Cell Signaling

Subramanian et al, Cell Signal. 2024;2(1):120-125.

Commentary

The interplay of regulatory T cells, endoplasmic reticulum stress, and unfolded protein response activation in post-transplant alloimmune hepatitis and autoimmune hepatitis

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Received date: June 20, 2024
Accepted date: August 02, 2024

Citation: Subramanian K, Ekong UD. The interplay of regulatory T cells, endoplasmic reticulum stress, and unfolded protein response activation in post-transplant alloimmune hepatitis and autoimmune hepatitis. Cell Signal. 2024;2(1):120-125.

Abstract

Autoimmune hepatitis and post-transplant alloimmune hepatitis are inflammatory conditions observed in the native and transplanted liver respectively. Regulatory T cells play a crucial role in the maintenance of immune tolerance and prevention of autoimmunity. Endoplasmic reticulum stress with unfolded protein response activation have been reported in circulating regulatory T cells suggesting a possible link between them. This review explores the role of regulatory T cells in autoimmunity focusing on their function and regulation in the liver. It also highlights the involvement of endoplasmic reticulum stress and unfolded protein response activation in autoimmune diseases. Understanding the interplay between endoplasmic reticulum stress, unfolded protein response activation and regulatory T cells may provide insights into disease pathogenesis and identify novel therapeutic targets for treatment of autoimmune liver diseases.

Keywords: Activating transcription factor 6 (ATF6), Regulatory T cell dysregulation, CCAAT/enhancer-binding protein homology protein (CHOP), Human endogenous retrovirus (HERV)

Abbreviation: ABCA12: ATP-Binding Cassette A12; ATF4: Activating Transcription Factor 4; ATF6: Activating Transcription Factor 6; ATP: Adenosine Triphosphate; BiP: Binding Immunoglobulin Protein; C/EBPβ: CCAAT/Enhancer-Binding Protein Beta; CHOP: CCAAT/Enhancer-Binding Protein Homology Protein; CXCR4: CXC Motif Chemokine Receptor 4; dnAIH: De novo Autoimmune Hepatitis; eIF2α-p: Phosphorylated Translation Initiation Factor; Env-HERV1: Envelope Protein of HERV1_I; ER: Endoplasmic Reticulum; ERAD: ER-Associated Protein Degradation; FOXP3: Forkhead Box Protein P3; Gal9: Galectin-9; IRE1: Inositol-Requiring Enzyme 1; KLF4: Krüppel-like Factor 4; LAG3: Lymphocyte Activation Gene 3; PD-1: Programmed Cell Death Protein 1; PERK: Protein Kinase RNA-like ER kinase; pSTAT-5: Phospho Signal Transducer and Activator of Transcription 5; RA: Rheumatoid Arthritis; RORC: RAR Related Orphan Receptor C; SLE: Systemic Lupus Erythematosus; STAT3: Signal Transducer and Activator of Transcription 3; T1D: Type 1 Diabetes; TCR: T cell Receptor; Tim-3: T cell Immunoglobulin Domain and Mucin Domain-3; TLR2: Toll-like Receptors (TLR) 2; TLR4: Toll-like Receptors (TLR) 4; Tregs: Regulatory T cells; UPR: Unfolded Protein Response; XBP1: Spliced X-box Protein

Introduction

The incidence and prevalence of autoimmune hepatitis (AIH) globally is 1.28 per 100,000 population-years (95% CI, 1.01-1.63) and 15.65 per 100,000 population (95% CI, 13.42-18.24), respectively [1]. The incidence and prevalence in children is 0.4 and 3.0 cases per 100,000 children [2], and in adults 17 per 100,000 [3,4]. Post-transplant alloimmune hepatitis also called *de novo* autoimmune hepatitis (*dn*AIH) is an uncommon but serious condition observed in the transplanted

