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Review

Familial Mediterranean fever: the molecular pathways from stress exposure to attacks

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Abstract

FMF is an autoinflammatory disease characterized by recurrent attacks and increased IL-1 synthesis owing to activation of the pyrin inflammasome. Although knowledge of the mechanisms leading to the activation of pyrin inflammasome is increasing, it is still unknown why the disease is characterized by attack. The emergence of FMF attacks after emotional stress and the induction of attacks with metaraminol in previous decades suggested that stress-induced sympathoadrenal system activation might play a role in inflammasome activation and triggering attacks. In this review, we will review the possible molecular mechanism of stress mediators on the inflammation pathway and inflammasome activation. Studies on stress mediators and their impact on inflammation pathways will provide a better understanding of stress-related exacerbation mechanisms in both autoinflammatory and autoimmune diseases. This review provides a new perspective on this subject and will contribute to new studies.

Key words: Familial Mediterranean fever, attacks, stress, catecholamines, epinephrine, norepinephrine, inflammasome, glucocorticoids

Rheumatology key messages

- FMF is characterized by irregular paroxysmal fever and serositis attacks.
- It is still unknown why FMF is characterized by attack.
- Stress-induced sympathoadrenal system activation might play a role in inflammasome activation and triggering attacks.

Introduction

FMF is a common, Mendelian-inherited monogenic autoinflammatory disease characterized by irregular paroxysmal fever and serositis attacks [1]. Amyloid A amyloidosis is the most important complication [2]. In monogenic autoinflammatory disorders, the increased inflammatory response results from either 'gain-of-function' or 'loss-of-function' of the genes involved in the innate immune system [3]. FMF is associated with inherited variants in the Mediterranean fever gene (*MEFV*), which encodes the pyrin protein. Although we do not fully understand the mechanisms of pyrin inflammasome activation, it has been suggested that FMF mutations are gain-of-function with a gene dosage effect [4]. One of the most convincing elucidations about the pyrin regulation is the one related to the change in host Ras homologous protein guanosine triphosphate (Rho GTPase) activity. The Ras homologue family member A (RhoA)-dependent serine/threonine-protein kinases PKN1 and PKN2 directly phosphorylate pyrin at positions Ser208 and Ser242. This gives rise to contact of pyrin with the chaperone proteins 143-3ε and 14-3-3τ. This interaction retains pyrin in an inactivate state and prevents the formation of an active inflammasome. The inactivation of RhoA causes a decrease in PKN1 and PKN2 activity and results in decreased levels of phosphorylated pyrin. This in turn releases pyrin from the inhibitory 14-3-3 proteins and accelerated the formation of an active pyrin inflammasome [5]. Despite the increased knowledge of the mechanisms leading to the activation of pyrin inflammasome, it is still unknown why

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the disease is characterized by attacks. Some papers and reviews related to FMF have defined FMF as a disease characterized by 'unprovoked' or 'spontaneous' or 'unpredictable' attacks. However, most patients with FMF have a phenotype characterized by hyperinflammatory episodes that are manifested by a stimulus rather than a constitutively autonomous IL-1 beta (IL-1β) production seen in patients with severe cryopyrin-associated periodic syndrome [6]. These self-limited inflammatory episodes emerge only by stimulation of the innate immune system by an insult [7].

