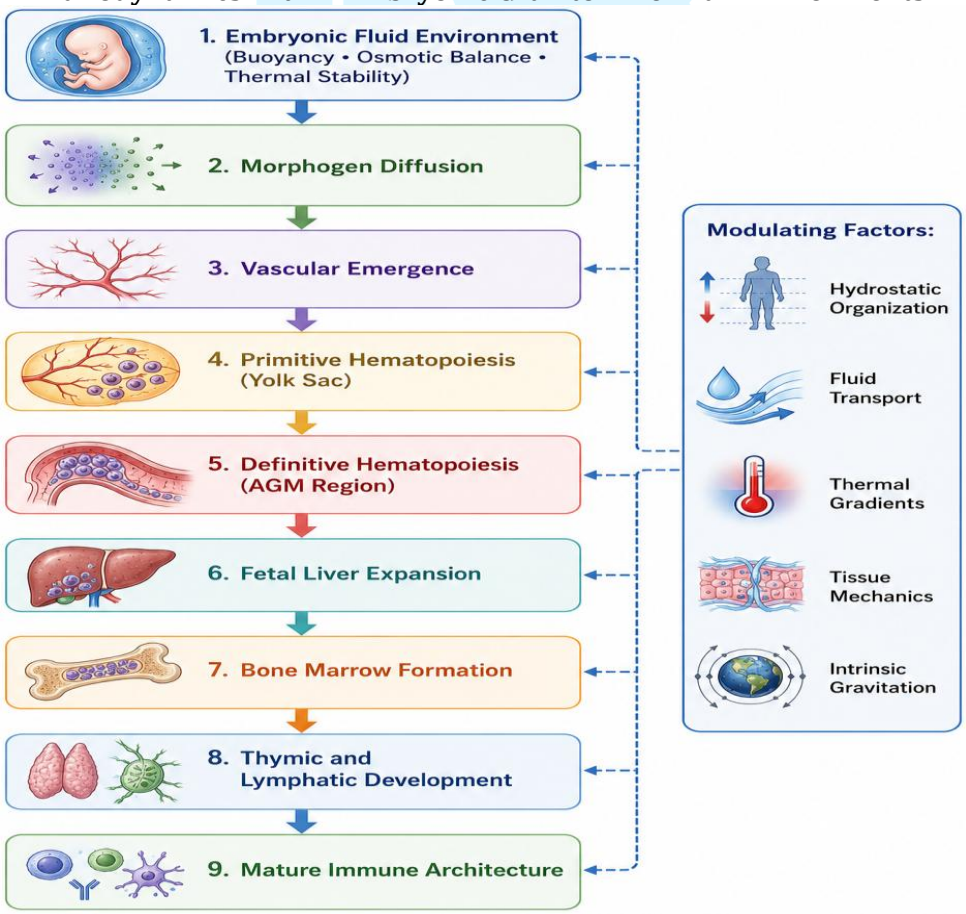

Fig. 8 Embryonic fluid environments support morphogen transport, vascular emergence, hematopoiesis, thymic development, and lymphatic differentiation. The figure illustrates how hydrostatic organization, fluid transport, thermal regulation, tissue mechanics, and mass-dependent structure contribute to the emergence of immune architecture during development

Experimental observations under altered gravity conditions further suggest that developmental processes, including cellular differentiation, cytoskeletal organization, gene expression, and tissue morphogenesis, may exhibit sensitivity to gravitational influences (Sajdel-Sulkowska, 2008). Within the Gravito-Thermal Immunodynamics framework, immune ontogeny may therefore be interpreted as a process occurring within coordinated hydrostatic, osmotic, thermal, and biomechanical environments that guide tissue assembly and functional maturation. This perspective complements established genetic and molecular models by emphasizing the role of physical organization in shaping immune architecture from its earliest developmental origins.

