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Review

# From Molecular Dysregulation to Systemic Disease: Mechanistic Insights into Pathogenesis

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**Abstract:**
The classical perspective of disease as a localized organ failure has been greatly replaced with the paradigm that views illness as a family-wide derailment that can be traced to molecular-scale errors. In this article, the pathogenic continuum of molecular lesion to dysfunction of the organ is traced, leading to the argument of various etiologies focusing on three overlapping primary themes of immune dysregulation, protein homeostasis (proteostasis) loss, and cellular stress. These themes are not independent, but they interact in pathogenic cross-talk, developing self-enhancing loops that spread destruction. We consider underlying pathophysiology, such as Treg / Th17 imbalance, propagation of prion like proteins and immunometabolic reprogramming, which enhance the original insults. This dysregulation intensifies into microenvironmental axes (food gut-brain-immune axis and stromal-immune feedback loops) that propagate and institutionalize tissues pathology. We employ this integrative framework to show paradigmatic systemic diseases, such as rheumatoid arthritis, system sclerosis, multiple system atrophy, and inflammatory bowel disease, in which common mechanisms are observed to have different clinical phenotypes. Lastly, we argue that such a mechanistic knowledge requires a shift onto network-based therapeutics and systems-level diagnostics that will address the higher points of dysregulation and not the terminal points of tissue destruction. Such view conceptualizes pathogenesis as a dynamic, multiscale process and offers the roadmap to creating next-generation, mechanism-informed interventions.

**Keywords:** Immune Dysregulation, Proteostasis, Neuroinflammation, Inflammaging, Gut-Brain Axis, Autoimmunity



## Introduction

The contemporary concept of human disease is a radical change in the paradigm shift of understanding diseases as failures of individual organs to functioning as a system failure that begins at the molecular level [1]. Pathogenesis is not static but a dynamic continuum a cascade of failures which builds upwards upon the biochemical lesions in cells to the breakdown of tissue and organ functions. This prelude is to put this multiscale journey into perspective and to create three overlapping core themes of immune dysregulation, loss of protein homeostasis, and cellular stress, which are key nexus points where molecular errors get magnified into systemic pathology. Systemic disease usually starts with a molecular lesion, a minute fault imprinted into the basic equipment of life. This lesion may have a thousand different forms: a single-nucleotide polymorphism (SNP) making a subtle change in the function of a protein, epigenetic alteration silencing

an essential tumor suppressor gene, or even a post-translational change resulting in the misfolding of a protein. At first these errors are corrected by cellular homeostatic mechanisms- DNA repair, protein chaperones, antioxidant systems. Disease commences with an overloading of the strength of bio networks and the inability of the lesion to be contained. The further evolution is an account of complex emergence. An unfolded protein, e.g. a-synuclein in Parkinson disease is not just a cell rubbish issue. It replicates additional misfolding, diffuses between neurons and initiates neuroinflammatory responses in microglia. This cellular distress is transmitted to the environment changing the extracellular environment and causing cytokines and damage-associated molecular patterns (DAMPs) [2]. These cues, in their turn, attract and re-educate immune cells, converting a local protein-folding mistake into a permanent site of inflammation. The niche subsequently interferes with tissue structure-in the brain, fibrosis of the liver, or the erosion of bones in joints. This continuum is not a linear one but rather feed-forward loops and tipping points define it. Indicatively, during atherosclerosis, the adhesion molecule expression is enhanced by the hypertensive or oxidized lipid-induced endothelial cell stress. This attracts monocytes which differentiate into macrophages, eat lipids and transform into inflammatory foam cells [3]. These cells have increased production of cytokines and proteases, which continue to harm the endothelium and stabilize the plaque, a typical self-perpetuating pathogenic loop. The organ dysfunction that we are familiar with that is clinically diagnosed as heart failure, cirrhosis, dementia, is only the end, apparent end result of this long-term, interrelated molecular and cellular play. An understanding of this continuum makes us change how we diagnose and treat disorders, compelling us to find upstream drivers and network-based interventions instead of only responding to the late-stage symptoms [4].

**Core themes: immune dysregulation, protein homeostasis, and cellular stress**

While the molecular origins of disease are diverse, their paths to system-wide impact frequently converge on three interconnected biological themes that act as major amplifiers of pathology.

**Immune dysregulation: the sentinel turned aggressor**

The immune system is the supreme controller of homeostasis within the body charged with the responsibility of defense, repair and clearance. Its dysregulation is hence powerful generator of disease. In autoimmune diseases such as lupus, the pathogenesis is frequently the loss of self-tolerance, which results in a cytokine storm of autoantibodies that stick together in immune complexes and depose at the kidney, skin, and joints. Outside the autoimmunity, immune dysregulation is reflected in the form of chronic non-resolving inflammation. In some diseases such as rheumatoid arthritis or inflammatory bowel disease, the immune cells are constantly used through a complex of genetic vulnerability, environmental stimuli (e.g., dysbiotic gut microbiota), and self-harm signals. This makes the inflammatory environment self-sustaining, which directly kills tissue and initiates resident fibroblasts, resulting in permanent fibrosis. In addition, immunometabolism concept exposes that the metabolic status of immune cells determines the functionality. The presence of a shift in the glycolysis state of macrophages (the so-called Warburg effect in immune cells) stimulates a pro-inflammatory phenotype, which connects cellular bioenergetics with the inflammatory response. Loss of Protein Homeostasis (Proteostasis): The Quality Control Crisis [5].

