

Immune mechanisms underlying energy and fatigue in immune-inflammatory rheumatic diseases: a narrative review

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ABSTRACT

Emerging research suggests that subjective experiences of energy and fatigue reflect dynamic immune system states, integrating emotional and physiological processes. Here we review evidence that energy and fatigue are distinct mood states with unique neurochemical, metabolic, and immunologic profiles, shaped by immunometabolism and immune resilience. We propose that immune system activation reallocates energy resources, influencing these states and contributing to fatigue in disease. Understanding this immune-energy interplay offers novel clinical insights, suggesting that interventions targeting immune resilience, such as tailored nutrition, exercise, emotional well-being cultivation, and novel pharmacological strategies, may alleviate fatigue and enhance vitality in rheumatologic conditions. This framework shifts the focus from symptom suppression to restoring immune-supported energy, with potential to improve patient quality of life.

The feeling immune system

Current biomedical research increasingly views disease not only through genetic defects (SNPs, CNVs, gene deletions) or impaired signalling pathways, but through crosstalk between body systems (for example the cardiovascular and metabolic systems) and, more recently, patients' lived experiences (1-4). This shift underlies the rise of lifestyle medicine (5-7), which treats health as an emergent property of the interaction between body, mind and context, incorporating factors not traditionally considered biomedical, such as socioeconomic status, education, job satisfaction, personality, living conditions and emotional wellness (5, 7-9).

Fatigue is a common and well-studied feature of human pathology (10-12). Many researchers treat vigour or energy as simply the opposite end of the fatigue continuum, *i.e.* if you're energetic, you're not fatigued (13, 14), but emerging evidence indicates energy and fatigue are distinct, unipolar moods that can co-occur (15-18). This distinction matters clinically: feelings of energy and fatigue are highly subjective, and cultural differences can make the two difficult to distinguish (19,20); fatigue itself may be physical or mental, shaped further by environment, BMI, personality, and socioeconomic context (21-23).

Fatigue accompanies a wide range of diseases, including cancer (24) and rheumatologic autoimmune conditions such as rheumatoid arthritis (RA) (25, 26) and systemic lupus erythematosus (SLE) (26, 27). In RA, 40-80% of patients report significant fatigue despite treat-to-target strategies (28); in SLE, fatigue affects 50-90% of patients and often predicts disability and quality-of-life impairment more accurately than disease activity indices (29). Conventional disease markers, joint counts, CRP, ESR, rarely account for fatigue severity (30-32), suggesting that fatigue in rheumatology is not simply a passive consequence of inflammation but a distinct psychoimmunological state.

In this review, we explore this hypothesis, examining the immune system as the biological substrate linking psychological states to the subjective experience of energy and fatigue. We first outline the principles of affective immunology (33) and the distinction between energy and fatigue as independent mood states; we then examine how immunometabolism and immune resilience (34, 35), as a salutogenic target,

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shape these states; finally, we discuss interventions that support immune-driven energy in rheumatologic disease.

Affective immunology: mirroring between emotions and immune repertoire

Affective immunology posits a revolutionary proposition: the immune and emotional systems are not separate entities but two dynamic, plastic reservoirs in constant allostatic equilibrium, serving as parallel tools through which the organism adapts to and interacts with the environment (33). Both systems distinguish between beneficial and harmful stimuli; both undergo continuous development and remodelling; they mirror each other, and both are exquisitely sensitive to environmental challenges including pathogens, stressors, social experiences, and lifestyle factors. This differs from common theories of neuro-immune communication in that it treats the immune system as one end of a seesaw, with the other end comprising everything in life we experience through our senses and our unique perspective, our personality or lived life.

These ideas build upon a long history of psycho-neuro-endocrine-immune research, including extensive work in rheumatic diseases linking psychological and environmental factors with neuroendocrine regulation, metabolism and immune function (36). They are also supported by well-established associations between personality traits (37-39), psychological stress (40, 41), lifestyle factors (42, 43) and measurable immune functions. A landmark meta-analysis by Segerstrom and Miller (44) showed that brief, acute stressors upregulate natural immunity, whereas prolonged or chronic stressors globally suppress immune function; other work links higher conscientiousness to lower inflammatory markers and higher extraversion to increased inflammation (39). This immune-emotional coupling is remarkably fast: the immune system registers and responds to an emotion (laughter, anxiety, joy, grief) within 30 minutes to an hour (45-47). Anxious thought measurably diminishes immune function within this window (48), while mirthful laughter increases NK

cell cytotoxic activity within 12 hours (49). In our own murine studies and those of others (50-52), distinct stressors, environmental enrichment (53-55), social isolation (56, 57), daily handling (58), elicit distinct cellular and gene-expression immune signatures, a pattern confirmed across many subsequent studies (59-64).