10. Aging and Immune Senescence

Aging is accompanied by progressive changes in the immune, vascular, lymphatic, nervous, and musculoskeletal systems that collectively contribute to declining immune competence, commonly referred to as immunosenescence. Traditional explanations emphasize molecular and cellular mechanisms including genomic instability, telomere shortening, mitochondrial dysfunction, stem-cell exhaustion, epigenetic alterations, and chronic inflammatory signalling. However, aging is also associated with substantial changes in tissue mechanics, fluid distribution, vascular function, thermoregulation, and organ architecture that may influence immune function in parallel with these molecular processes (Nikolich-Zugich, 2018; Fulop et al., 2023). With advancing age, tissues undergo progressive alterations in elasticity, hydration, extracellular matrix composition, and structural organization. Simultaneously, changes in body composition modify the distribution of water, adipose tissue, and lean mass. These adaptations influence tissue perfusion, fluid transport, oxygen delivery, and immune-cell trafficking, thereby altering the physical microenvironments within which immune responses occur.

One of the most significant age-related changes is the decline in vascular and lymphatic efficiency. Arterial stiffening, endothelial dysfunction, reduced microvascular adaptability, and impaired lymphatic pumping diminish the delivery of immune cells, nutrients, and oxygen while reducing the clearance of inflammatory mediators and metabolic waste products (Lakatta and Levy, 2003; Da Mesquita et al., 2018). These changes contribute to reduced immune surveillance, delayed tissue repair, oedema formation, and impaired resilience to physiological stress. Thermoregulatory capacity also declines with age.

Older individuals frequently exhibit diminished heat generation, altered vascular responsiveness, and reduced febrile responses during infection (Castle, 2000). Such changes may impair immune activation and contribute to the atypical clinical presentation of infectious diseases in elderly populations.

A hallmark of aging is the development of chronic low-grade inflammation, often termed inflammaging. Persistent elevations in pro-inflammatory cytokines, oxidative stress, and innate immune activation contribute to tissue dysfunction and age-related disease (Franceschi et al., 2018). In addition to molecular factors, impaired lymphatic drainage, reduced glymphatic transport, and diminished fluid-mediated clearance mechanisms may facilitate the accumulation of inflammatory mediators within aging tissues. Age-related changes are particularly evident within the nervous system.

Reduced cerebrospinal fluid turnover, impaired glymphatic clearance, and altered intracranial compliance decrease the removal of metabolic waste products and inflammatory signals from neural tissues, potentially contributing to chronic neuroinflammation and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Nedergaard and Goldman, 2020).

From the perspective of Gravito-Thermal Immunodynamics, immunosenescence may be interpreted as a progressive reorganization of the body's gravito-thermal architecture. Aging alters tissue mechanics, vascular and lymphatic transport, fluid distribution, thermoregulatory efficiency, and biomechanical responsiveness, thereby modifying the physical environments within which immune processes operate. These changes influence immune-cell trafficking, inflammatory regulation, waste clearance, tissue repair, and host defence across multiple organ systems. This interpretation does not replace established molecular theories of aging but complements them by emphasizing the interaction between biological and physical processes. Integrating concepts from immunology, fluid physiology, biomechanics, thermodynamics, and aging biology may therefore provide a broader framework for understanding immune decline and promoting healthy aging.