Cells spend colossal resources on proteostasis- the correct synthesis, folding, traffic and degradation of proteins. Disintegration of this system is one of the main pathogenic mechanisms. Neurodegenerative diseases are characterized by protein misfolding and aggregation; amyloid-b and tau in Alzheimer, a-synuclein in Parkinson and huntingtin in Huntington disease. These aggregates are not mere passive debris but are actively toxic, perturbing cell organelles, saturating the ubiquitin-proteasome and autophagy-lysosome degradation systems, and anding other aggregation in a prion-like structure. At the same time, disease is caused by dysregulated systems of proteolytic activity. Protein complexes known as inflammasomes which activate inflammatory cytokines such as IL-1b are commonly activated through perturbations in proteostasis. On the other hand, the lack of autophagy, which is one of the main clearance mechanisms of defective organelles and protein aggregates, is associated with aging,

infection, and metabolic disease. Therefore, any defect in the quality control of proteins can cause direct cell death, cause inflammation and can serve as a reservoir of pathological seeds multiplying the damage. Cellular Stress: The Pandemic to Dysfunction [6-8].

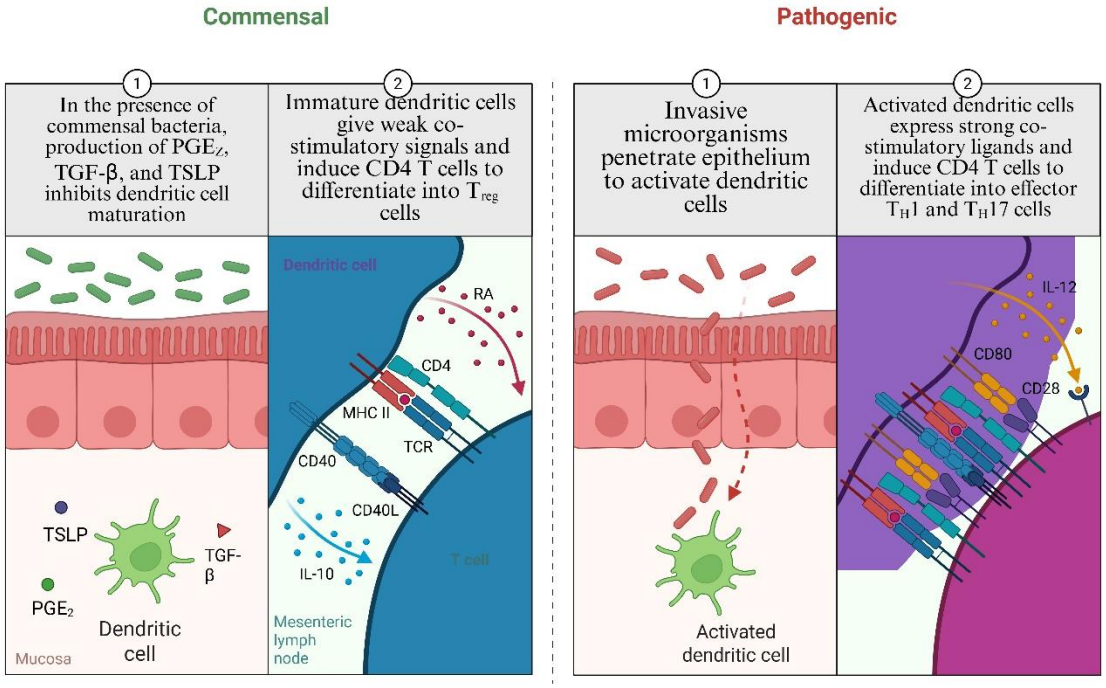


**Fig: 1** Immune response to commensal vs. pathogenic bacteria

Cells are constantly under stressors, reactive oxygen species (ROS), DNA damage, changes in nutrients or hypoxia. Adaptive stress responses, such as unfolded protein response (UPR) in the endoplasmic reticulum (ER) or the oxidative stress response are life sustaining. Nevertheless, in the case of chronic or overwhelming stress, it results in the formation of a maladaptive state that plays the key role in pathogenesis. An example of such stresses is ER stress where the misfolded protein load surpasses the ability of the ER to fold the protein. Whereas early protective UPR aims to achieve equilibrium, continuous ER stress responses leading to pro-inflammatory and pro-apoptotic signals, and providing contribution to diabetes-associated and hepatocytes-damaging processes, respectively. Another stress nexus is Mitochondrial dysfunction. Being the giant of the cell and a significant contributor to ROS, damaged mitochondria not only do not match the energy needs but also give out molecules such as mitochondrial DNA, which are the potent DAMPs, contributing to the inflammasome initiation and sterile inflammation. This forms a vicious cycle of inflammation leading to damage of the mitochondria which subsequently leads to inflation [9]. These three themes are Interconnected Everywhere The three themes are not independent. They are connections of a fine net of pathogenic crosstalk. Protein misfolding may be caused by cellular stress (e.g., oxidative stress) and put a strain on proteostasis. The immune system is dysregulated as a result of activated immune sensors (e.g. microglia through TLRs) due to the presence of misfolded proteins. This could be followed by further oxidative stress and ER stress in nearby cells caused by inflammatory cytokines. An excellent example is the gut-brain-immune axis systemic disease. Gut barrier integrity can be compromised by an environmental stressor (dysbiosis) and this allows the entry of bacterial products into circulation. This causes a condition of systemic immune activation (immune dysregulation) and low-grade inflammation, which may encourage neuroinflammation and affect

protein aggregation in the brain, possibly affecting diseases ranging up to Parkinson disease [10].

**Foundational molecular and cellular mechanisms**

The mechanisms of disease propagation by a molecular error to systemic condition necessitate amplification mechanisms that destabilize the major cell functions. In this section, the author explores three of the underlying pillars of pathogenesis the failure of the immune surveillance system, the failure of protein quality control, and cellular metabolic deregulation. They are not independent pathways but highly interrelated systems in which failure generates the persistent cellular stress which leads to tissue injury and organ failure [11].