FMF mutations in pyrin decrease the threshold of activation of pyrin inflammasome frequently activated by RhoA inhibiting toxins produced by both Gram-positive and Gram-negative bacteria. The virulent factors of various infectious agents have an effect on Rho GTPase. These virulent factors have been shown to increase pyrin inflammasome activation in *in vitro* tests. However, in the results obtained from clinical experience and study data, the role of infectious agents as triggers in patients with FMF is negligible [8, 9]. So, what could be the endogenous or exogenous factors affecting inflammasome activation similar to infectious agents? Patients with FMF give us the answer to this question by making use of their own experience. Approximately two-thirds of patients with FMF reported that their attacks were triggered by emotional stress or other psychological causes [8–15]. Interestingly, years ago, triggering FMF attacks with a synthetic sympathomimetic drug metaraminol, which was used as a diagnostic test [16], suggested that there might be a relationship between the stress-induced sympathoadrenal system activation and FMF attacks. Based on this information, if there is a close relationship between emotional stress and attacks, it is tempting to speculate that stress mediators epinephrine, norepinephrine and glucocorticoids (GCs) may play a role in inflammation pathways and in inflammasome activation. In this manuscript, we will review the possible molecular role of stress mediators in the inflammation pathway and inflammasome activation.

Stress as a trigger for FMF attacks

There are many studies on the risk factors that trigger FMF attacks. It is well known that physical and emotional stressors trigger FMF attacks, for which increased colchicine dosing is applied during these periods in clinical practice [17]. Moreover, rest periods and vacations free from stress may provide temporary relief [18]. School exams, social affairs, out-of-town travel and job interviews were found to be the most common trigger factors for attacks [8, 9, 14]. Family dysfunction and hostility in paediatric FMF patients are positively associated with attacks [10, 11]. It would be meaningful to investigate whether the use of antidepressant drugs in these patients would have an effect on attack frequency. In one study, selective serotonin reuptake inhibitors reduced the attack frequency in patients with colchicine-unresponsive FMF who also had depression [12]. An interesting study was performed by Yenokyan and Armenian [13]. The authors used conditional logistic regression to compare the frequencies of exposure to stressful events. Multiple stressful life experiences predicted FMF attacks two days following the event. An additional stressful incident was associated with an estimated 70% increase in the odds of having an FMF attack on the second day [13].

In patients with FMF, some *MEFV* variants may determine phenotypic features and the development of amyloid A-type amyloidosis. Therefore, it is interesting to investigate whether different *MEFV* variants are affected by different triggers. Avagyan *et al.* [15] investigated possible triggers for FMF attacks and their relationship with disease genotype. They reported that patients with the M694V mutation were more affected by emotional stress. They could not show any relationship between cold-induced attacks and *MEFV* mutations.

Metaraminol-induced FMF attack

The relationship between stress and FMF attacks has been known for a long time [19]. In 1984, it was suggested that FMF was probably the result of an inborn error of catecholamine metabolism [16]. The hypothesis was based on two observations. The first was the case reported by Hayashi *et al.* [20] in 1976 of a Japanese patient with periodic peritonitis in whom attacks were inhibited by reserpine and could be triggered by noradrenaline infusion. The second was the finding that long-term therapy with small daily dosages of reserpine either completely suppressed or significantly reduced the frequency of attacks in 60% of 22 patients treated for an average of 13.6 months [21].

From these clinical experiences, the metaraminol provocation test was used as a diagnostic tool to trigger attacks. Metaraminol is a sympathomimetic, adrenoceptor stimulant. It directly and indirectly stimulates the alpha receptors in the sympathetic nervous system. Barakat *et al.* [16] administered 10 mg metaraminol i.v. to 21 patients with FMF and provoked a mild and short-term attack in all patients. They could not demonstrate attack in control cases. The metaraminol-induced symptoms were similar to natural disease attacks and could be prevented with prophylactic colchicine therapy. In another case report, metaraminol induced serositis and Mollaret's meningitis in a patient with FMF [22]. Similar to these studies, Huppertz *et al.* [23] provoked attack in 55% of patients with FMF with administration of metaraminol. No attacks occurred in the normal control group. Interestingly, Hayashi *et al.* [20] suppressed attacks with reserpine in a patient with FMF. They reported increased urinary excretion of adrenalin in this patient.