Aging, Fluid Architecture, and Immune Senescence

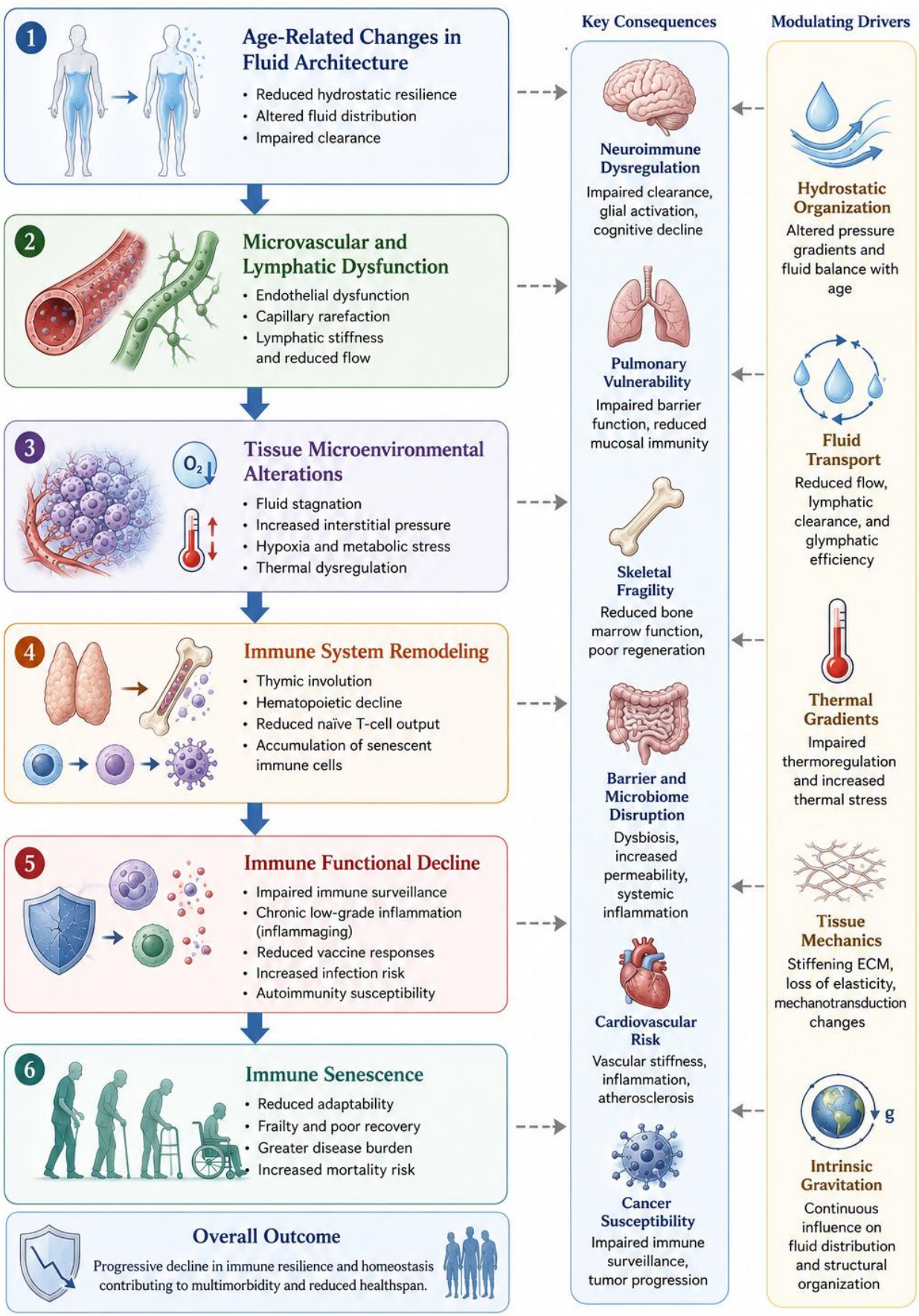

Fig. 9 Age-associated changes in vascular function, lymphatic transport, tissue mechanics, thermoregulation, and fluid distribution contribute to chronic inflammation, impaired immune surveillance, reduced repair capacity, and progressive immune decline. The figure illustrates the proposed gravito-thermal pathway linking physical aging processes with immunosenescence

11. Toward a Unified Physical Layer of Immunology

Modern immunology has achieved remarkable success in elucidating the molecular foundations of immune function, including antigen recognition, cytokine signalling, cellular differentiation, immune memory, and host-pathogen interactions. However, immune processes do not occur in isolation from their physical environment. Every immune response unfolds within tissues characterized by fluid movement, pressure gradients, thermal exchanges, biomechanical constraints, and mass-dependent structural organization. A comprehensive understanding of immunity may therefore require integration of both biological and physical perspectives.