The same external event is experienced differently across people and over time: our emotional “fingerprint” shapes immune function at the cellular and molecular level. Qualitative variations in well-being recruit divergent gene-regulatory programs: eudaimonic well-being, such as purpose, growth, meaning, mastery, positive relationships, down-regulates the Conserved Transcriptional Response to Adversity (CTRA), a stress-related profile of increased pro-inflammatory and decreased antiviral/antibody gene expression (65-71), whereas hedonic well-being paradoxically upregulates CTRA despite similar subjective positivity (62, 66, 70). The immune system thus appears to act as a biological ‘meaning detector,’ more sensitive to eudaimonic than hedonic sources of happiness.

Two levels of control operate within this emotion-lifestyle-immune continuum: external factors (social pressures, socioeconomic status, relationships) shape daily life, while personality and emotional style filter these inputs, amplifying or buffering their immunological impact. Time adds a further dimension, the frequency and duration of emotional states shape outcomes. Acute stress transiently increases NK cells and neutrophils, whereas repetitive, unpredictable stress in rodents (72) and chronic psychosocial stress in humans (44) reshape the immune repertoire toward strategies that preserve survival-relevant efficiency.

Metabolism is tightly coupled to this system (73): host defence is energetically expensive (74, 75), requiring trade-offs with programs like thermoregulation. Mounting an immune response can consume 25-30% of basal metabolic rate, with even a modest fever requiring 250+ additional kilocalories daily (75). This concept has an important precedent in rheumatology. Earlier

work proposed that immune activation generates an “energy appeal reaction”, whereby the energetic demands of the activated immune system reshape neuroendocrine and metabolic regulation to redirect energy-rich fuels towards immune defence. While adaptive during acute inflammation, persistence of this response in chronic immune-inflammatory disease may contribute to systemic manifestations including sickness behaviour, insulin resistance, altered lipid metabolism and body composition, neuroendocrine changes, anaemia and bone loss (76, 77). Immunometabolism research shows that immune cell subsets rely on distinct metabolic pathways (78-81): pro-inflammatory M1 macrophages and Th1/Th17 cells favour rapid but inefficient aerobic glycolysis (82, 83), while anti-inflammatory M2 macrophages and regulatory T cells favour efficient mitochondrial oxidative phosphorylation associated with tissue repair (84-87). In immune-inflammatory rheumatic diseases, however, macrophage activation is increasingly understood as a dynamic continuum rather than a strict M1/M2 dichotomy. Macrophages can shift between pro-inflammatory, regulatory and pro-fibrotic phenotypes in response to cytokines, tissue-derived signals and interactions with neighbouring cells, thereby contributing to the persistence and resolution of inflammation as well as tissue remodelling (88). Taken together, this metabolic and phenotypic plasticity suggests that the immune system does not merely consume energy but actively governs its availability -- so that subjective vigor or exhaustion may reflect the conscious perception of these resource allocations (Fig. 1).

Energy and fatigue as distinct, unipolar mood states

To understand energy and fatigue biologically, we must first define them clearly. Traditionally viewed as opposite ends of a single continuum, research pioneered by one of us (AB) has shown that energy and fatigue are in fact two distinct, unipolar mood states (15-17, 89-91), each with unique mental and physical components and separate biological correlates.

