PAMP-DAMPS interactions mediates development and progression of multiple sclerosis

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1. ABSTRACT

Multiple sclerosis (MS) is a disease presumably associated with chronic immune stimulation promoted by either pathogens or autoimmune processes. It has been hypothesized that MS could be the result of previous viral infections rendering a permanent immune stimulation that could be triggered by molecular similarities, or by modulating the antigens expression of major histocompatibility complex (MHC) on target cells, which in turn act as super antigens. During immune stimulation occurs the recruitment of immunological cells, resulting in local tissue damage and leading to the release of damage-associated molecular patterns (DAMPs), which also act as inflammation inducers. Recently, it has been proposed that the association between pathogen-associated molecular patterns (PAMPs) with DAMPs constitutes an additional level of immune regulation. The properties of DAMPs to act as carriers of PAMPs and their role as enhancers or inhibitors of PAMPs could play a role during inflammatory responses triggered by infections. Here, we focused this review in outcomes which support the hypothesis that particular PAMP–DAMPs interactions could regulated the relapse and progressive disability observed in multiple sclerosis.

2. INTRODUCTION

Multiple sclerosis (MS) has been described as an inflammatory, demyelinating and neurodegenerative disease which cause damage in Central Nervous System (CNS). MS affects mainly young adults and it causes non-traumatic disability; therefore, it has a great socioeconomic impact in both family and patients. During the development of MS, several neurologic symptoms are originated and they are followed by neurologic disorders that remain latent in patients, increasing their physical disability and eliciting a complete socioeconomic dependence beyond 30 years, resulting in a plethora of neurological symptoms in the most productive stage of the patient’s life (1). MS affects women two-fold more than men and has a peak onset between 20 and 40 years old; however, it also may be found in children and occasionally in individuals aged above 60 years old. (2).

During the natural course of the disease, more than 60% of patients develop the relapsing–remitting form of MS (known as RRMS). At this stage, some neurological symptoms may arise followed by a partial or complete recovery of the patient (3-5). However, a high percentage of patients affected by RRMS (up to 90% younger than 25 years old) develop secondary progressive multiple sclerosis (SPMS), which is characterized by neurological degeneration without any relapsing episodes (3-7). Approximately, 15% of MS patients are diagnosed with primary progressive MS (PPMS) which show neurological symptoms that advance progressively from the beginning of the disease (3-5,8).

Besides the complexity of the pathophysiology of MS disease, several factors have been postulated in its development, such as genetic susceptibility, environmental conditions, and an abnormal immune-mediated response leading to autoimmunity which causes focal destruction of myelin, axonal loss and inflammatory cells infiltrate (9). MS is characterized by chronic inflammation of the CNS that led to auto-reactivity immune in cells that destroy many components of the
CNS. Oligodendrocytes form glial scar in the nervous tissue, and the myelin sheaths of axons are affected (5). Particularly, the demyelinated plaques observed in MS patients consist in a well-delimited area with scarce cells characterized by loss of myelin sheath in neurons with relative preservation of their axons and the formation of astrocytic scars (10).

The presence of active plaques is the result of brain blood barrier (BBB) leakage, glial scar formation and the presence of inflammatory infiltrates (10). These infiltrates consist of auto reactive lymphocyte T cells, macrophages, and mast cells, which could reach to the CNS inducing a pro-inflammatory response, followed by local tissue damage (11-13). The formation of active plaques initiates when mononuclear cell infiltrates, which are concentrated in perivascular spaces, induce the destruction of myelin sheath. These infiltrates are composed mainly by B and T cells, plasmatic cells, and macrophages (14). Poskanzer introduced the hypothesis that MS is a late consequence of an infectious disease which is frequently acquired in childhood (15). More than 30 viral antigens, including virus for rabies, herpes simplex virus, varicella zoster, measles, corona virus, canine distemper virus, HTLV-1, and Epstein-Barr virus (EBV) have been tested to demonstrate the presence of antibodies in serum from patients with MS (14,16-21).