liver that can lead to chronic rejection, graft loss, and a need for liver re-transplantation [5]. Its frequency is higher in children [6] (5%-10%) than in adults (1%-3%) [7]. Regulatory T cell (Treg) dysfunction has been observed in children with post-transplant alloimmune hepatitis, specifically, circulating Tregs of children with post-transplant alloimmune hepatitis exhibit higher frequencies of pro-inflammatory IFN-γ and IL-17 cytokines despite having a fully demethylated Foxp3 locus. The driver behind Th1-like Tregs is thought to be IL-12 production by monocytes/macrophages. Inflammasome activation of $CD14^+$ monocytes, mediated via Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4), is responsible for IL-12 production. IL-12 drives Tregs to adopt a Th1-like phenotype with aberrant production of IFN-γ, contributing to Treg dysfunction [8,9]. Downregulation of TLR2 and TLR4 on $CD14^+$ monocytes abrogate IL-12 production by monocytes and thus IFN-γ production by Tregs, resulting in partial recovery of Treg suppressor function [9]. The above reports underscore the significance of monocytes in driving the development of a proinflammatory Treg phenotype in post-transplant alloimmune hepatitis. The exact cause of AIH is not fully understood, but it is believed to involve a combination of genetic, environmental, and immunological factors. In several studies, mainly involving pediatric patients, it has been shown that peripheral blood Tregs are reduced in frequency and their function impaired [10-12]. Other observations reported include effector CD4 T cells that are less susceptible to Treg restraints; specifically, defects caused by reduced T cell immunoglobulin and mucin domain 3 (Tim-3) levels on effector T cells and Galectin-9 (Gal9) on Tregs render effector cells resistant to Treg control, implicating the failure of immune control on both sides [13]. Liver injury is perpetuated and progresses due to an imbalance between effector and regulatory cells [14]. Additionally, effector T cells are activated and produce pro-inflammatory cytokines which induces inflammation in the liver [15-17]. Th17 cell activation is also linked to liver injury in AIH, primarily through inflammation and the initiation of pro-fibrotic processes [18,19]. Reduced Treg function in AIH is associated with impaired Treg ability to produce IL-10 and Treg inability to upregulate phospho signal transducer and activator of transcription 5 (pSTAT-5) in response to IL-2 [20,21]. Tissue damage and inflammation leads to elevated levels of extracellular adenosine triphosphate (ATP). CD39 is an enzyme that breaks down extracellular ATP/ADP into AMP that is converted to the immunosuppressive molecule adenosine 5'-ectoenzyme CD73 [22]. An imbalance of Tregs and Th17 cells has been observed and reported in AIH and is attributed to decreased CD39 levels. Decreased $CD39^+$ Treg frequency reduce ATP/ADP hydrolysis activity and thus conversion of ATP to adenosine, resulting in failure of suppression of IL-17 production by effector CD4 T cells [23,24], which contributes to loss of immune tolerance and AIH [23,25,26].

Endoplasmic Reticulum Stress in Autoimmune and Alloimmune Liver Disease

The endoplasmic reticulum (ER) is crucial for protein synthesis, folding, and modification. When overwhelmed by oxidative stress or inflammation, misfolded proteins accumulate, leading to ER stress and triggering the unfolded protein response (UPR) [27]. The UPR is mediated by three main transmembrane proteins located in the ER membrane: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). These proteins are usually kept inactive by the ER chaperone protein BiP. Upon ER stress, BiP dissociates, activating these sensors and initiating the UPR signaling cascade [28,29]. Human Endogenous Retroviruses (HERVs) induce ER stress and activate the UPR [30,31]. Dysregulation of the UPR has been implicated in the development of several human diseases [32]. We observed up-regulation of the envelope protein of HERV1_I (env-HERV1) and UPR activation in peripheral blood Tregs and livers of children with post-transplant alloimmune hepatitis and AIH. Increased levels of ATF6A, spliced X-box protein (XBP1s), phosphorylated translation initiation factor (eIF2α-p) and CCAAT/enhancer-binding protein homology protein (CHOP) were observed. ER stress was HERV-mediated as the envelope protein of HERV1 interacted with ATF6 in peripheral blood Tregs [33]. ER stress has been implicated in the pathogenesis of other autoimmune diseases specifically, ER stress-induced β-cell dysfunction and development of type 1 diabetes (T1D) [34], ER stress in synoviocytes and chondrocytes and development of inflammation in rheumatoid arthritis (RA) patients [35]. Other examples include ER stress in B cells, macrophages, T cells, dendritic cells, and neutrophils contributing to systemic lupus erythematosus (SLE) [36–39], and ER stress in keratinocytes thought to contribute to the development of psoriasis [40].