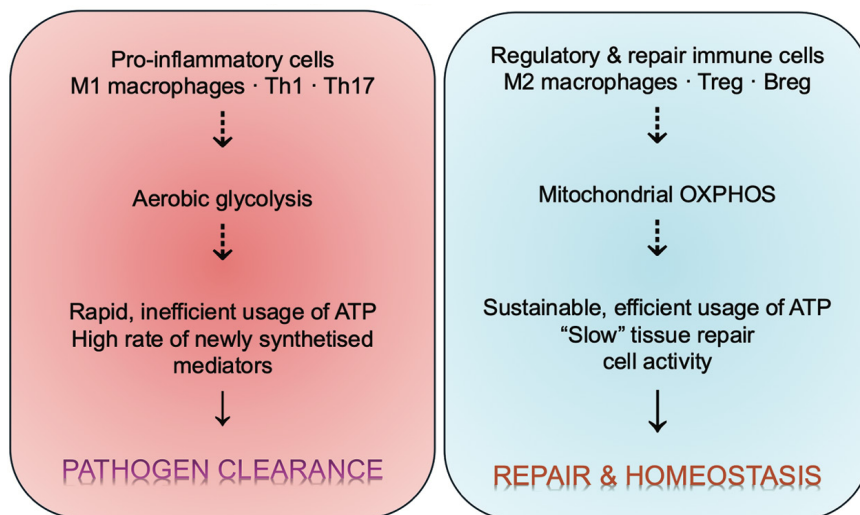


Fig. 1. Metabolic reprogramming across immune cell states.

Pro-inflammatory subsets (M1-like macrophages, Th1, Th17) preferentially engage aerobic glycolysis, a rapid but inefficient pathway that supports high rates of newly synthesised mediators and drives pathogen clearance. Regulatory and repair-associated subsets (M2-like macrophages, Treg, Breg) instead rely on mitochondrial oxidative phosphorylation (OXPHOS), a slower but more sustainable route to ATP that supports tissue repair and homeostasis. This metabolic divergence couples an immune cell's inflammatory phenotype to its functional output and, by extension, to the host's broader energy economy.

Energy is an individual's potential or availability to perform mental and physical activity, synonyms include vigour, vitality, and being "full of pep". Fatigue, by contrast, is the subjective perception of reduced capacity or persistent exhaustion that interferes with function. Critically, these states can co-exist: an individual may feel simultaneously energetic and fatigued (92), for example, after intense but meaningful work, one might report both high energy and high fatigue (92, 93).

Boolani *et al.* demonstrated that predictors of energy differ from predictors of fatigue in a cohort of healthy young adults (93): poor sleep quality, more sitting time, and higher mental workload predicted fatigue, while better sleep quality, lower resting metabolic rate, and lower resting muscle oxygen saturation predicted higher energy. The correlation between energy and fatigue was only moderate ($r = -.35$), reinforcing their conceptual independence. Factor-analytic studies confirm this: predictors of fatigue explain 46.1% of its variance, versus only 22.7% for energy, with minimal predictor overlap, suggesting they arise from distinct physiological pathways (93).

Two proteomic studies from Boolani *et al.* provide direct biological support. A

salivary proteomics investigation (94) identified distinct molecular signatures for energy and fatigue: energy was enriched in ATP biosynthesis, oxidative phosphorylation, humoral immune response, and complement/coagulation pathways, plus disease-gene clusters linked to cardiomyopathy; fatigue was characterised by catabolism, ubiquitination, unfolded protein response, oxidative stress, and innate immune/complement activation. These profiles overlapped only partially, supporting genuinely separate biological states.

A complementary exercise-heat-stress study (95) found that dehydration amplified physical and mental fatigue without differentially suppressing energy. Increased mental energy correlated with greater blood CO₂ change (more efficient aerobic ATP generation; $p = 0.02$); increased mental fatigue correlated with attenuated blood chloride decreases, linked to catabolic immune signalling ($p = 0.04$); and preserved haemoglobin correlated with increased physical energy ($p = 0.04$), together grounding the energy-fatigue distinction in converging proteomic, exercise-physiology, and biochemical evidence. Physiologically, energy and fatigue are regulated by distinct neurochemical systems while both remaining aligned

with evolutionary survival strategies. Energy is associated with an approach-oriented system designed for activities such as hunting, exploration, and social engagement, with dopamine, norepinephrine, and glucose metabolism as its primary neurochemical correlates (92); high trait energy correlates with efficient ATP production (intact oxidative phosphorylation), lower resting muscle oxygen saturation, and paradoxically a lower resting metabolic rate, indicating metabolic efficiency rather than excessive mobilisation (92, 93). Fatigue, instead, represents an avoidance-oriented system evolved to promote rest, healing, and recovery during illness (96, 97), with serotonin, histamine, and pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) as its primary correlates. Fatigue is characterised metabolically by mitochondrial dysfunction, lower glycolytic rates and decreased mitochondrial membrane potential (98, 99), and a pathological shift toward less efficient anaerobic glycolysis with lactate accumulation in brain and muscle (100). This creates an energy paradox: the body consumes substantial resources through inefficient metabolism while producing inadequate ATP for function, manifesting subjectively as exhaustion despite resource mobilisation, with elevated reactive oxygen species and oxidative stress further characterising fatigue states.