Currently, the main candidate related with MS is Epstein-Barr virus (EBV). Although this has not been confirmed as specific trigger for this disease; several authors suggest that EBV is involved in the initial disease phase. (22,23). This virus might induce damage on myelin sheaths by autoimmune processes triggered by molecular mimicry, expression and overexpression of MHC antigens on target cells, and also, EBV might act as super antigens (24). During the beginning and the development of MS, the persistent cell infection by virus infiltrates the CNS and modulates the immune response, activating both T and B cells, similar process that occurs when a pathogenic infection is involved (25-27). Besides, there are other mechanisms of activation of TLR where pathogens-associated molecular patterns (PAMPs) are not involved, which consist in endogenous inflammatory mediators called damage-associated molecular patterns (DAMPs) that also regulate immune response. However, the role played by DAMPs in inflammation/immunity during virus infection has little been studied (28).

3. IMMUNOMODULATION OF TLR BY PAMP-DAMPS

The pattern recognition receptors family (PRRs) is known to be the first line of defense against foreign pathogens which detects distinct evolutionarily conserved structures. PRRs are comprised by TLRs, which are activated either by PAMPs, DAMPs or by the PAMP- DAMPs complex. This association is essential to initiate the development of several autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and MS (29-31). These receptors can be found in the outer of surface cells, into the membrane of endosomes of several cell types, or non-immune and immune cells, where TLRs mainly recognize macrophages, B cells (32) and other antigen presenting cells (APCs) such as dendritic cells (DCs) (32,33). Several TLRs including types 1, 2, 4, 6, and 10 are expressed in the outer membrane where they recognized and respond primarily to bacterial and viral antigens surface associated to PAMPs. Also, TLRs 3, 7, 8 and 9 are preferentially activated by viral antigens, being able to recognize specific nucleic acid (either DNA or RNA) based PAMPs of intracellular pathogens (34).

The interaction of TLRs with PAMPs and DAMPs causes the activation of genes encoding for pro-inflammatory cytokines, chemokines, and co-stimulatory molecules that consequently trigger innate immune responses and prime antigen-specific T cells (35). Also, PAMPs and DAMPs are able to activate NFκB, which in turn may triggers PI3K/AKT and Ras/MAPK signaling that are involved in both cell survival and mitogenic process (36). Abnormal TLR stimulation contributes to the development of many inflammatory and autoimmune diseases (35,37).

The repertory of DAMPs is determined by some factors such as the type of cell death, cell- line as well as the damaged tissue (38). Cell death processes and biochemical pathways determine the kind of DAMPs exposed, released, and their function. The DAMPs that trigger the activation of inflammasome include the mammalian cytosolic double-stranded RNA, low intracellular K+ levels, some heat shock proteins (Hsp) and gp96 (39,40). Hsp90 and Hsp70 enhance immune responses through a chaperone activity; where the generation of Hsp- antigen complexes promotes the presentation of unlinked antigens, maturation of APC and stimulation of cytotoxic T lymphocytes through MHC class I (41). In the innate immune system, Hsp act as immune-stimulators, suggesting that those proteins can contributed to the development of the autoimmune response after cell damage (24,42) (Figure 1).

Sometimes, PAMPs and DAMPs bind to the same receptors modulating their activation through TLRs promoting the synthesis of cytokines (43,44). This PAMP–DAMPS association is currently proposed as a new modality of immune regulation which depends on the pre-existing collection of PAMPs and DAMPs, the assembly of the PAMP–DAMPS complexes, and the repertoire of PAMPs and DAMPs. Finally, PAMPs can induce the release of DAMPs during an infectious process, eliciting the release of others DAMPs (45). Besides, it has been described that many DAMPs could act as adjuvants, for example, genomic double- stranded DNA enhanced
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Diverse studies had described that PAMPs and/or DAMPs by themselves are able to modulate the course of inflammation and activate adaptive immunity response (50, 51). Piccini describes that lipopolysaccharide (LPS) from Gram-negative bacteria could act as a PAMP capable to bind to some DAMPs, such as HMGB1, Hsp70, Hsp90, surfactant protein A and α-defensins. (35). These complexes are recognized by TLR4 allowing the release of TNF-α and IL-6 and thus perpetuating the damage to tissue due to inflammation (52).