**Destruction of immune homeostasis**

The immune system is kept at a delicate balance between maintaining a vigilant defense mechanism and tolerating the self. It disintegrates to form a master switch of systemic pathology, which is usually initiated at critical regulation nodes. Regulatory T cells (Tregs) a specialized form of CD4+ T cells characterized by the expression of the transcription factor FOXP3 are at the center of peripheral tolerance. FOX3 is not just a marker but the ultimate controller of Treg progeny and activity. It coordinates an anti-proliferation of effector T cells and cytokine production program which involves cytokine deprivation, direct T cells inhibition and disruption of metabolic state. FOXP3 gene mutations result in a lethal autoimmune disease, IPEX syndrome, and thus its non-redundancy. Tregs can also show functional deficiencies or be unstable even in ordinary autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes and fail to suppress autoreactive reactions [12]. The failure is done in a cytokine milieu that is dysregulated. Of special importance is the balance of the pro-inflammatory T-helper 17 (Th17) cells and the Tregs. FOXP3 can be induced by transforming growth factor-b (TGF-b) and lead to Treg differentiation in an anti-inflammatory state of rest. But in the company of inflammatory cytokine such as interleukin-6 (IL-6), TGF-b has the opposite effect and induces the transformations of pro-inflammatory Th17 cells. This fate switch induced by cytokines shows how inflammation may actively resist tolerance. Moreover, the positive feedback loops of cytokines, including tumor necrosis factor-alpha (TNF-a), IL-1, and IL-23 stabilize pathogenic Th17 cells and suppress Treg activity and activate innate immune cells, solidifying a chronic inflammatory condition [13-15].

**Epigenetic and post-translational control**

It is a masterpiece of regulation on the immune response, which is highly fined by the layers of regulation that go beyond the genetic code. Epigenetic changes, including DNA and histone acetylation of the FOXP3 locus, play a key role in the development and functioning of stable Tregs. The FOXP3 gene uses conserved non-coding sequences which require the process of demethylation to maintain a steady level of expression and any fault in this process is associated with the autoimmune propensity [16].

MicroRNAs (miRNAs) are fine-tuners at the post-transcriptional level. As an illustration, inhibitory action of proteins in Treg signaling by miRNA-155, which is increased in inflammatory states, and inhibitory action of NF-kB signaling by miRNA-146a occur. An even more recent discovery, RNA modification, specifically N6-methyladenosine (m6A) methylation, are made by the stability, splicing, and translation efficiency of immune transcripts via m6A modifications on mRNA molecules deposited by the writer protein, such as METTL3. The m6A in dendritic cells controls the level of response by modulating the breakdown of transcripts of pro-inflammatory cytokines. m6A regulates differentiation and functionality in T cells. This layer of epitranscriptomic dysregulation is becoming a new pathway in autoimmune and inflammatory diseases, and connects environmental provocation to a switch in immune genes expression [17].

**Protein misfolding and defective clearance**

Cellular health depends on a precise balance between protein synthesis, folding, and degradation—a state known as proteostasis. The failure of this system leads to the accumulation of toxic species that damage cells and trigger inflammation.

**α-Synuclein aggregation and propagation in neurodegeneration**

A good paradigmatic example of protein misfolding as the cause of disease is a-synuclein (a-syn) protein. It is a presynaptic protein, which is soluble in its native state. In pathological states, it folds improperly

into b-sheet-rich oligomers and eventually into insoluble fibrils to create neuronal-inclusive bodies being the hallmark of the Parkinson's disease and other synucleinopathies called Lewy bodies. The oligomeric species are highly toxic, interfering with lipid membranes, disrupting mitochondrial activity and overwhelming the clearance through proteasomal and autophagic pathways. This has led to a critical finding that a-syn misfolded may be prion-like. It may be secreted by the affected neurons using exosomes or naked deduction, internalized in adjacent or connected cells, and used as a seed to induce the mislays of native a-syn in other cells. This cell-to-cell propagation is along the neuroanatomic lines, and that is why the pathology has a stereotypical pattern of progression in the brain. This is the process that attracts microglia and astrocytes initiating chronic neuroinflammation that enhances the neuronal damage and forms a vicious circle where the inflammation leads to further deterioration of protein clearance [18].