The Gravito-Thermal Immunodynamics framework proposes that immune function emerges from the continuous interaction of molecular signalling networks with fluid mechanics, thermodynamic regulation, hydrostatic organization, tissue biomechanics, and mass-dependent architecture. Within this view, immune processes are embedded within dynamic physical environments that influence the transport, distribution, activation, and coordination of immune components throughout the organism.

The preceding sections have illustrated how hydrostatic forces influence vascular perfusion, lymphatic transport, oedema formation, and leukocyte trafficking; how thermogenesis contributes to inflammation and fever; how cerebrospinal fluid and glymphatic pathways participate in neuroimmune regulation; how microgravity alters immune competence; and how tumour progression, embryonic development, and immune aging are influenced by fluid-mediated and biomechanical environments. Collectively, these observations suggest that immune organization depends not only upon molecular information but also upon the physical architectures within which biological processes occur.

Within this framework, immunity may be interpreted as a multiscale adaptive system operating across molecular, cellular, tissue, organ, organismal, and environmental levels. At the molecular level, immune responses are governed by signalling pathways, receptor interactions, metabolism, and gene regulation. At the cellular level, immune cells continuously respond to chemical gradients, mechanical forces, thermal conditions, and fluid flows. At the tissue level, vascular networks, extracellular matrices, interstitial compartments, and lymphatic pathways establish the physical environments that shape immune behaviour. At the organismal level, circulation, thermoregulation, fluid transport, and pressure gradients integrate local immune responses into coordinated systemic function.

A central feature of the present framework is the concept of intrinsic gravitation, which extends the traditional recognition of external gravity as a determinant of circulation and fluid distribution. The model proposes that mass-dependent organization contributes to biological architecture through its influence on hydrostatic regulation, fluid transport, thermogenesis, tissue mechanics, and structural stability.

Although many aspects of these relationships remain theoretical and require experimental validation, they provide a potential physical context for interpreting diverse observations spanning inflammation, neuroimmunology, cancer biology, developmental immunology, aging, and space medicine. Importantly, the proposed framework does not seek to replace established molecular immunology. Cytokine signalling, antigen presentation, immune-cell activation, gene regulation, and cellular differentiation remain fundamental determinants of immune function. Rather, Gravito-Thermal Immunodynamics proposes an additional physical layer that continuously interacts with these molecular processes.

Understanding the reciprocal relationships between biological signalling and physical organization may provide a more complete systems-level interpretation of immunity. The framework also encourages greater integration among immunology, biophysics, mechanobiology, systems biology, thermodynamics, vascular physiology, neurobiology, and space medicine. Advances in imaging, computational modelling, biomechanics, fluid dynamics, and systems analysis increasingly permit the investigation of immune phenomena beyond purely molecular scales.

Such interdisciplinary approaches may reveal previously unrecognized mechanisms linking physical organization with immune behaviour. From this perspective, immunity may be viewed as a dynamic gravito-thermal-hydraulic system integrating molecular information, metabolic energy, fluid transport, tissue mechanics, and environmental interactions. The resulting model offers a conceptual bridge between molecular immunology and systems biophysics and may prove useful for understanding chronic inflammation, oedema, neurodegeneration, immune aging, cancer progression, altered immunity during spaceflight, and developmental immune organization. Ultimately, the Gravito-Thermal Immunodynamics framework is intended as a conceptual synthesis rather than a definitive theory. Its central proposition is that immune organization emerges from continuous interactions between biological information and physical structure across multiple scales of organization. By recognizing the complementary roles of molecular signalling, fluid mechanics, thermodynamics, tissue biomechanics,

and gravito-hydraulic regulation, a broader understanding of immune function may emerge and stimulate future interdisciplinary investigation.