Evidence for the immunological basis of fatigue and energy

The core argument of this review is that subjective energy and fatigue are directly linked to the immune system's functional and metabolic state, palpable readouts of immunological activity rather than abstract psychological constructs. Evidence spans circulating cytokines, cellular energy expenditure, and the gut-immune axis.

A body of research links fatigue in disease to a detectable pro-inflammatory blood "signature" (101, 102). In a comparison of a post-stroke cohort with a general-population cohort, fatigue associated with elevated interleukin-8 (IL-8) in stroke patients and interferon-gamma-inducible protein 10 (IP-10) in the general population (103). However,

the magnitude invites caution: the reported differences of 3-5 pg/mL for IL-8 and IP-10 fall several orders of magnitude below the nanomolar concentrations (roughly 1,000-8,000 pg/mL) required for receptor activation on immune effector cells *in vitro*, and the authors themselves reported that these associations lost statistical significance after correction for multiple comparisons, suggesting the purported “signature” may reflect statistical noise rather than a biologically coherent inflammatory phenotype.

This cytokine-fatigue link has been further explored in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a ‘gold-standard’ example of fatigue’s pathophysiology. A comprehensive study of 192 ME/CFS patients and 392 healthy controls found that, of 51 cytokines assessed simultaneously in plasma, only Transforming Growth Factor-beta (TGF-beta) and resistin differed on average, while 17 others were associated with disease severity, most prominently CCL11 (Eotaxin-1), CXCL10 (IP-10), IFN-gamma, IL-12p70, leptin, and Leukaemia Inhibitory Factor (LIF) (101). The authors corrected for multiple testing and stratified patients by severity to isolate a true symptom-cytokine correlation, but cytokine levels were reported as median fluorescence intensity rather than absolute serum concentrations, making it difficult to assess whether the observed differences are mechanistically sufficient to drive receptor signalling *in vivo*.

These findings show that fatigue correlates with detectable immune perturbations, but a cytokine-centric model cannot explain the subjective states of energy and fatigue in healthy individuals, where cytokine levels remain stable while energy and vitality vary considerably, pointing instead to metabolic or bioenergetic mechanisms operating independently of inflammatory status.

As mentioned above, the immune response is among the most metabolically expensive physiological processes (104). When the immune system is activated, immune cells undergo rapid metabolic reprogramming to meet the high energy demands of mounting a defence (105), with profound implica-

tions for the host’s overall energy budget: mammals allocate energy among three major maintenance programs, basal metabolic rate, locomotor activity, and adaptive thermogenesis (106, 107). According to the “selfish immune system” (108) and “selfish brain” (109) theories, the immune system and central nervous system occupy the highest priority in this hierarchy during crises; neither is willing to sacrifice its function for other organs, forcing trade-offs elsewhere. The trade-off between immunity and thermogenesis is particularly instructive: when an individual faces immune challenge while also requiring thermoregulation, the body makes a strategic decision, abandoning homeothermy and lowering core body temperature to redirect maximal energy toward immune defence (110-112), not metabolic failure, but a regulated, adaptive trade-off reflecting an evolutionary calculation that surviving acute infection outweighs maintaining normal temperature.

Beyond cytokine profiles, some of the most reproducible immunological evidence linking fatigue to immune dysfunction comes from measurements of NK cell function. A 2024 meta-analysis pooling 28 published studies demonstrated that NK cell cytotoxicity in ME/CFS patients is reduced to approximately half of healthy control levels, yielding a large effect size (Hedges’ $g = 0.96$), a finding notable precisely because it is reproducible, unlike the cytokine associations discussed above, and has been documented since 1987 (113, 114). Proposed mechanisms include suppressed mTOR signalling, impaired granule release, and metabolic failure in NK cells, all of which align with the immunometabolic framework developed in this review and can be read as a quantifiable index of the immune system’s failure to sustain energy-demanding effector functions, a cellular-level correlate of the fatigue state.

Plasmacytoid dendritic cells (pDCs) and constitutive type I interferon signalling implicate a further mechanism: a 2025 cell-free RNA study identified pDCs as the most elevated immune cell type in ME/CFS patients (115), consistent with persistent antiviral alarm (116, 117).

Type I interferons are among the most energetically costly cytokine responses (118, 119), and interferon-induced sickness behaviour in hepatitis C treatment remains one of the clearest examples of immune activation causing profound fatigue in humans (120-122).