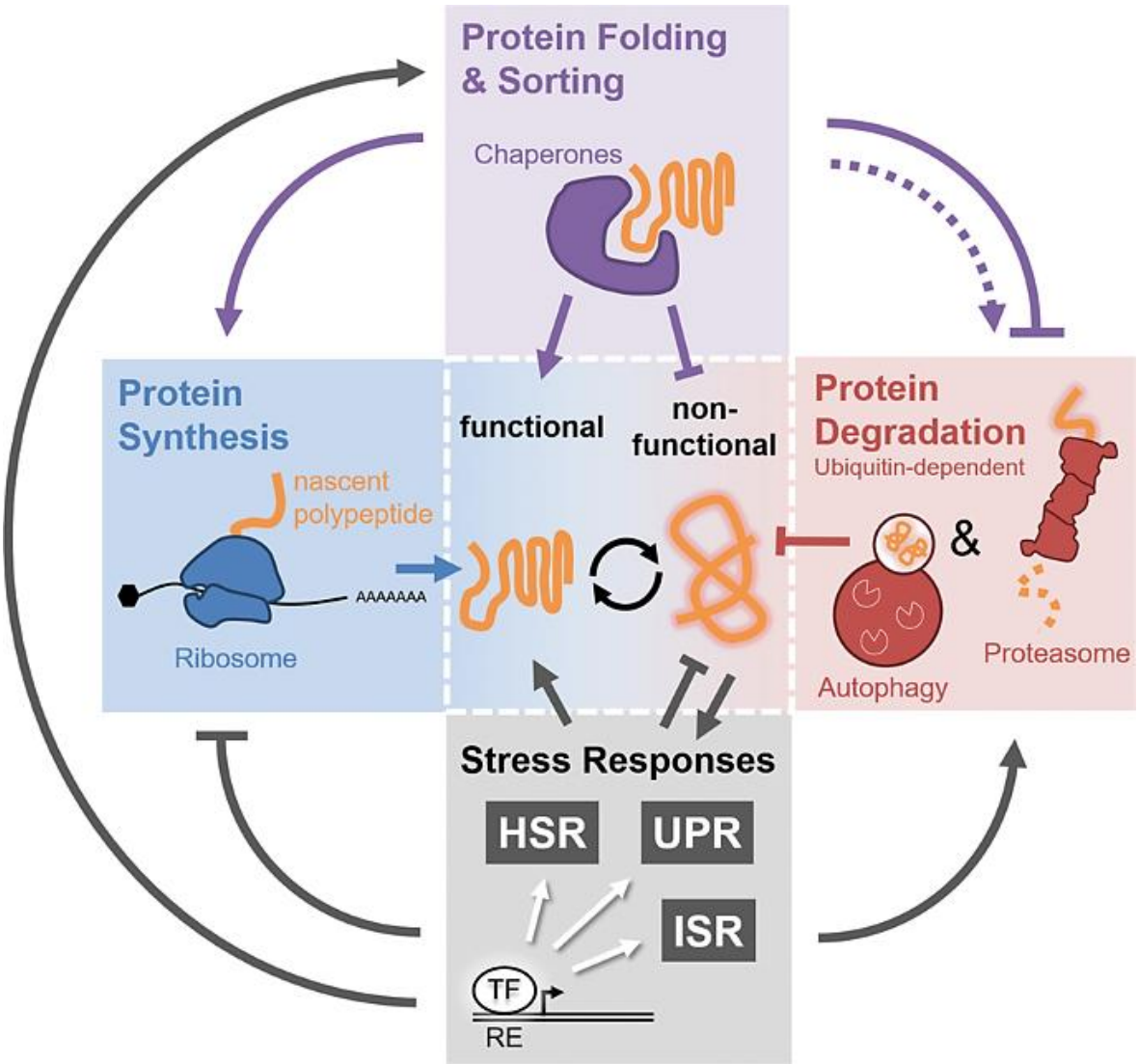


**Fig: 2** Metabolic regulation of proteostasis pathways

**Inflammasome activation and autophagy in immune-mediated disease**

The machine that removes misfold proteins is directly associated with the signaling of inflammation. The inflammasome is a cytosolic multi-protein complex, specifically, the NLRP3 one, which detects proteostatic stress, such as crystalline aggregates, extracellular ATP, and lysosomal damage (which can be caused by an impaired autophagy). On activation, it cleaves pro-caspase-1 into active caspase-1, which

in turn cleaves pro-IL-1b and pro-IL-18 into their powerful, active inflammatory versions [19]. The lysosomal breaking down pathway, autophagy, of cytoplasmic material is a key counterbalance. It gets rid of impaired mitochondria (mitophagy), protein aggregates (aggrephagy), and alien pathogens (xenophagy). Impaired autophagy is a twofold mechanism of pathogenesis: it permits the deposition of damaged material and aggregates, and it increases directly inflammasome activation. An example is that dysfunctional accumulated dysfunctional and ROS-leaking mitochondria due to impaired mitophagy release mitochondrial DNA, a potent activator of NLRP3. This nexus is why genetic defects in autophagy proteins have been associated with inflammatory diseases and why autophagy-inducing strategies are being considered as a therapeutic approach to a host of diseases such as Crohn's disease to neurodegenerative disorders [20].

**Table 1:** Core themes of pathogenesis

| Core Theme | Definition & Key Dysfunction | Primary Molecular/Cellular Mechanisms | Exemplary Disease Associations |
|---|---|---|---|
| Immune Dysregulation | Breakdown of self-tolerance and resolution, leading to chronic inflammation. | - Treg/Th17 imbalance & FOXP3 dysfunction<br>- Cytokine network dysregulation (e.g., TNF-α, IL-6, IL-17)<br>- Epitranscriptomic control ($m^6A$) | Rheumatoid Arthritis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease |
| Loss of Protein Homeostasis | Collapse of systems for protein synthesis, folding, and degradation. | - Protein misfolding & aggregation (e.g., α-synuclein)<br>- Inflammasome activation (NLRP3)<br>- Impaired autophagy & lysosomal clearance | Parkinson's Disease, Alzheimer's Disease, Multiple System Atrophy |
| Cellular & Metabolic Stress | Maladaptive response to chronic insults, disrupting bioenergetics and signaling. | - ER stress & Unfolded Protein Response (UPR)<br>- Mitochondrial dysfunction & mtDAMP release<br>- Metabolic reprogramming (Glycolysis vs. OXPHOS) | Type 2 Diabetes, Non-alcoholic |

**Metabolic and bioenergetic dysregulation**

The recent area of immunometabolism has shown that cell metabolic processes are not housekeeping processes, but basic regulators of immune cell fate, protein homeostasis, and inflammatory response. Immunometabolism: Alterations in Glycolysis vs. Oxidative Phosphorylation Immune cells can dynamically reorganize their metabolism to aid their active condition. Resting T cells or M2 macrophages (quiescent/anti-inflammatory cells) mostly use oxidative phosphorylation (OXPHOS) and fatty acid oxidation as their energy source. Conversely, when polarized by pathogens or inflammatory cues, such cells as effector T cells (Th1, Th17) and pro-inflammatory M1 macrophages switch to aerobic glycolysis (the "Warburg effect") despite the presence of oxygen [21]. This accelerated degradation of glucose to lactate is ineffective in generating ATP but supplies biosynthetic precursors (such as nucleotides, amino acids, and lipids) that are required in quick proliferation and production of cytokines. This reorganization of metabolic processes is mediated by major nutrient sensor AMPK and mTOR, which enhances glycolysis and suppresses autophagy and supports inflammatory phenotypes. On the contrary, activation of AMPK enhances OXPHOS and autophagy, which prefer regulatory or anti-inflammatory conditions. As such, the immune

functioning is predetermined by the metabolic condition. This glycolytic program becomes stuck in chronic inflammatory diseases forming a vicious cycle of inflammatory cells that are hard to get rid of. A new approach to regulate immune responses is to target these metabolic pathways (e.g., by using mTOR inhibitors or by using derivatives that induce OXPHOS) [22-25].