As is well known, reserpine is an adrenergic blocking agent used to treat mild-to-moderate hypertension via the disruption of norepinephrine vesicular storage. Its antihypertensive action is a result of its ability to deplete catecholamines from peripheral sympathetic nerve endings. Barakat *et al.* [24] investigated dopamine beta hydroxylase (DBH) activity in patients with FMF, which is the enzyme that catalyses the conversion of DBH to

dopamine and noradrenaline. DBH was significantly higher in untreated symptom-free patients and in patients with acute attacks than in controls. Colchicine treatment reduced DBH activity to control levels. This situation was attempted to be explained by colchicine's direct effect on the rate of DBH synthesis, release or removal or all of the enzyme kinetics.

Based on the information outlined above, how can stress and stress-related mediators affect the immune system, and lead to inflammation?

The interaction between stress, the sympathoadrenal system and immune system

Stress, in an 'integrated definition', is 'a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates the physiologic fight or flight system in the body' [25]. Homeostasis is defined as the ability of the body to maintain the stability of the internal environment. Definitions of the duration and type of stressors vary greatly. Acute stress is defined as exposure to stressor for several hours, subacute stress is stress that persists for several days, and chronic stress continues for weeks or months [26]. There is a range of intermediate types of stress such as repeated short-term stress with return to resting baseline between 'hits', and prolonged short-term stress with delayed/minimal return to resting baseline [27]. Following exposure to emotional stress, the sympathetic nervous system is activated and release epinephrine and norepinephrine into circulation. Following this sympathetic nervous system activation, the hypothalamic–pituitary adrenal axis is activated slowly and stimulates the secretion of GCs by the adrenals. These stress-responsive hormones affect the cardiovascular, musculoskeletal, neuroendocrine and immune systems to elicit 'fight or flight' action. Neuroanatomic and neurochemical studies have shown that primary and secondary lymphoid organs such as the bone marrow, thymus, spleen, lymph nodes and gut, and bronchus-associated lymphoid tissue are innervated by sympathetic nerve fibers. Activation of postganglionic splenic sympathetic nerve fibers leads to the release of norepinephrine at the neuroimmune junction [28]. In the event of any psychological stress, an increase in G protein-coupled receptor (GPCR) density occurs in the membrane of blood mononuclear cells in response to increased catecholamines, and the density of GPCR is positively correlated with epinephrine levels [29]. GPCRs, comprising the largest cell surface receptor family, regulate a diverse array of intracellular signalling cascades in response to hormones, neurotransmitters, ions, photons, odorants and other stimuli, and are involved in a wide range of physiologic regulation, as well as pathologic conditions [30]. Activation of GPCRs and binding of the heterotrimeric G protein to its receptor (coupling) triggers nucleotide exchange, leading to the separation of the G protein into $G\alpha$ and $G\beta\gamma$ subunits. Both subunits regulate different downstream effector proteins.

Catecholamines and inflammation

Catecholamines have an inflammation-inducing role through their effects on the intracellular signalling system via GPCRs. Beta $(\beta)_2$ adrenergic signals interact with the nuclear factor-kappa B (NF-κB) signalling cascade at multiple levels including in the plasma membrane, in the cytoplasm and in the nucleus, engaging diverse molecular switches, scaffolding proteins and transcriptional cofactors [31]. The influential role of stress in inflammatory activity was studied in laboratory conditions that allow the assessment of temporal pattern of cytokine responses and use of standardized stress stimulation procedures such as the Trier Social Stress Test [32, 33]. Laboratory studies showed that acute stress was associated with significant increases in IL-1β, IL-1 receptor antagonist and IL-6, and TNF-α [34]. Norepinephrine stimulated the secretion of inflammatory components by increasing the phosphorylation of mitogen-activated protein kinases through an α receptor-dependent pathway [35]. The mechanisms converting psychosocial stress into mononuclear cell activation were investigated by Bierhaus *et al.* [36]. Nineteen healthy volunteers had their adrenocorticotropic hormone, cortisol, epinephrine and norepinephrine levels measured after exposure to Trier Social Stress Test, and significant increases in all parameters were detected in 17 of 19 individuals. NF-κB binding activity was also increased in these individuals' peripheral blood mononuclear cells due to norepinephrine stimulation within 10 min. No increase in NF-κB binding activity was observed in two patients without catecholamine and cortisol increase. When the stress was removed, NF-κB activation rapidly returned to basal levels in the majority of participants. In another study, acute psychologic stress increased circulating levels of IL-6 and IL-1β, and this response could be prevented with the use of β blockers [37].