Several reports suggest an association between infection and re-activation of Human Herpes Virus (HHV) during MS course. For example, the HHV type 1 has been isolated from the cerebrospinal samples of patients during the first manifestations of MS (54). Also, the reactivation of HHV-6 has been associated with MS exacerbation (55-60). On the other hand, EBV infection is frequently associated with autoimmun disorders, such as RA, MS, Sjogren’s syndrome (SS), thyroiditis and hepatitis autoimmune (61-68). EBV is characterized for its ability to infect, and to persist in a silence mode inside B-lymphocytes for the lifetime in infected patients. It has been found the presence of EBV into infected cells in the vast majority of MS cases, although the association between EBV in MS remains in controversy.

During the infection with HHV, some conserved herpesvirus protein kinases (CHPKs) have been associated with Hsp 90, which participates in the viral replication and infection promoting the immune recognition of antigens in MS (69-71). Likewise, Hsp 90 regulates the immunomodulation of γδ T cells in the acute phase of infection with EBV on B cell (72).

Also, it has been described that the number of circulating γδ T cells are increased in patients with MS during the early onset of the disease; however, the depletion of γδ T cells in the CNS before the onset of acute disease, or during the chronic stage, causes significant reduction in the severity of the clinical symptoms (73).
Particularly, it was demonstrated that the depletion of the γδ T-cells during the acute stage of EAE in animals, resulted in a significant reduction of inflammatory and demyelination processes. According to this, it could be possible that during the early phase of HHV infection, Hsp 90 is able to interact with γδ T cells eliciting the release of Th1-type cytokines that tend to produce the inflammatory responses to kill intracellular viruses. In spite that the numbers of γδ T cells are decreased during chronic stages, and the production of Hsp90 is continuous, some pathways could be activated due their interactions with PPRs, thus perpetuating an immune response within active plaques in MS.

Previous studies have indicated that Hsp70 is a critical molecule in MS pathogenesis (74). In the EAE model induced by Myelin Oligodendrocyte Glycoprotein (MOG), indicated that Hsp70.1 could play a role in both the immune response and cytoprotection of CNS cells. In addition, extracellular Hsp70 can act as an adjuvant that promotes adaptive immune responses against specific antigens. Additionally, complexes of Hsp70 and MOG or PLP were present in the CNS of mice with EAE (75). In this context, complexes of Hsp70 and MOG or proteolipid protein (PLP) were found in MS lesions. Also, it has been shown an increase in the protein expression of inducible Hsp70 in T lymphocytes (CD4+ and CD8+) and monocytes from under basal conditions that may reflect the immunological activation (74). These data suggest that during the initial stages of MS/EAE the inflammatory response acts as a preconditioning stimulus to induce the expression of Hsp70 as well as the releasing of this protein from glial cells in order to avoid neuronal damage in the successive neurodegenerative stages (76).

In the Japanese encephalitis (JE) induced by HPV, Hsp70/90 produce a subsequent inflammatory reaction regulated by TLR4 during viral replication (77). These results indicate that deficient TLR4 (-/-) mice showed enhanced resistance to JE, however some data revealed that TLR4 reduction also provided potent type I IFN innate responses through enhanced induction of antiviral ISG genes by alternative activation of IRF-3 and NF-κB in myeloid-derived DCs and macrophages. Also, TLR4-/- mice showed an alteration of plasmacytoid DCs subpopulation and CD4+Foxp3+ regulatory T cells, which were closely associated with enhanced type I IFN innate immune and JEV-specific CD4+ and CD8+ T cell responses (77). These Hsp proteins act as “protectors” to eliminate viruses during early stage of the infection; however, if this damage remains constant, the releasing of Hsp promotes a persistent inflammation, thus contributing to the MS development.