**Mitochondrial dysfunction as a central driver**

Mitochondria sit at the crossroads of metabolism, apoptosis, and inflammation. Their dysfunction is a central feature of aging ("inflammaging") and many chronic diseases. When mitochondria are damaged—by ROS, toxins, or genetic mutations—they lose their membrane potential, produce less ATP, and generate more ROS, creating oxidative stress that further damages proteins, lipids, and DNA. Crucially, damaged mitochondria become signaling organelles. They release mitochondrial DAMPs (mtDAMPs), such as mitochondrial DNA and formylated peptides, into the cytosol. These molecules are recognized by innate immune sensors like NLRP3 and cGAS-STING, triggering inflammasome activation and type I interferon responses, respectively. This directly links an intracellular organelle defect to sterile inflammation. Furthermore, mitochondrial dysfunction impairs the cell's ability to meet energy demands, exacerbating proteostatic stress by limiting the ATP required for chaperone function and proteasomal activity. This creates a pathogenic triad where metabolic failure, protein misfolding, and inflammation all reinforce one another, driving the progression of systemic diseases from neurodegeneration to heart failure [26].

**Microenvironmental and tissue-level pathogenic crosstalk**

Molecular and cellular dysfunction increasing to an overt systemic disease is not a passive diffusion of damage, but an active program of communication within the microenvironment of the body via special networks. This is the critical period of pathogenesis that signifies the tissue-level synthesis of dysregulation in which local dysfunctions in homeostasis appeal to physiological axes and cellular cross-talk to amplify and institutionalize dysfunction way beyond the site of initial injury. The pathway between a leaky gut and neuroinflammation, a stressed fibroblast and an organ fibrosis, immune activation and bone erosion is an example of how systemic disease is formed through maladaptive conversations between epithelial barriers, the nervous system, stromal cells and the immune system. These conversations bring in isolated cellular distress into a self-sustaining, logical program of pathology [27].

The gut-brain-immune axis is, perhaps, a canonical example of systemic propagation, with a major violation of a peripheral barrier potentially restoring immune tone and neurological health to the rest of the body. The stability of the axis depends on symbiotic relationship with a diverse gut microbiota and the integrity of the intestinal epithelial barrier, which is a single layer of the cell lining strengthened by tight junction proteins. The precipitating factor is usually microbial dysbiosis; a change in the composition of the microbial community due to dietary changes, antibiotics or infection. This dysbiosis lowers the production of beneficial, anti-inflammatory metabolites such as the short-chain fatty acids (SCFAs), which play an important role in nourishing the epithelial cells and promoting the regulatory T cells, and may also increase the number of pathogenic ones, which release pro-inflammatory molecules or have invasive abilities. These pathobionts also have the ability to destroy the protective mucus layer, which causes the release of cytokine TNF-a and IL-1b into the intestines, which directly suppress tight junction proteins such as occludin and results in a condition of high intestinal permeability, or leaky gut. This damaged wall permits the entry of bacterial endotoxins, the lipopolysaccharide (LPS) being the most important, and other microbial products into the systemic circulation. The resultant chronic endotoxemia of low grade serves as a sustained inflammatory stimulus: LPS triggers Kupffer cells in the liver to activate TLR4, which induces hepatic inflammation which is central to metabolic disease, and circulating inflammatory cytokines such as IL-6 pre-condition peripheral immune cells and suppress the blood-brain barrier. This systemic inflammatory cascade has access to the central nervous system and causes the activation of resident microglia and the activation of neuroinflammatory pathways that are involved in disorders as diverse as depression and anxiety, and even Parkinson disease, where it has been shown that pathological proteins such as a-synuclein may

actually start in the enteric nervous system and then spread to the brain. Therefore, the gut axis can be described as an impressive transducer that transforms local environmental and microbial disruptions into a body-wide signal, which alters the work of the remote organs [28-30].

At the same time, in certain tissues, a second pathogenic layer of crosstalk between neuro-immune and stromal-immune interactions occurs, which is especially decisive in the process of fibrotic disease and chronic inflammation. The nervous system does not simply spectate but acts as a participant of tissue pathology. The release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) by the sensory nerve fibers is in response to the local vascularity that is damaged in the skin, lungs, and liver among those organs prone to fibrosis. The signals may bind directly receptors on resident fibroblasts, inducing their growth and development into a-smooth muscle actin-positive myofibroblasts, which are the main collagen-producing cells in fibrosis. This generates a direct nerve-to-fibroblast pro-fibrotic axis, which is observed in such diseases as systemic sclerosis. In a wider sense, the immune system develops the most predominant signals that accelerate and maintain these populations of fibroblasts. In rheumatoid arthritis, e.g., IL-17 of helper T cells and TNF-a of macrophages collaborate to stimulate synovial fibroblasts which in turn prisoner more cytokines and tissue-damaging enzymes, which in turn leads the macrophages to produce more TNF-a, etc. These stimulated, pathologic-related fibroblasts assume an inflammatory memory and in many cases, these remain long after the initial immune insult has been forgotten. They turn out to be the primary organizers of the sick tissue microenvironment, enlisting other immune cells, and secrete factors that modify the local extracellular matrix (ECM). This perturbation of the ECM leads to the last stage of tissue pathogenesis: compromised special homeostatic mechanisms governing organ structure and function. Two ideal systems include the dynamic equilibrium of bone remodeling and the controlled turnover of the connective tissue [31]. The homeostasis of the bone, controlled by the strict regulation of the interactions between osteoclasts and osteoblasts, is highly sensitive to the immune activity - this interaction formalized by the osteoimmunology. The most significant molecular triad consists of RANKL, its receptor RANK and decoy receptor osteoprotegerin (OPG). The RANKL/OPG ratio strictly regulates the formation of osteoclasts in health. This system however is tragically hijacked by inflammation. Cytokines such as TNF-a and more importantly IL-17 in the inflamed joints of rheumatoid arthritis or psoriatic arthritis cause a dramatic increase in the expression of RANKL in the synovial fibroblasts and the immune cells themselves. This causes rampant, localized bone erosion the radiographic manifestation of these diseases. Systemic inflammation may, at the same time, inhibit the osteoblast activity, thereby causing generalized osteoporosis. This process defines how immune dysregulation directly orders a particular tissue-resident pathway to inflict structural injury [32].