Catecholamines and REDD1 upregulation

Polymorphonuclear neutrophils from patients with FMF in remission are resistant to induction of neutrophil extracellular trap (NET) release [38]. Induction of autophagy reduces the threshold for NET formation in FMF polymorphonuclear neutrophils isolated during remission. It has been reported that a mammalian target of rapamycin (mTOR) inhibitor, rapamycin, led to autophagy induction and NET formation [39]. The authors suggested that autophagy induction rendered FMF-remission polymorphonuclear neutrophils more susceptible to NET release after suitable inflammatory stimuli. Regulated in development and DNA damage responses 1 (REDD1) is a highly conserved stress response protein. REDD1, found in immune cells including neutrophils and macrophages, is upregulated by hypoxia, endoplasmic reticulum stress, oxidative stress, DNA damage and

energy stress. [40]. Endogenous REDD1 is required for both dissociations of endogenous tuberous sclerosis complex 2 (TSC2)/14-3-3 and inhibition of mTOR complex 1 (mTORC1) in response to hypoxia. REDD1 rapidly inactivates mTORC1 in a TSC1/2-dependent manner [41, 42] and functions as a molecular shuttle to remove inhibitory 14-3-3 proteins from TSC2.

In recent years, preclinical studies have suggested that REDD1 also plays a role in stress-related inflammasome activation [43, 44]. Yanagawa *et al.* tested REDD1 expression in a murine macrophage cell line RAW264.7 and murine peritoneal macrophages by using stress hormones epinephrine and norepinephrine. They showed increased expression of both *REDD1* mRNA and its protein as a result of short-term exposure to epinephrine and norepinephrine. This epinephrine-induced REDD1 expression was completely antagonized by using the β2-adrenoceptor selective antagonist ICI 118 551, whereas the β2-adrenoceptor-specific agonist salmeterol increased REDD1 expression [44].

REDD1 regulates the neutrophil-dependent inflammatory response in FMF [45]. Skendros *et al.* [46] suggested that REDD1 induction might play a role in the relationship between stress and FMF phenotype. Neutrophils from patients with FMF during an attack-free period were resistant to autophagy-mediated NET release [38], which could be overcome through REDD1 expression [46]. REDD1 was significantly overexpressed during FMF attacks associated with autophagy induction. The stress-related mediator epinephrine decreased this threshold, leading to autophagy-driven NET release, whereas pretreatment with the β-adrenergic receptor antagonist propranolol abolished REDD1 upregulation and NET release. Endothelin-1, thrombin and IL-1β, which are used as inflammation stimulators, did not alter the RNA expression of REDD1. This situation seems to be a condition specific to catecholamines.

As a result, REDD1 activation develops due to the effect of the stress mediator epinephrine, and high bioactive IL-1β containing NET release develops with the increase of autophagy [46] (Fig. 1).

One of the mysteries regarding FMF is that attacks have self-limited features. Apostolidou *et al.* [38] suggested that NETs downregulated further NETosis, accelerating the resolution of attacks, and increased the threshold for attack initiation by attenuating the release of pro-inflammatory NETs as a compensatory homeostatic mechanism. Another mechanism for limiting attacks may be related to the relationship between mTORC1 and REDD1. An interesting part of the relationship between REDD1 and mTORC1 is the presence of a feedback mechanism in which inhibition of mTORC1 results in a REDD1 protein stability decrease and a consequent decrease in REDD1 expression [47]. This mTORC1–REDD1 feedback mechanism limits the inhibitory action of REDD1 [47]. At this point, it is tempting to speculate that this feedback loop may be an alternative or additional pathway for self-limited attacks of FMF. Stress-induced REDD1 expression leads to mTORC1 inhibition and then autophagy induction. Inhibited mTORC1 results in a REDD1 protein stability decline. Thus, mTORC1 reduces its own inhibition by decreasing REDD1 stability (Fig. 2). This hypothesis needs to be tested in further preclinical studies.