Gravito–Thermal Immunodynamics: A Unified Physical Layer of Immunity

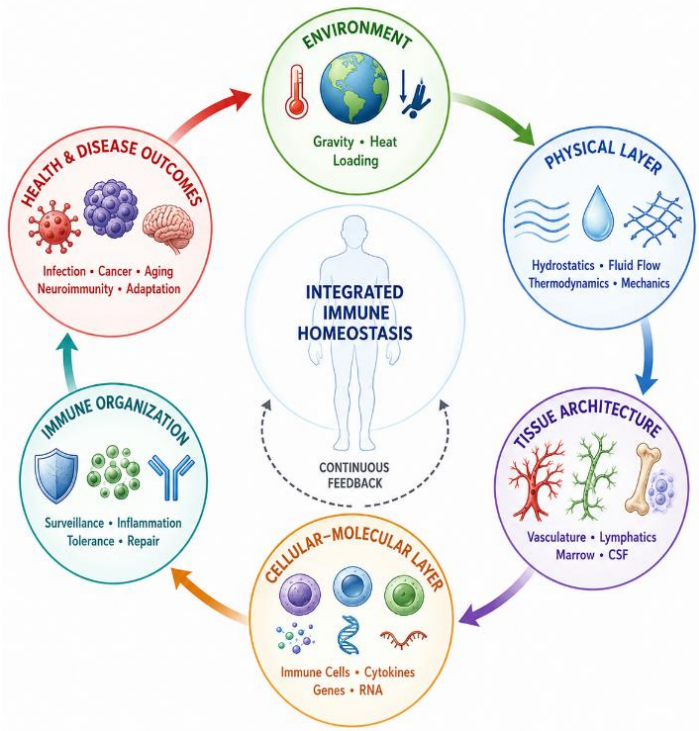

Fig. 10 The figure summarizes immunity as a multiscale system integrating molecular regulation, fluid transport, thermodynamics, tissue mechanics, hydrostatic organization, and environmental influences. Interactions among these biological and physical processes collectively shape immune function, adaptation, disease progression, and physiological homeostasis

12. Gravito-Thermal Immunodynamics in the Context of Modern Immunology

Over the past two decades, immunology has progressively evolved from a discipline focused primarily on cellular and molecular mechanisms toward a broader systems-level understanding incorporating tissue microenvironments, metabolism, RNA regulation, biomechanics, and multicellular organization. Several landmark discoveries recognized by Nobel Prizes have contributed to this transition and provide a useful context for evaluating the present Gravito-Thermal Immunodynamics framework.

The 2011 Nobel Prize in Physiology or Medicine, awarded for discoveries concerning dendritic cells and Toll-like receptor-mediated innate immunity, established the central importance of environmental sensing in immune regulation (Steinman, 2012). Although these discoveries were primarily molecular in nature, innate immune activation is invariably accompanied by vascular adaptation, fluid redistribution, leukocyte migration, and local thermogenic responses, linking molecular recognition to tissue-level physiological reorganization.

The 2018 Nobel Prize for immune checkpoint inhibition demonstrated how tumour immunity is regulated through pathways such as CTLA-4 and PD-1 (Allison, 2015; Honjo, 2017). Subsequent studies have shown that tumour responses are influenced not only by immune signalling but also by interstitial pressure, vascular architecture, hypoxia, extracellular matrix organization, and fluid transport. These findings highlight the importance of the physical microenvironment in shaping immune outcomes.

The 2023 Nobel Prize recognizing mRNA vaccine technology further emphasized the importance of dynamic immune programming through RNA-mediated mechanisms. Effective immune responses require coordinated interactions among antigen transport, lymphatic circulation, cellular uptake, inflammatory signalling, and tissue transport systems. The success of mRNA vaccines illustrates the close integration of molecular information with physiological transport networks.