The most direct metabolic evidence comes from measurements of energy currency within immune cells: a 2025 multi-omics study documented elevated AMP/ADP and a reduced ATP/ADP ratio in PBMCs from ME/CFS patients (123), a state of chronic cellular energy stress moving beyond the limitations of cytokine measurement, alongside skewing toward less mature T-cell subsets and reduced terminal NK populations.

A complementary line of evidence concerns epigenetic reprogramming of T cells toward exhaustion (124, 125): CD8+ T cells in ME/CFS appear epigenetically predisposed toward terminal exhaustion, connecting directly to the TCF7/immune-resilience framework below; if TCF7 expression preserves T-cell stemness, its epigenetic silencing may convert transient fatigue into the self-perpetuating exhaustion of chronic disease, explaining both the chronicity of fatigue and its resistance to anti-inflammatory therapy.

The immune bridge: translating living conditions into energy states

Having established links between energy/fatigue and immune-metabolic states in health and disease, we can construct an integrative model converting psychosocial inputs into immunometabolic responses perceived as energy or fatigue (Fig. 2).

Psychosocial inputs (emotions, personality, relationships, meaning, socioeconomic context) are mirrored in the immune system, which manages available energy alongside the brain to guarantee survival. Positive psychological states and social resources act as immunoboosters and energy-enhancing therapies (126, 127). Even at the level of cytokines, a sense of purpose in life, the extent to which individuals perceive their lives as having direction and meaningful goals (126), associates with lower inflammatory markers (128, 129); longitudinal research

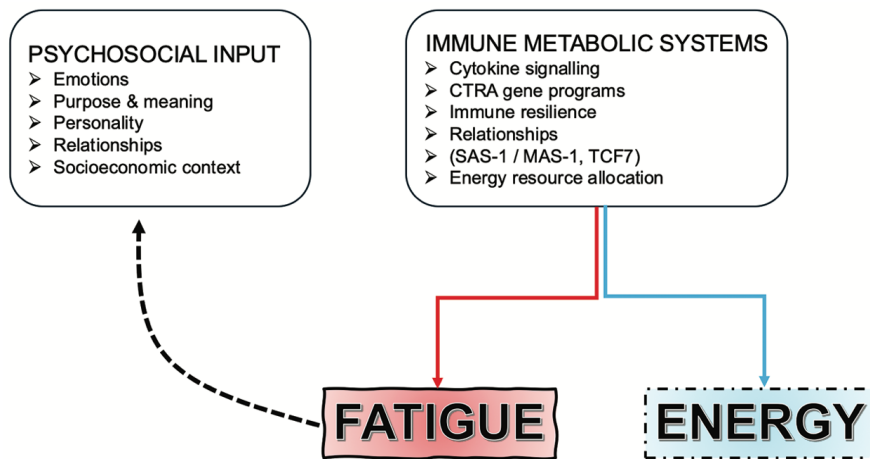


Fig. 2. The immune bridge: from lived experience to felt energy.

Psychosocial inputs (emotions, purpose and meaning, personality, relationships, socioeconomic context) are integrated by the immune-metabolic system (cytokine signalling, CTRA gene programs, immune resilience signatures (SAS-1/MAS-1, TCF7), and energy resource allocation) which in turn determines whether an individual experiences fatigue or energy. The dashed feedback arrow indicates that the resulting mood state feeds back to shape subsequent psychosocial experience, closing the loop between lived experience and immune function.

in older adults shows higher purpose predicts reduced IL-6 and CRP over time, independent of demographics, health behaviours, and baseline health (128, 130). These associations appear causal rather than merely correlational: within-person increases in purpose over time correspond to decreases in inflammation, suggesting that interventions to enhance meaning and purpose could serve as novel anti-inflammatory strategies. Consistent with this, a 2020 study by Slavich *et al.* showed psychological therapies can reduce disease-causing inflammation, with benefits lasting at least six months post-treatment (131). Purpose is well known to associate with a state of energy, also defined as “subjective vitality,” the conscious experience of having energy available to the self (132, 133), and, ranging from the Japanese concept of Ikigai to Western longitudinal studies, purpose acts as a distinct metabolic cue predicting both self-reported vigour and objective reductions in inflammatory markers and allostatic load (134, 135), reflecting a eudaimonic state in which brain and immune system collaborate to release rather than conserve metabolic resources.