Catecholamines and Rho GTPase

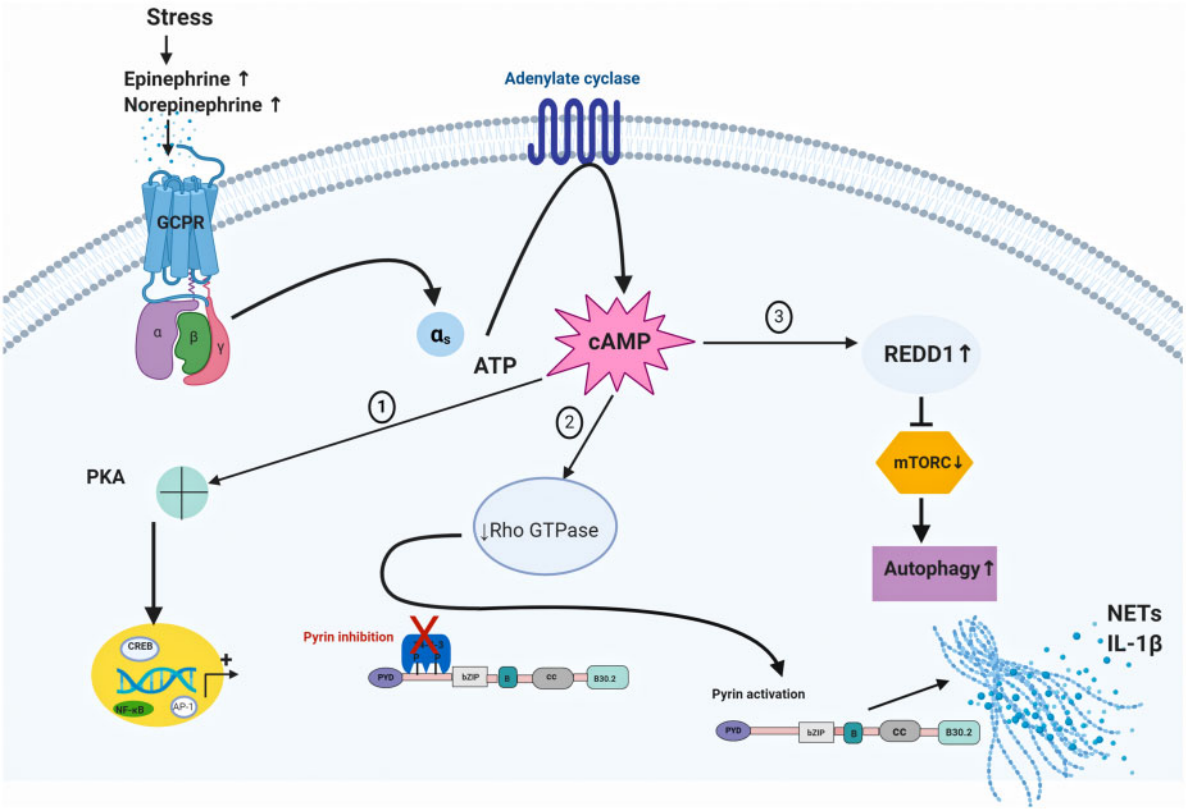
Pyrin is an inflammasome sensor that detects inhibition of RhoA subfamily GTPase activity. It is now well known that there is an inverse correlation between RhoA activation and pyrin inflammasome activation [5]. Exogenous factors and endogenous mediators/ligands may influence RhoA activation. Isoproterenol, non-selectively stimulates β adrenergic receptors with very little effect on alpha receptors, is a synthetic sympathomimetic compound related to epinephrine, and inhibits RhoA GTPase activity similar to C3 transferase of *Clostridium botulinum* by increasing the level of cyclic adenosine monophosphate (cAMP) in innate immune cells [48].