Nowadays, it is unclear the role-played by HMGB1 during the establishment of MS, or its contribution in boost progressive autoimmune disease. HMGB1 is a ubiquitous nuclear protein which is continuously released from necrotic cells or it is unrestrictedly secreted by monocytes, macrophages and DC’s (78,79). HMGB1 contributes to the nuclear homeostasis by acting as an extracellular alert signal when tissues are injured; therefore HMGB1 could act as a typical DAMP molecule (79,80). Even when some authors suggest that HMGB1 participates during non-pathogenic inflammatory processes, but it is required to initiates sterile inflammation following tissues injury (81), there is enough evidence that implicates to this nuclear protein during infections. It has been showed that the releasing of HMGB1 is promoted by pro inflammatory cytokines generated during HIV-1 infection, and also it is able to activate the replication in latent HIV-1 (82). Besides, during early response of infectious or some damage process, extracellular HMGB1 is able to trigger inflammation, (83). HMGB1 has been detected in the nuclei of nervous cells (84), and there are significant extracellular levels of HMGB1 as well as the receptors for advanced glycation end products (RAGE), TLR2, and TLR4 in cerebrospinal samples of MS patients (85). Furthermore, microglia and macrophages express cytosolic HMGB1 and this expression is increased in active plaques of MS patients and in the EAE model (85). HMGB1-mediated TLR2, TLR4, TLR9 and RAGE signaling pathways are involved in the NF-κB modulation, thus participating in the releasing of pro-inflammatory molecules from macrophages and promoting the recruitment of inflammatory mediators through endothelial barriers of damaged tissue such as it has been observed in EAE mice model (86).

Neutralization of HMGB1 ameliorates experimental autoimmune encephalomyelitis, and this amelioration was associated with defective systemic T cell activation and decreased T cell recruitment into the CNS (87). Also, in patients with amyotrophic lateral sclerosis (ALS) the levels of HMGB1 are increased in spinal cord tissues when they were compared with Alzheimer's disease, Parkinson's disease, and healthy control subjects. Also the amount of auto-antibodies against HMGB1 correlated with the severity of the disease (88). On the other hand, it has been observed that high levels of HMGB1 and tenascin C are present in the serum of septic patients (78,89), while in systemic lupus erythematosus (SLE) high levels of DNA have been associated with immune complexes in serum, including the nucleosome-HMGB1 complex (90-92). In several cases, increased levels of endogenous TLR are considered as markers of the progress disease; also, high levels of extracellular HMGB1 recognized active lesions in MS patients correlating with a dynamic inflammatory process (85).

Other DAMPs associated with MS are beta amyloid (β-AP) and S100 proteins which have been involved in tissue homeostasis and regeneration/repairing processes above of all acute injury. These molecules are proposed as important neural damage
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markers during diverse courses of MS however their relationship with virus is still unknown (93-95). The β-AP is generated by proteolytic cleavage of its precursor beta amyloid precursor protein (β-APP), and it is frequently found in brain active plaques. β-APP is a multifunctional protein which expression is induced in several nervous cells in response the acute injury (96,97). The overexpression of β-APP is promoted by S100B proteins which are members of calgranulins proteins. These S100 proteins are prominent molecular mediators in several diseases, including microbial infections, degenerative and autoimmune disease and cancer. (98). S-100β protein is highly expressed during brain injury, ischemia, neurodegenerative, inflammatory, and psychiatric disorders and it has been implicated in driving the progression of MS (99). In cerebrospinal fluid of patient with MS during relapse disease high levels of S-100B have been found (93). Furthermore, S100 proteins inhibit kinases activity, regulate the enzymes associated with energetic metabolism, stimulate Ca2+ release induced by calcium in sarcoplasmic reticulum membrane, and contribute to the stability of cytoskeleton constituents (100).

S100A9 is another member of S100 proteins and it is implicated in leukocyte migration and chemotaxis, leukocyte activation, and it has potent anti-oxidant activity (101,102). S100A9 is a consistent marker of inflammation and a pro-inflammatory molecule during the primary immune response. Increased plasma levels of S100A9 are related with diseases that involve inflammatory processes such as cystic fibrosis, chronic bronchitis, and RA (103,104). Recent reports have suggested that S100A9 acts as an extra antimicrobial peptide during the primary immune response, by limiting microbial propagation and by avoiding tissue inflammation (105,106). In addition, S100A9 acts as a critical host-derived molecular pattern to regulate inflammatory response outcome and disease during infection by exacerbating the pro-inflammatory response, cell-death, and viral pathogenesis. Extracellular S100A9 regulates two key mechanisms that contribute to inflammation during Influenza A Virus (IAV) infection. These processes are the pro-inflammatory cytokine releasing during early infection, and the other mechanism is the induction of apoptosis, being an independent T response of virus replication. In addition, S100A9 alone can directly activate TLR4/ MyD88 pathway (in the absence of LPS) and it contributes to the regulation of inflammatory process during IAV infection (28). The S100A9 gene is activated by the DDX21-TRIF, which regulates inflammation trough DDX21-TRIF-S100A9-TLR4-MyD88 (28).