Consequences of ER Stress and UPR Activation in Autoimmune and Alloimmune Liver Disease

The UPR affects nearly every aspect of the secretory pathway, including protein synthesis, transport to the ER, folding, maturation, quality control, protein trafficking, and the elimination of misfolded proteins by autophagy and ER-associated protein degradation (ERAD) [27,41]. In higher eukaryotes, UPR activation results in transient cell-cycle arrest at G1/S, and transcription of UPR target genes. Cells can adapt to stress or undergo apoptosis if homeostasis is not restored [42]. In post-transplant alloimmune hepatitis and AIH, peripheral blood Tregs undergo early apoptosis with increased PD1 and LAG3 expression suggesting a relationship between ER stress/unremitting UPR activation and immune checkpoint expression [33]. The association between ER stress induced apoptosis and disease pathogenesis is not limited to autoimmune/alloimmune liver disease as chronic ER stress-induced apoptosis of pancreatic β-cells in Type-1-Diabetes contributes to disease pathogenesis by reducing insulin production and secretion, while diminished activity of the transcription factors *ATF6* and *XBP1s* inhibits adaptive responses [43]. In Rheumatoid Arthritis, ER stress-induced apoptosis in synovial fibroblasts and chondrocytes contributes to joint destruction by activating GRP78, IRE1, XBP1s, ATF6, and eIF2a-P in macrophages and synovial tissues [35,44]. Additionally, ER-stress-induced apoptosis through transcriptional activation of CHOP leads to increased anti-apoptotic molecule Bcl-2 and caspase-6 signaling pathway in T cells in SLE [45]. Lastly, ER stress induced apoptosis of keratinocytes upregulates ABCA12 and KLF4 through XBP-1, and C/EBPβ through ATF4, which drives the abnormal skin cell proliferation and differentiation observed in psoriasis [46].

Dysregulation of Immune Responses following UPR Activation

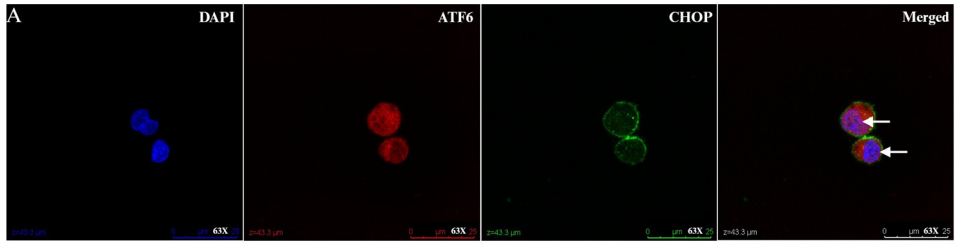
UPR activation has been linked to regulation of innate and adaptive immune responses. IRE1 and PERK signaling pathways play critical roles in modulating the production of pro-inflammatory cytokines and antigen presentation [47]. UPR activation regulates differentiation, plasticity, effector function, and apoptosis of $CD4^+$

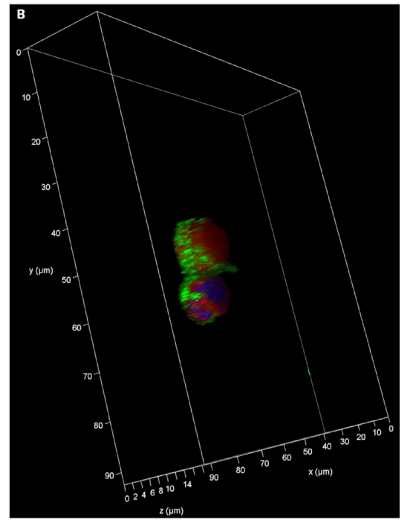
T cells and is important to $CD4^+$ T cell activation [48-50]. UPR activation is linked to B cell and classic dendritic cell differentiation and is necessary for antibody secretion from plasma cells [51,52]. As Tregs maintain immune tolerance and prevent autoimmunity, dysregulation of the UPR can disrupt their normal function and contribute to autoimmunity. In AIH and post-transplant alloimmune hepatitis, following UPR activation, ATF6 binds to the transcription promoter regions of RORC and STAT3 and drives Treg differentiation to Th17-like Tregs. Downregulation of UPR activation results in down regulation of the Th17 transcription factors, *RORC* and *STAT3*, and *IL-17A* mRNA. This is accompanied by partial recovery of Treg suppressive function supporting a relationship between UPR activation and adaptive immune response in alloimmune liver disease [33]. While we observed Treg dysregulation and dysfunction in ER-stressed peripheral blood Tregs of children with alloimmune liver disease, Feng *et al.* report their observation of enhanced TCR-induced activation and functional activity of BALB/c mice Tregs following thapsigargin-induced ER stress [53].