The functional similarity between cAMP and C3 transferase is comparable in terms of influencing the shape, movement and function of the cells. For instance, both compounds behave similarly in inhibiting platelet aggregation and in inhibiting the microfilament assembly of neutrophils [49–52]. In another study, epinephrine-mediated increased cAMP was shown to perform Weibel-Palade body exocytosis with the effect of Rho GTPase Rac1 [53].

GC-induced priming of innate immunity

GCs, which are important stress hormones, have the potential to act in any tissue under normal physiologic conditions. In patients with FMF, peak plasma cortisol levels increased during attacks compared with attack-free periods after stimulation with synthetic adrenocorticotropic hormone administration [54]. In FMF patients, basal adrenocorticotropic hormone levels were found to be increased in the attack-free period compared with disease-controlled patients and healthy control individuals [55]. In this study, although an early blunted cortisol response was observed during the insulin-induced hypoglycemia test, there was no significant difference between patients with FMF and healthy controls [55]. As a result, patients with FMF exhibit an appropriate GC response to stressful conditions. So, what are the roles of increased GCs in this process? GCs are generally considered anti-inflammatory. GCs create this effect by inhibiting the activity of proinflammatory transcriptional factors such as NF-κB and activating protein 1 (AP-1) [56]. Although GCs are known to be anti-inflammatory during ongoing inflammation [51] they have far more pleomorphic effects than is thought and cannot simply be categorized as anti-inflammatory [57, 58]. Recent studies have shown that GCs may also have proinflammatory effects on the innate immune system [59]. Stress-induced GCs show both anti-inflammatory effects and a priming effect on innate immune cells, which is considered to be a neuroendocrine signal or alarmin

Fig. 1 Schematic illustration of stress-induced attacks of FMF through multiple biological pathways.



cAMP is generated by activation of adenylyl cyclases, which convert ATP to cAMP. The canonical cAMP signalling pathway is PKA. cAMP molecules bind the PKA regulatory subunits of the PKA holoenzyme, which results in the release of the two catalytic subunits that subsequently translocate to the nucleus. Cyclic element-binding protein and activator protein are also up-regulated, leading to the expression of proinflammatory genes (1). Increased cAMP inhibits Rho GTPase similar to C3 transferase of *Clostridium botulinum* and leads to pyrin inflammasome activation (2). Epinephrine and norepinephrine increase gene expression of REDD1 through a cAMP-mediated pathway. REDD1 inhibits mTORC and gives rise to increased autophagy and NETs formation (3). **Abbreviations:** cAMP: cyclic adenosine monophosphate; ATP: adenosine triphosphate; PKA: protein kinase A; Rho GTPase: Ras homologous protein guanosine triphosphate; REDD1: regulated in development and DNA damage responses 1; mTORC: mammalian target of rapamycin inhibitor complex; NET: neutrophil extracellular trap.

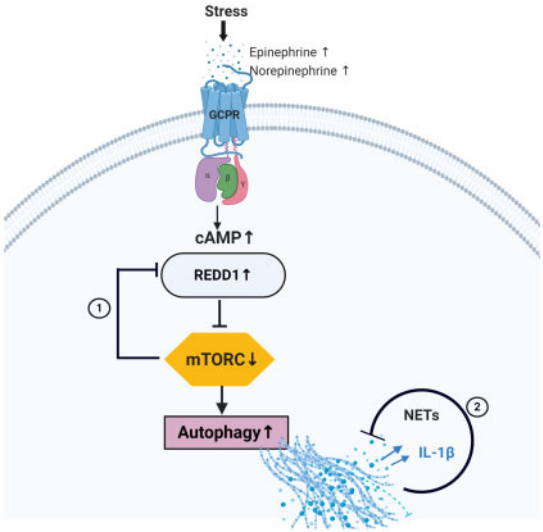
[58]. This response prepares and strengthen the innate immune system to restore homeostasis [57, 58] and sensitizes the innate immune system against potential 'dangers' [60]. The combination of GCs and inflammatory cytokines increases the Toll-like receptors (TLR) level and this requires both activation and translocation of NF-κB to the nucleus [61, 62] (Fig. 3).