These immune benefits extend to discrete positive emotions (136–138): increases in positive emotion correspond to decreased pro-inflammatory and

interferon-response gene expression (139, 140), differing from the CTRA profile of adversity (65). Awe shows particularly strong inverse associations with pro-inflammatory cytokines (138, 141), and prosocial behaviours, kindness (142, 143), volunteering (144, 145), improve CTRA profiles, suggesting biological benefits that may include increased energy or reduced fatigue.

A parallel literature on immune resilience (IR) shows how the immune system can be “designed” to generate rather than deplete energy. As defined by Ahuja, Manoharan *et al.* (34), IR is the capacity to preserve or rapidly restore immune function against inflammatory stressors, measurable via two transcriptomic signatures: a Survival-Associated Signature (SAS-1) and Mortality-Associated Signature (MAS-1).

Central to high IR is the expression of the master regulator T-cell factor 7 (TCF7), a transcription factor essential for maintaining the “stemness” and regenerative capacity of T cells (146, 147). The TCF7 gene encodes TCF1, a Wnt-pathway-dependent master regulator of T-cell stemness and regenerative potential (148, 149). Individuals with high TCF7 expression maintain anti-aging immune profiles characterised by increased naive T cells, reduced T-cell exhaustion, and balanced inflammatory responses (150, 151); this trait

is a core component of SAS-1, which integrates immunocompetence with inflammation control, actively resisting the three major drivers of mortality: inflammaging, immunosenescence, and cellular senescence. The clinical impact is potentially profound: 40-year-olds with high immune resilience have mortality and disease profiles equivalent to 55-year-olds without it, a 15.5-year survival advantage that is, remarkably, age-independent, with IR-preservers maintaining robust pathogen defences into extreme old age (150).

In this framework, a high-functioning TCF7 network acts as a “biological warranty” for resetting after inflammatory challenge, promoting recovery and longevity. By contrast, in ME/CFS, CD8+ T cells show reduced TCF7 chromatin accessibility alongside upregulated exhaustion markers (PD-1, TOX, SLAMF6) and metabolic reprogramming toward glycolysis, a signature of failed regenerative capacity (152). Loss of IR appears central to the chronic inflammation defining many modern diseases; restoring TCF7 expression becomes not merely disease treatment but a shift toward resilience and energy (Fig. 3).

Towards immunological biomarkers of fatigue

The evidence reviewed above highlights a key limitation of the cytokine-centric approach: plasma cytokine levels, while statistically associated with fatigue in some studies, are mechanistically insufficient to explain either the severity or the universality of fatigue symptoms, particularly in conditions where cytokine levels remain stable yet subjective energy and vitality vary considerably. This disconnect calls for a shift in biomarker strategy, from extracellular inflammatory mediators toward functional and metabolic indices measured within immune cells themselves. Three candidate biomarker domains emerge from the current evidence. First, NK cell cytotoxicity, the most reproducible immune finding in fatigue research ($g=0.96$), reflects the immune system’s capacity to sustain energetically demanding effector activity (114). Second, intracellular energy metabolism in PBMCs, the ATP/

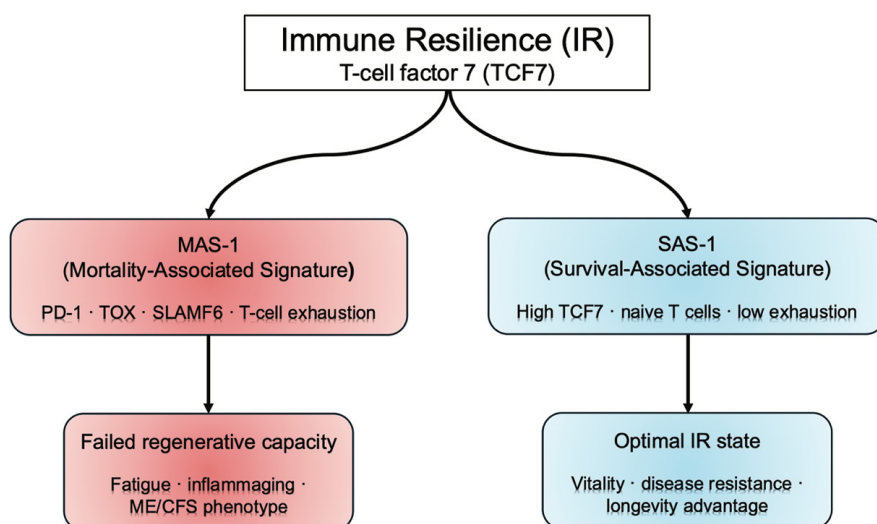


Fig. 3. Immune resilience as a determinant of energy and fatigue.