Liver Infiltrating Tregs in Autoimmune and Alloimmune Liver Disease

Liver-infiltrating Tregs are a distinct population of Tregs that migrate from the peripheral blood to the liver in response to local signals. They are enriched in the liver and exhibit unique phenotypic and functional characteristics compared to circulating Tregs [54]. They are thought to play a crucial role in modulating immune responses within the liver microenvironment particularly in the context of AIH and post-transplant alloimmune hepatitis. Ye *et al.* report that up to 18% of T cells in inflamed areas of the human liver with AIH are FoxP3 expressing Tregs [55]. The published literature on human liver infiltrating Tregs in AIH is varied with increased number of intrahepatic Tregs whose presence is linked to heightened activity and inflammation in the liver reported by some groups [56,57], while others report a disproportionate enrichment of intrahepatic Tregs in untreated pediatric AIH accompanied by a decrease in Treg frequency during treatment attributed to the decrease in IL-2 levels [20,58]. Taubert *et al.* have observed that their cohort of untreated patients with AIH have a constant Treg/T-effector ratio with no changes in Tregs in the circulation despite the presence of T-effectors in the liver. They speculate that following discontinuation of immunosuppression, high rates of relapse may be caused by a disproportional decrease of intrahepatic Tregs [58].

In addition to the expression of foxp3, liver infiltrating Tregs express higher levels of the chemokine receptors CXCR3 and CCR4 compared to peripheral blood Tregs [55]. This is significant in the context of a liver microenvironment that is characterized by an abundance of pro-inflammatory cytokines such as IL-6, IL-12, TNF, IFN-γ, and professional antigen-presenting dendritic cells. This microenvironment might hinder the function of intrahepatic Tregs either by impairing Treg suppression of effector cells or by increasing effector cell resistance to Treg suppression [59]. The liver microenvironment also plays a crucial role in the survival, differentiation, and apoptosis of both effector and regulatory lymphocytes [59]. Given our observation of regulation of the adaptive immune response in circulating Tregs following UPR activation, our laboratory has studied liver infiltrating Tregs in AIH and observes a suggestion of UPR activation as evidenced by ATF6α and CHOP activation (**Figure 1**). We propose more research that investigates crosstalk between ER stress, UPR activation and Treg function in autoimmune liver disease (**Figure 2**).