Similarly, the 2024 Nobel Prize for the discovery of microRNA revealed an additional regulatory layer controlling immune differentiation, inflammation, antiviral responses, and immune tolerance. MicroRNA expression is influenced by metabolic state, oxidative stress, hypoxia, thermal stress, and mechanical stimuli, indicating that gene regulation itself may be responsive to broader physiological and biophysical conditions.

Collectively, these advances reflect an increasing recognition that immune function is dynamic, context-dependent, and integrated across multiple levels of biological organization. The Gravito-Thermal Immunodynamics framework does not challenge these molecular discoveries. Rather, it proposes that the mechanisms identified by modern immunology operate within a broader physical continuum characterized by fluid transport, hydrostatic gradients, thermodynamic regulation, tissue biomechanics, vascular organization, lymphatic circulation, and environmental loading.

From this perspective, immunity may be viewed as a coupled physical-biological system in which molecular signalling, RNA regulation, cellular behaviour, and tissue architecture interact continuously with fluid dynamics, heat generation, pressure gradients, and biomechanical constraints. Such an interpretation provides a conceptual bridge linking molecular immunology with mechanobiology, neuroimmunology, cancer biology, developmental immunology, aging research, systems biology, and space medicine.

Rather than replacing established paradigms, Gravito-Thermal Immunodynamics seeks to complement contemporary immunology by emphasizing the physical environments within which

immune processes occur. In doing so, it offers a potential framework for integrating molecular regulation with the fluid, thermal, mechanical, and gravitational contexts that contribute to immune organization across multiple scales.

13. Conclusion

Modern immunology has provided profound insights into the molecular mechanisms governing immune recognition, signalling, regulation, and memory. The present synthesis proposes that these processes operate within a broader physical environment shaped by fluid dynamics, hydrostatic pressures, thermodynamic gradients, vascular transport, lymphatic circulation, tissue mechanics, and mass-dependent biological organization. Immune function therefore emerges not only from biochemical communication but also from the physical conditions that influence the transport, distribution, activation, and coordination of immune components throughout the organism.

The Gravito-Thermal Immunodynamics framework introduced in this article seeks to integrate these biological and physical dimensions into a unified conceptual perspective. Across multiple levels of organization, fluid transport, thermogenesis, pressure gradients, tissue architecture, and gravity-dependent physiological processes appear to influence immune behaviour. Inflammation, fever, oedema formation, lymphatic transport, neuroimmune regulation, hematopoiesis, cancer-associated immune remodelling, developmental immunology, immune aging, and the physiological adaptations observed during spaceflight may each be interpreted within a broader gravito-thermal continuum linking molecular events with systems-level physical processes.

The framework does not seek to replace established molecular immunology. Rather, it proposes an additional physical layer through which molecular mechanisms interact continuously with fluid mechanics, thermodynamics, biomechanics, and hydrostatic organization. In this sense, Gravito-Thermal Immunodynamics may be viewed as a systems-level extension of contemporary immunology that complements existing biological paradigms while encouraging interdisciplinary integration. Importantly, the framework remains conceptual and hypothesis-generating. Many of its propositions require rigorous experimental validation, quantitative modelling, and comparative investigation across terrestrial and altered-gravity environments. Future studies may help clarify how fluid transport, thermal regulation, tissue mechanics, and gravitational conditions influence immune-cell trafficking, inflammatory responses, immune development, aging, and disease progression.

Ultimately, the central proposition of Gravito-Thermal Immunodynamics is that immune organization represents an emergent property of coupled biological and physical processes operating across multiple scales of life. By integrating concepts from immunology, biophysics, fluid mechanics, thermodynamics, systems biology, developmental biology, neurovascular science, and space medicine, the framework offers a broader perspective for exploring the physical foundations of immunity and the organization of living systems.

Conflict of Interest

The authors declare that there is no conflict of interest

Dedication

The authors respectfully dedicate this work to the memory of Sukla Bhattacharjee—beloved spouse, mother, and mother-in-law—whose love, sacrifice, encouragement, and enduring influence continue to inspire our lives and scholarly pursuits.

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