Immune resilience (IR), centred on expression of T-cell factor 7 (TCF7), diverges into two transcriptomic signatures. The Mortality-Associated Signature (MAS-1), marked by PD-1, TOX and SLAMF6 expression and T-cell exhaustion, reflects failed regenerative capacity and is associated with fatigue, inflammaging, and the ME/CFS phenotype. The Survival-Associated Signature (SAS-1), marked by high TCF7 expression, naive T-cell maintenance, and low exhaustion, reflects an optimal IR state associated with vitality, disease resistance, and a longevity advantage.

ADP ratio and kynurenine-pathway metabolites regulating NAD⁺ synthesis, offers a direct index of cellular energy stress mapping onto subjective exhaustion (123). Third, transcriptomic signatures combining TCF7 expression, pDC activation, and SAS-1 may together constitute a multi-component immune vitality index capturing both inflammatory and regenerative dimensions (34, 150). Standardising these assays and validating them against patient-reported energy and fatigue in rheumatologic cohorts represents a tractable next step for translational research.

Proteomic analysis by Boolani *et al.* (94) corroborates these findings at the salivary level: energy states were enriched in purine nucleotide synthesis and ATP biosynthesis, while fatigue states showed catabolic and oxidative stress signatures, a molecular parallel to the PBMC energy stress documented by Heng *et al.* (123), strengthening the case that immune cell metabolic state is the common substrate of the energy-fatigue dimension.

Therapeutic approaches: modulating immunity to enhance energy

The proposed immunological model of energy and fatigue has direct therapeutic

implications: if fatigue reflects immune dysregulation, interventions that modulate the immune system should serve as effective treatments. The plasticity of the emotional-immune-metabolic continuum (33) enables multiple pathways shifting individuals from fatigue-supporting toward energy-supporting immune states.

In health, accessible lifestyle and emotional interventions can reduce fatigue and promote energy by targeting immune function and resilience, promoting eu-inflammation, a physiological, protective inflammatory response that maintains tissue health and initiates repair (153, 154), distinct from chronic low-grade disease-associated inflammation. Chronic endurance training improves mitochondrial biogenesis in muscle and immune cells; cardiorespiratory fitness (VO₂ peak) correlates positively with immune cell mitochondrial respiration and inversely with inflammatory markers (155, 156), mapping onto the observation that high trait energy associates with efficient mitochondrial function and lower resting metabolic rate. Regular exercise also increases regulatory T cells, NK cell killing capacity, and reduces Th1/Th17 polarisation (157–159), creating an eu-inflammatory baseline even at

rest. Eudaimonic interventions, cultivating purpose, meaning, and authentic relationships, offer a comparably powerful shift, downregulating CTRA and reprogramming immune cells toward eu-inflammatory gene expression independent of life circumstances.

How would this change in disease, particularly in rheumatology patients? Viewing fatigue through this immunological lens offers new therapeutic avenues for clinical practice. Environmental rheumatology increasingly recognises that rheumatologic diseases result not from genetic determinism but from environmental factors, such as infections, pollutants, diet, psychosocial stress, occupational exposures, triggering autoimmunity in genetically susceptible individuals. The affective immunology framework extends this view to emotions, personality traits, and social circumstances as key environmental determinants of disease progression and fatigue levels. Rather than focusing solely on symptom suppression, clinicians can aim to restore the underlying immune homeostasis. As conceptualised by Ruslan Medzhitov, homeostasis is the fundamental process of maintaining all regulated variables (cell number, tissue structure, metabolic waste) within acceptable, stable ranges, with inflammation as a defence response to deviations from this normal state (160, 161). In chronic conditions like those rheumatology patients experience, this homeostatic balance is lost, resulting in persistent, non-resolving inflammation. By using the same lifestyle, emotional, and potentially future pharmacologic approaches that build resilience and maintain eu-inflammation in healthy individuals, clinicians can help restore a balanced, resilient immune state in patients (Fig. 4).