Both S100A9 and S100A8 have been implicated in activation of TLR4 pathway during LPS stimulation (107,108). These myeloid-related proteins are constitutively expressed in neutrophils (109), and they are released at the sites of injury. By binding to RAGE and TLR4, these receptors trigger a proinflammatory response (110). This effect has been documented during the alveolar inflammatory response after endotoxemia and could be implicated in MS (111) (Figure 2).
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![Figure 3. Perpetual generation of active plaques by PAMP-DAMP's in MS.](image)

Once the Herpes virus family reaches the CNS tissue, B cells internalize them and the viral replicative cycle begins. Infected cells release new viral particles (PAMPs) and DAMPs which in turn signal through microglia, macrophages, astrocytes, and T-cells. These cells generate pro-inflammatory cytokines which eventually can disturb the protective function of oligodendrocytes leading to the damage of myelin sheets on neurons, named active plaques in MS.

Finally, the detection of oligoclonal bands in the cerebrospinal fluid (CSF) of MS patients, the presence of B cells and plasma cells in MS plaques, and the occurrence in MS lesions of substantial depositions of antibodies and complement (112,113) suggest that B cells and antibodies are crucial in the progression and pathogenesis of MS.

B lymphocyte activating factor of the tumor necrosis factor superfamily (BAFF) is a fundamental cytokine for B cell homeostasis that can play a dual role in immunity, by regulating both innate and adaptive immune responses and by sustaining autoimmunity. BAFF is highly expressed in spleen and lymph nodes and it is mainly produced by macrophages, monocytes, and dendritic cells. Also, it is produced by astrocytes in CNS (114). In several autoimmune diseases, including MS, high levels of BAFF have been detected in serum (115-117). Overexpression of BAFF is associated with the pathogenesis of MS when EBV infection is involved. It has been shown that BAFF overexpression leads to an expansion of the B-cell compartment and autoimmunity in mice (118). Also, high amounts of BAFF remain elevated in mice that developed relapsing-remitting and chronic-relapsing EAE (119).

In brain samples of MS harboring large EBV deposits revealed that most of the B cells in white matter lesions, meninges, and eptopic B-cell follicles are CD27+ and co-express latent membrane protein 1, latent membrane protein 2A and 2 EBV-encoded proteins that provide survival and maturation signals to B cells (120). In MS plaques, BAFF expression has been found that it is up-regulated at levels comparable to those detected in lymphatic tissues (121). Similarly, mRNA levels of BAFF were increased in monocytes, and in B and T cells of MS patients (117). However, MS patients and headache controls had the same levels of BAFF protein in CSF and plasma (117,122). These findings support the idea that the up-regulated BAFF expression in autoimmune diseases, such as EAE and MS is able to contributing to CNS tissue damage, due to its ability of sustain the survival of auto reactive B cells (119).