**Table 2: Mechanistic integration in systemic diseases**

| Disease | Primary Theme | Key Mechanism | Resulting Systemic Pathology |
|---|---|---|---|
| Rheumatoid Arthritis (RA) | Immune Dysregulation | Th17-driven synovitis; RANKL/OPG axis dysregulation | Synovial pannus, bone erosion, accelerated atherosclerosis |
| Systemic Sclerosis (SSc) | Immune + Cellular Stress | Vasculopathy → TGF-β activation of fibroblasts; Neuro-fibroblast axis | Skin & organ fibrosis (lungs, GI tract), vascular rarefaction |
| Multiple System Atrophy (MSA) | Protein Homeostasis + Immune | α-Synuclein aggregation in oligodendrocytes; Glial activation | Widespread neurodegeneration, parkinsonism, ataxia, autonomic failure |
| Inflammatory Bowel Disease (IBD) | Immune + Cellular Stress | Barrier dysfunction ("leaky gut"); Dysbiosis → Th1/Th17 imbalance | Chronic colitis, transmural inflammation, fistula formation |

Parallel dysregulation is observed in fibrotic tissue remodeling, in which the physiological, restorative deposition of ECM is changed to pathological scarring. The myofibroblasts activated deposit excess, disorganised and highly cross-linked collagen. Most importantly, the ECM per se becomes an active signaling structure. In the process of fibrogenesis ECM proteins are cleaved into bioactive matrikine fragments by enzymes such as matrix metalloproteinases (MMPs). Such matrikines include particular fragments of elastin or collagen and are able to bind integrin receptors present on fibroblasts and immune cells and further promote pro-fibrotic and inflammatory responses [33]. This creates a vicious circle of death: inflammation triggers the production of abnormal ECM by fibroblasts, and the products of the decomposition of such ECM (matrikines) stimulate further inflammation and the activation of fibroblasts. Moreover, fibroblasts detect the stiffening of the matrix over time through mechanotransduction signaling (e.g. through the transcriptional activity of YAP/TAZ), a process that supports their stimulated condition as myofibroblasts. It causes fibrosis to become self-sustaining, and in many cases it progresses without stimulus by the initial trigger of inflammation as in the unstoppable course of idiopathic pulmonary fibrosis or liver cirrhosis. In short, the microenvironment is the determining stage at which the possibility of systemic disease is fulfilled. Gut-brain-immune axis offers a pathway through which pathology is spread within the organ systems. Neuro-immune and stromal-immune interactions entrap chronic activation and fibrosis states in tissues. Ultimately, all these processes culminate in the destabilization of the fragile homeostatic regimes of each tissue, e.g. the RANKL/OPG balance in bone or the matrikine-controlled ECM balance in connective tissue. This multi-layered crosstalk should be understood because it indicates the symptoms of organ failure is the culmination of a long-term, maladaptive dialogue between the cells of different types. The therapeutic approaches necessary should thus not only work towards silencing the misbehaving immune cells or eliminating a poisonous protein, but also help in interrupting these pathogenic dialogs and re-establishing the language of homeostasis in the tissue microenvironment [34].

**Systemic disease manifestations: integrating mechanistic insights**

The manifestation of molecular dysregulation, unsuccessful cell homeostasis and maladaptive tissue crosstalk leads to the identifiable clinical syndromes we are recognizing as particular diseases. This part discusses the paradigmatic conditions in terms of the integrated mechanistic perspective that was developed earlier, showing how different combinations and proportions of pathogenic themes, such as immune dysregulation, proteostatic failure, and metabolic stress, combine with each other to organize unique but frequently overlapping approaches to systemic disease. Whether it is the joint destruction of autoimmune arthritis or the inexorable fibrosis of scleroderma or the spreading proteinopathy of neurodegeneration, these diseases are not solitary things, but expressive manifestations of common underlying biological concepts [35].

**Systemic autoimmune and inflammatory diseases**

Rheumatoid arthritis (RA) is a classic example of how local failure of immunoregulation leads to systemic disease with implications on multiple organs. The pathogenesis begins with an immune tolerance loss, probably conditioned by genetic risk factors (e.g., shared epitope with HLA-DR genes) and environmental factors (e.g., smoking, dysbiosis with microorganisms). It results in the circulation of the autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), which create immune complexes. The complexes accumulate in the synovial membrane which stimulate resident macrophages and fibroblasts through Fc receptors. The hyperplastic tissue that develops is the inflamed synovium, which becomes an invasive pannus tissue, and this occurs due to a profound regulation of the cytokine network. An overabundance of pro-inflammatory T-helper 17 (Th17) cells over regulatory T (Treg) cells is also a dominant characteristic, whereby cytokines such as IL-6, TGF-b, and IL-21 stimulate the pathogenic differentiation of Th17. Such Th17 cells, activated macrophages, fill the joint with TNF-a, IL-1, and especially, IL-17. IL-17 also synergizes with TNF-a in order to stimulate the production of matrix metalloproteinases (MMPs) and RANKL (Receptor Activator of NF-kB Ligand) by synovial fibroblasts [36].

**Systemic lupus erythematosus: loss of tolerance and multi-organ damage**

Systemic Lupus Erythematosus (SLE) is a systemic failure of self-tolerance, which is typified by pathogenic autoantibodies targeting nuclear elements (e.g., double-stranded DNA, histones). The pathogenesis of the mechanistic origin is a coordinated malfunction of several immune checkpoints. There is also poor clearance of apoptotic debris, in part because of complement deficiencies (e.g. C1q) and results in the maintenance of nuclear autoantigens. When this debris is phagocytosed by the dendritic cells, self-antigens are presented, and volumes of type I interferons (IFNs) are produced, which forms an effective interferon-alpha signature stimulating further adaptive immunity. As a consequence of dysregulated co-stimulation and loss of Treg activity B cells receive excessive T cell help receiving unregulated proliferation and class-switching resulting in the production of the pathogenic autoantibodies. This leads to deposition of the immune complex in the vessel walls (type III hypersensitivity) which triggers the complement resulting in inflammation and damage of tissues in the skin (malar rash), kidney (lupus nephritis), joints, and in the brain. It is a self-reinforcing cycle because tissue damage causes an increased release of nuclear antigens which in turn stimulate the production of additional autoantibodies. Moreover, the hyperactivated state of immune cells is also provided by metabolic reprogramming, i.e., increased glycolysis in lymphocytes. The systemic character of the loss of tolerance is directly bearing the stamp of the multi-organ involvement of SLE where a basic malfunction in the management of cellular debris increases to an inflammatory process in nearly all organ systems [37].