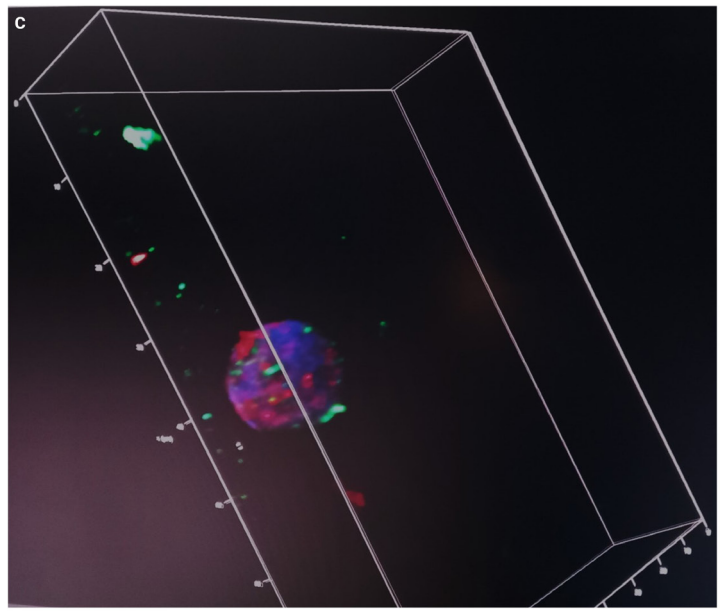


Figure 1. Liver infiltrating regulatory T cells (Tregs) in health and disease. Intrahepatic lymphocytes extracted from fresh liver tissue of non-transplanted control and autoimmune hepatitis patient were enriched for CD4, then stained with CD45, CD25, and CD127, before undergoing fluorescence activated cell sorting on an Aria sorter for liver infiltrating Tregs (defined as $CD4^{+}CD25^{hi}CD127^{-}$). $1X10^{5}$ liver infiltrating Tregs were cultured in TCM media with rIL-2 for 48-hours, fixed with 4% paraformaldehyde for 10-minutes, and then stained with ATF6α and CHOP. Representative confocal micrographs showing: **(A)** nuclear localization of ATF6 (red) in Tregs from a non-transplanted control liver (white arrow). Nuclei are labeled with DAPI (blue). There is absence of nuclear localization of CHOP (green). Scale bars 50 µm. **(B)** Representative Z stack confocal image acquired with 3D Leica SP8 of Tregs from a non-transplanted control liver with absence of nuclear localization of CHOP (green). Magnification 63X. **(C)** Representative Z stack confocal image acquired with 3D Leica SP8 of Tregs from an autoimmune hepatitis liver showing co-localization of ATF6 (red) with DAPI (blue) and CHOP (green). Magnification 63X.

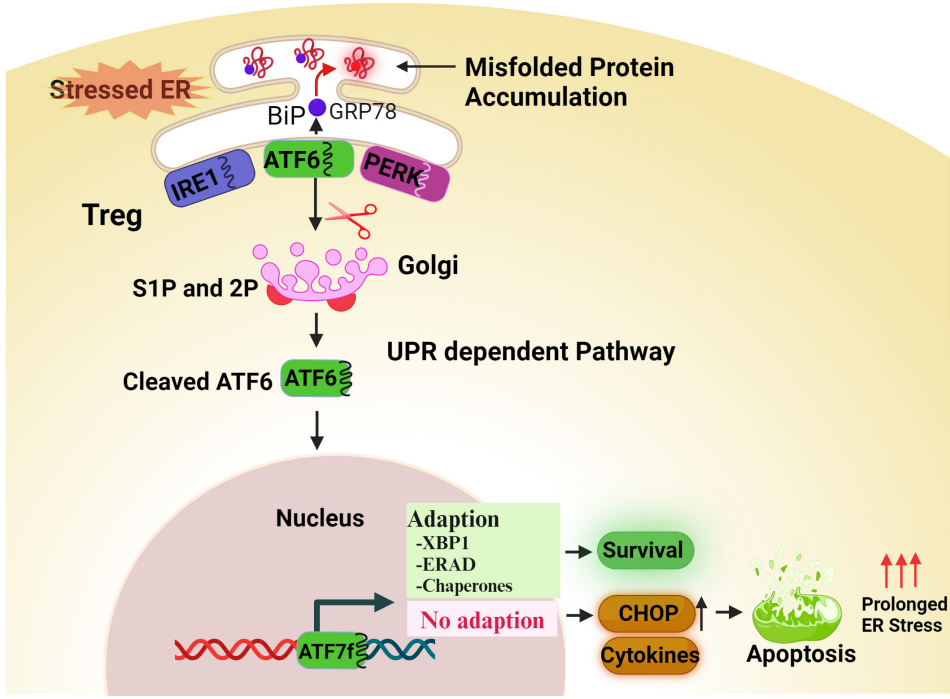


Figure 2. Proposed schematic model shows the interaction between regulatory T cells (Tregs) and endoplasmic reticulum (ER) stress / unfolded protein response (UPR) activation indicating potential crosstalk with impact on Treg function.

Conclusion

More research is needed to clarify the complex relationship between Treg function, ER stress, and UPR activation in human autoimmune liver disease as new insights into these interactions may pave the way for development of targeted therapeutic interventions aimed at restoring immune homeostasis and mitigating liver injury.

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