During a viral infection several intracellular functions are affected. This damage could be related with the viral prevalence in patients and the development of brain damage. For example, when HIV-1 infects cells, Tat protein induce an increase in the 1-amyloid generation, promotes its accumulation in endolysosomes, enhances the enlargement of these organelles, elevates their internal pH, and increases the activity of the enzyme BACE-1, which converts the precursor of β-amyloid protein to its active form (123). It is known that neurons are cells which possess elaborated endolysosomes and by disturbing the generation of β- amyloid and its precursor, it is possible to alter the endocytic pathway followed for the intracellular traffic of this protein with its consequent accumulation. This process has been related with cognitive disorders seen in Alzheimer’s disease, associated with patients infected with HIV and also it could be present during the generation of active plaques in MS (93,123,124). Particularly, when EBV particles are internalized by B-cells, the activity of diverse proteins such as EBV-determined nuclear antigen (EBNA2), EBER, BZLF-1 and latent membrane- proteins (LMP) play a key role not only during viral replication, but also in the progression of the disease (125). After infection, EBNA2 is released and it is followed by others EBNA, LMP and EBERs. The expression of EBER is related with the viral life cycle and it plays an important role in antiviral innate immunity. EBER constitutively activates RIG1, leading to the activation of downstream molecules such as NFκ β and IRF-3, which induce type-1 interferon and IL-10. Furthermore, EBERs is released by EBV infected cells as complex with La, which promotes the release of type-1 IFN and inflammatory cytokines, thus leading to subsequent immune activation by TLR-3 (126-129). Additionally, it has been described that β-amyloid is also accumulated in the nuclei of human brain endothelial cells, which are the main components of the BBB. The breakage of this barrier has been involved in the infiltration of mononuclear cells to the CNS, which promotes inflammatory processes (9). LMP1 is localized in lipid micro-domains and designated lipid rafts, located on the plasma membrane. LMP1 has no intrinsic enzymatic activity but instead aggregates cellular proteins of the tumor necrosis factor receptor signaling pathway to activate transcription factor NF- κB. These proteins not only contributes to replication and immortalization of
B-Cell, but also they are able to drive immune response through diverse pathways. In several pathologies associated with viruses, it has been described the role of viral proteins in the generation of DAMPs, being reported for HIV, EBV and HHV infections (69,71,123). In patients with VZV have been detected some proteins considered as markers for neuronal damage, such as S-100β protein, neurofilament protein (NFL) and glial fibrillary acidic proteins (GFAP) in cerebrospinal fluid (130). Particularly, S100B has also been detected in MS patients (93). Therefore, it is possible that these proteins could be generated as the result of viral infections in CNS promoting a continuous inflammatory process and inducing a permanent release of several DAMP’s such as β-amyloid and S-100B between others (Figure 3).

5. CONCLUSIONS

All mammalian cells are supplied with a remarkable numbers of strategies for protection from several cell intruders, which in turn possess a huge diversity of PAMPs for the proper establishment of the infection. Once these cellular alarms identify foreign antigens composed by PAMPs, several biological reactions, such as inflammation, are elicited in order to eradicate pathogens. The “danger theory” proposed by Matzinger (131) explains how the immune response could produce an inflammatory reaction thought DAMPs in response to exogenous and endogenous pathogens, especially following injury or cellular death (110,132). When a virus infection is initiated, the innate immunity is activated and an antiviral and inflammatory response occurs, triggering an incessant release of DAMP’s as consequence of chronic infection or continuous injuries as it happens in MS. Unspecific identification of DAMPs by receptors involved in the recognizing of PAMPs, promotes the incoming and releasing of DAMPs in specific areas, which lead to an acute inflammation and continuous delivering of DAMPs; which in turn becomes a repetitive cycle that could elicit the progress of autoimmunity (133). We suggest that in MS, an initial stimulus produces scarce concentrations of DAMPs in tissue, which participate in an immune response to repair injured tissues. However, the relapsing stage of this disease is characterized by an extremely destructive tissue environment, where increased levels of DAMPs are produced during acute inflammation, leading to a chain reaction of damage. Increased rates of pro-inflammatory DAMPs could promote an extensive tissue injury, amplifying significantly the DAMPs levels in tissue in a local and/or systemical manner, which finally could create a perpetual state of tissue injury. Recently it has been proposed that suppressing DAMP’s to avoid the activation of TLRs could be considered as a new potential target in the treatment of autoimmune diseases such as MS, which may offer feasible alternatives to improve current therapies. Recent studies suggest that the inhibition of these molecules might minimize the symptoms related to the disease. Other strategies could be the blockage of DAMP’s necessary for the activation of TLRs, in order to inhibit specific co-receptors or accessory molecules essentials for the activation of this pathway, however, more approaches are needed to give us insight into the MS development.

6. ACKNOWLEDGMENTS

This work was supported by the National Council of Science and Technology of Mexico (CONACyT CB-180851) from Doctor Benjamin Pineda and by CONACyT FOSSIS-182362 from Doctor Sergio Moreno. All authors contributed as the same manner in the design and discussion. All authors have read and approved the manuscript and concur with the submission.

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PMid:23316484 PMCID: PMC3539075

Key Words: Pathogen-Associated Molecular Patterns, Damage-Associated Molecular Patterns, Multiple Sclerosis, Immune Response, Inflammation, Review

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