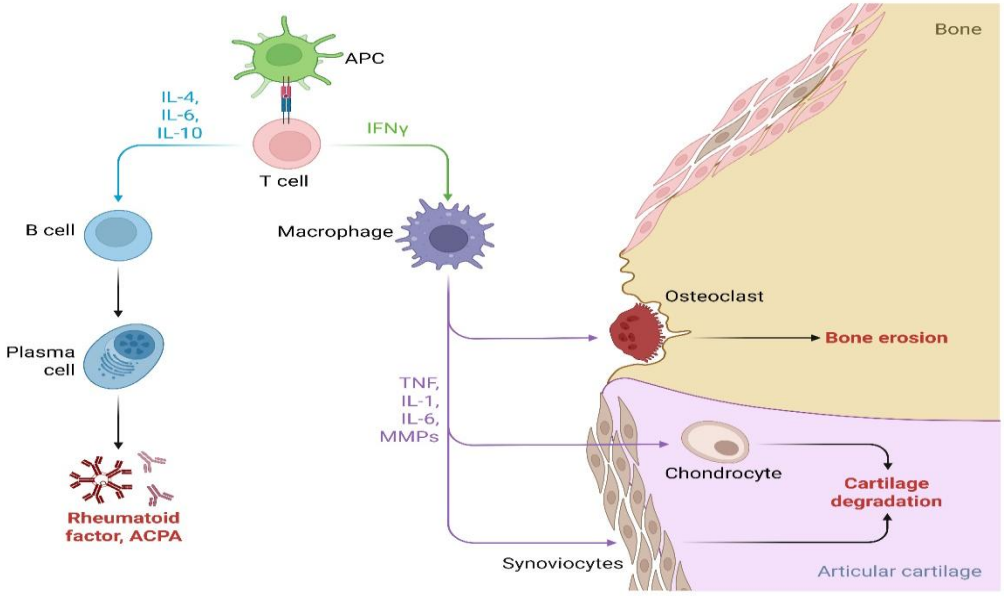


**Fig: 3** Immune cell interactions in rheumatoid arthritis pathogenesis

**Systemic sclerosis: vascular damage, autoimmunity, and fibrosis**

Systemic sclerosis (SSc, scleroderma) is the only disease that incorporates the combination of triad of vasculopathy, autoimmunity, and fibrosis into a progressive systemic disease. Microvascular endothelial cell injury is believed to be the first to occur resulting presumably due to environmental factors, cytotoxic lymphocytes or anti-endothelial antibodies. Vascular hyper-reactivity and rarefaction result in this damage and stimulate tissue ischemia. The destroyed endothelium discharges the vasoconstrictors and developmental factors such as endothelin-1 and PDGF activating perivascular fibroblasts. At the same time, autoimmune reaction with autoantibodies against topoisomerase I (Scl-70) or centromere is also dysregulated, which adds to the inflammatory climate [38].

Scarring involves the conversion of tissue-resident fibroblasts into a-smooth muscle actin-positive

myofibroblasts which synthesize excessive collagen and other ECM factors. Canonical signaling pathways, in particular, TGF-b/Smad, but also innate immune sensing (TLRs) and activation of profibrotic M2 macrophages drive this fibrotic response. More importantly, the nerve-fibroblast axis is also activated, wherein the neuropeptides secreted by sensory nerves enhance further activation of fibroblasts. Fibrosis is not just a deposition of scar tissue, but a disruption of matrikine signaling environment, in which fragmented components of the ECM maintain fibroblast activation and immune recruitment in a feed-forward loop, resulting in the permanent hardening of skin and internal organs such as the lungs, heart, and gastrointestinal tract.

**Neurodegenerative and neuroinflammatory disorders**

α-Synuclein Pathology and Glial Involvement Multiple system atrophy (MSA) is a fatal synucleinopathy that demonstrates how fatal cell-autonomous proteinopathy may interact with non-cell-autonomous neuroinflammation. The fundamental molecular pathology is aggregation and misfolding of a-synuclein in oligodendrocytes, myelinating cells of the central nervous system. This differs with the Parkinson disease where neurons are mainly affected. The glial cytoplasmic inclusions (GCIs) of the oligodendrocytes are unique. Misfolded a-synuclein accumulates in these support cells impairment of their function causes impaired myelination, and neurons of striatonigral and olivopontocerebellar pathways become dysfunctional and die. Importantly, there is a lot of glial involvement in the pathology. The release of the abnormal a-synuclein oligodendrocytes can be exhibited to the microglia and astrocytes. Microglia, which tries to clear the debris, becomes chronic, acquiring the pro-inflammatory phenotype, which releases cytokines (TNF-α, IL-1b) and reactive oxygen species, which further increases neuronal stress. Astrocytes can as well be a cause of toxicity and poor synaptic support. This generates a vicious cycle of proteostatic failure and neuroinflammation, in which protein aggregates trigger glial activation, and glial inflammatory mediators worsen neuronal proteostasis and neuronal function, leading to disease progression. The Scope of Chronic Neuroinflammation in Disease Spectrum [39].