This immune-metabolic model has several limitations. First, the relationship between immune-cell bioenergetics and fatigue remains largely correlational: whether cellular energy stress in PBMCs causally drives central fatigue cannot be resolved cross-sectionally; longitudinal, interventional studies are needed to establish directionality. Second, a scale gap separates cellular bioenergetic shifts in peripheral leuko-

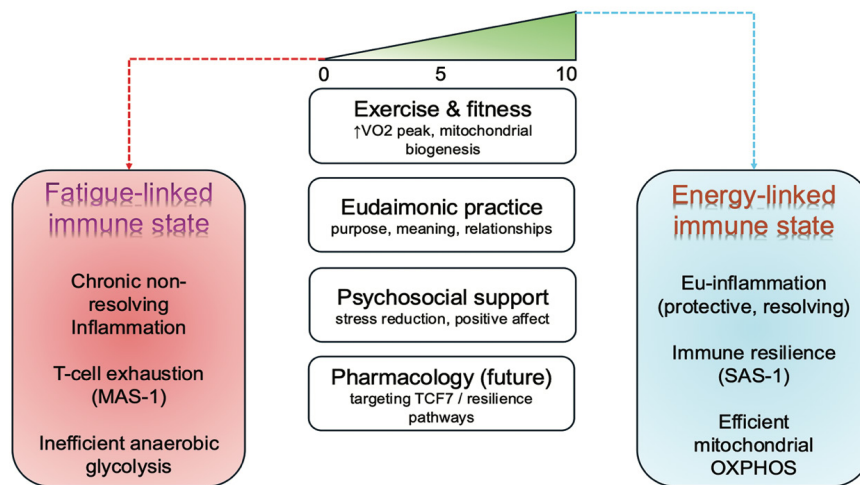


Fig. 4. Restoring immune-supported energy in rheumatic disease.

A conceptual continuum linking modifiable interventions to immune state and, ultimately, to the patient's experience of energy or fatigue. Exercise and fitness, eudaimonic practice, psychosocial support, and (prospectively) pharmacological targeting of resilience pathways promote a shift from a fatigue-linked immune state (chronic non-resolving inflammation, T-cell exhaustion/MAS-1, inefficient anaerobic glycolysis) toward an energy-linked immune state (eu-inflammation, immune resilience/SAS-1, efficient mitochondrial OXPHOS).

cytes from the conscious experience of fatigue; the pathways translating such signals into perceived exhaustion remain largely theoretical. Third, glycolytic reprogramming is not disease-specific, occurring across acute infection, inactivity, and other unrelated conditions, limiting its value as a biomarker. A further, more basic limitation is the absence of any validated experimental model of fatigue, particularly its emotionally modulated component, which constrains direct mechanistic testing rather than correlational inference.

Conclusions

Fatigue and energy in rheumatic disease should no longer be viewed as vague byproducts of inflammation, but as distinct, immunologically grounded mood states arising from specific configurations of emotional, metabolic, and immune activity. Reframing them as readouts of immune-metabolic trade-offs turns persistent fatigue from a purely subjective complaint into a biologically meaningful signal that the immune system is reallocating resources and, in many patients, failing to restore homeostasis.

Fatigue remains one of the most methodologically challenging domains in rheumatology: inherently subjective, temporally dynamic, and context-de-

pendent, making it difficult to quantify, model in animals, or recapitulate in vitro, which helps explain why decades of progress modelling joint inflammation, autoantibodies, and structural damage have not yielded comparably robust fatigue biomarkers, despite its central importance to patients' lives.

Clinically, fatigue represents a paradigmatic "invisible" symptom, rarely evident on examination or routine tests, yet reported by the majority of people with inflammatory rheumatic and musculoskeletal diseases as one of their most intrusive, disabling problems, often more burdensome than pain. Its invisibility to clinicians, employers, and even family members contributes to psychological distress, social withdrawal, and the feeling of being disbelieved or dismissed, adding a layer of affective suffering to an already complex disease burden.

Management should shift from suppressing a single symptom to restoring immune-supported energy through pharmacologic, lifestyle, and psychosocial strategies that promote eu-inflammation and immune resilience. Current EULAR recommendations already favour multifaceted, patient-centred fatigue care; this review suggests such approaches may work partly because they reshape the emotional-immune-

metabolic circuitry underpinning subjective vitality.

This perspective sets a clear research agenda: developing translational models that capture the subjective, invisible nature of fatigue; identifying immune-resilience signatures that predict trajectories of energy and exhaustion; and testing interventions (pharmacologic, behavioural, social) that deliberately cultivate these salutogenic immune states. This will require sustained collaboration between immunologists, rheumatologists, neuroscientists, psychologists, and, crucially, patients themselves, whose lived experience of "invisible" fatigue must guide the next generation of mechanistic and therapeutic studies.

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