In addition to MSA, chronic neuroinflammation is a key pillar in the pathogenesis of almost all neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease (PD). Amyloid-b plaques and, maybe, even more effective soluble oligomers activate microglia through pattern recognition receptors in AD. The response of the microglial is initially protective but is deregulated and chronic in the course of the disease. One of them is microglial priming, in which an initial injury (e.g., systemic infection, ageing) disarms microglia, leading them to overreact in response to subsequent difficulties. These chronic-activated microglia produce pro-inflammatory cytokines and glutamate, disrupt phagocytic removal of aggregates (a process referred to as defective microglial autophagy), and even add to the spread of tau pathology. Equally, in PD, misfolded a-synuclein is a danger-associated molecular pattern (DAMP), and it occurs that it mediates a neuroinflammatory response that is a major cause of the loss of dopaminergic neurons. Therefore, neuroinflammation is not a passive spectator response but rather a contributor of neuronal death and synaptic loss, which is a parallel therapeutic focus in a wide range of neurodegenerative diseases.

**Metabolic and environmentally triggered disorders**

The Inflammatory Bowel Disease: Barrier Dysfunction and the Imbalance in Immune Cells.

A prime example of the gut-immune axis failure is Inflammatory Bowel Disease (IBD), which is a collection of infectious diseases that includes Crohn and ulcerative colitis. Environmental stimuli cause disruption of the homeostatic communication between the commensal microbiota and the mucosal immune system in genetically susceptible people (e.g., variants of NOD2, ATG16L1). Defective intestinal epithelial barrier possibly by defective autophagy or tight junction regulation enables greater bacterial translocation. These microbes are detected by dendritic cells and macrophages in the lamina propria through pattern recognition receptors. In Crohn disease, the threat is not resolved by an impaired innate immune response, in which there is a failure in the killing of bacteria and regulation of inflammasomes. This results in dysadaptive and exaggerated T cell response. The effector T cells

(especially Th1 and Th17) and the regulatory T cells develop a critical imbalance. The pro-inflammatory environment, which is highly IL-12, IL-23, and IL-6, fosters Th1/Th17 preeminence, whereas Treg business or production is repressed. The activated effector T cells secrete IFN-g and IL-17 that further damage epithelium, raise permeability and activate fibroblasts, which enhances transmural fibrosis and fistula development. The breach of barriers, dysregulated microbial sensing, and imadaptive immune response is the cycle that sums up the local initiation and maintenance of systemic inflammation in a particular organ [40].

**Dietary influences on immune polarization**

Immune cell fate and function can be directly influenced by environmental factors, including diet, and these are able to affect the risk of systemic diseases. An excellent example here is the impact of high-salt diet. High statuses of sodium chloride have been demonstrated to support the differentiation of naive naive $CD4^+$ T cells into pro-inflammatory Th17 cells and also disrupt the immunosuppressive activity of Tregs. The mechanistic connection is the salt-induced expression of serum/glucocorticoid-regulated kinase 1 (SGK1) of T cells. SGK1 enhances the IL-23 receptor expression, rendering the T cells more susceptible to the Th17-polarizing signals, and changes the cellular metabolism. This immunological polarization by salt has been proposed to drive experimental autoimmune encephalomyelitis and hypertension, and it has been postulated to mediate the activity of autoimmune diseases in humans, which is a direct molecular link between a ubiquitous environmental exposure and systemic immune deregulation.

**Viral induced osteopathologies and arthritis**

Viral infections may serve as environmental inducers of systemic inflammatory diseases, and this may be by either molecular mimicry or bystander activation mechanisms. As an example, alphaviruses (e.g., Chikungunya, Ross River virus) infection may result in acute and frequent chronic arthritis. The virus infects the synovial tissues directly resulting in cell death and release of viral PAMPs and host DAMPs. This induces a strong innate immune reaction which produces type I IFNs, TNF-a and IL-6 which in turn draw monocytes and T cells into the joint. Some people do not have this acute inflammation resolving and develop a chronic arthropathy that may last a number of years after the infection. The persistence could be in the form of viral RNA or antigen remnants, sustained immune responses or the virally induced release of latent autoimmune responses. Likewise, parvovirus B19 and hepatitis C virus have been implicated in the development of arthritis and other rheumatic systemic reactions, demonstrating how a systemic viral infection can selectively and dysregulate joint homeostasis by way of inflammatory mediators.

**Conclusion**

The cascade that runs between a single molecular lesion and multiple organ failure is both complicated, but explicable, and is based on the same biological principles. The pathogenesis of a variety of systemic diseases, including autoimmune diseases, neurodegenerative diseases, and metabolic diseases, are coordinated by the dynamic interactions between immune dysregulation, proteostatic collapse and bioenergetic stress, as described in this analysis. These central themes serve as connective boosters, such that a localized error is hardly ever kept in check. Rather, pathology is diffused and embedded throughout the organism by means of feed-forward loops and maladaptive cross-talk in specialized axes, such as the gut-brain-immune and neuro-stromal networks. This unified perspective requires a critical reconceptualization of clinical disease. Examples of diseases like rheumatoid arthritis, systemic sclerosis, and multiple system atrophy are not only identified by their target organs but are systemic manifestations of defective homeostasis, and the similarities of their clinical manifestation are due to common mechanisms. The self-perpetuating fibrotic circuit, the chronic inflammatory niche, the vicious cycle of self-assembly of protein aggregates and neuroinflammation all are manifestations of the same underlying failure of biological regulation. Hence, the clinical imperative is obvious. What we need is a concurrent development of our diagnostic and curative approaches in response to this mechanistic knowledge. The diagnosis should not rely on the manifestation of overt organ dysfunction but seek early molecular indications and subclinical network disruptions that may be utilized through multi-omics

and AI-based stratification, as proposed in the translational views. Therapeutics should target more than just the suppression of palliative symptoms, to strategically inhibit the fundamental pathogenic dialogues, be the restoration of immune tolerance, augmentation of proteostatic clearance, regulation of cellular metabolism, or maintaining barrier integrity. It is hoped that a non-invasive therapy that remains agnostic to the ultimate diagnosis but is directed against these common upstream mechanisms might settle the matter.

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