TLRs on macrophages, neutrophils and other cell types have been shown to play an essential role in triggering the innate immune response by recognizing pathogen-associated molecular patterns and stimulating the activity of host immune cells against several microbial products [63]. Upregulated TLR2/4 is sensitized for ligands bound to TLRs, even if GCs fall to normal levels. These effects of GCs on TLRs may be related to a danger signal excitation such as high-mobility group box-1 protein (HMGB1) [64]. TLR increases even in non-attack periods in FMF patients [65]. In addition, sera from patients with attacks induces TLR in monocytes of healthy individuals [66].

Extracellular adenosine triphosphate (ATP) may act in an autocrine or paracrine way and may activate the P2 family of purinergic receptors expressed on numerous tissues. Exogenous GCs may amplify cell signalling initiated by extracellular ATP binding to the $P2Y_2R$ and increase ATP-induced IL-6 production [67]. After receptor binding, extracellular ATP may start and modify inflammation [68].

Animal models of neuroinflammation have shown that the increased GCs due to stress before immune stimulation act as proinflammatory agent with priming effects and increase neuroinflammation during a second inflammatory stimuli [69, 70]. After harmful injury, GCs lead to late upregulation of macrophage functions [71]. GC pretreatment causes significantly increased production of nitrite, IL-6 and TNF-α. mRNA for these inflammatory

Fig. 2 Proposed hypothetical mechanisms for self-limited attacks of FMF.



Stress-related mediators epinephrine and norepinephrine increase cAMP levels via GPCR. Increased cAMP decreases the threshold for REDD1 protein synthesis. Increased REDD1 inhibits mTORC and thus leads to increased autophagy and NET formation decorated with IL-1β. However, inhibited mTORC results in reduced REDD1 protein stability (1). In addition to this possible feedback loop, NETs provide a negative feedback mechanism that facilitates the resolution of attacks and increases the threshold for attacks as a compensatory homeostatic mechanism (2). **Abbreviations:** GPCR: G protein-coupled receptors; cAMP: cyclic adenosine monophosphate; REDD1: regulated in development and DNA damage responses 1; mTORC: mammalian target of rapamycin inhibitor complex; NET: neutrophil extracellular trap.

mediators was induced 6 h after corticosterone pretreatment, and associated with activation of NF-κB in the presence of activated GC receptors [71]. Increased GCs after stress facilitates the central and peripheral innate immune system with permissive effects [72]. In recent years, it has been claimed that GCs might increase cerebral inflammation in demyelinating diseases such as multiple sclerosis. In one study, GCs were shown to increase lipopolysaccharide-induced *NF-κB*, *TNF-α* and *IL-1β* gene activation in the frontal cortex and hippocampus [73].

Apart from these priming effects, GCs also have non-specific proinflammatory effects on the innate immune system. GC provides activation of innate immune system by increasing catecholamine release from adrenal glands [74]. Increased GCs amplify immune cell mobilization to the injury site [75, 76]. Released IL-1 and IL-6 during inflammation increases the synthesis of acute-phase proteins from the liver [59]. GCs potentiate these effects of IL-6 and IL-1 [77]. Moreover, GCs increase the expression of cytokine receptors [78]. Dhabhar *et al.* [79] suggested that GCs organized mobilized immune defenses and facilitated immune responding to damage and infection that could occur during fight/flight emergencies.

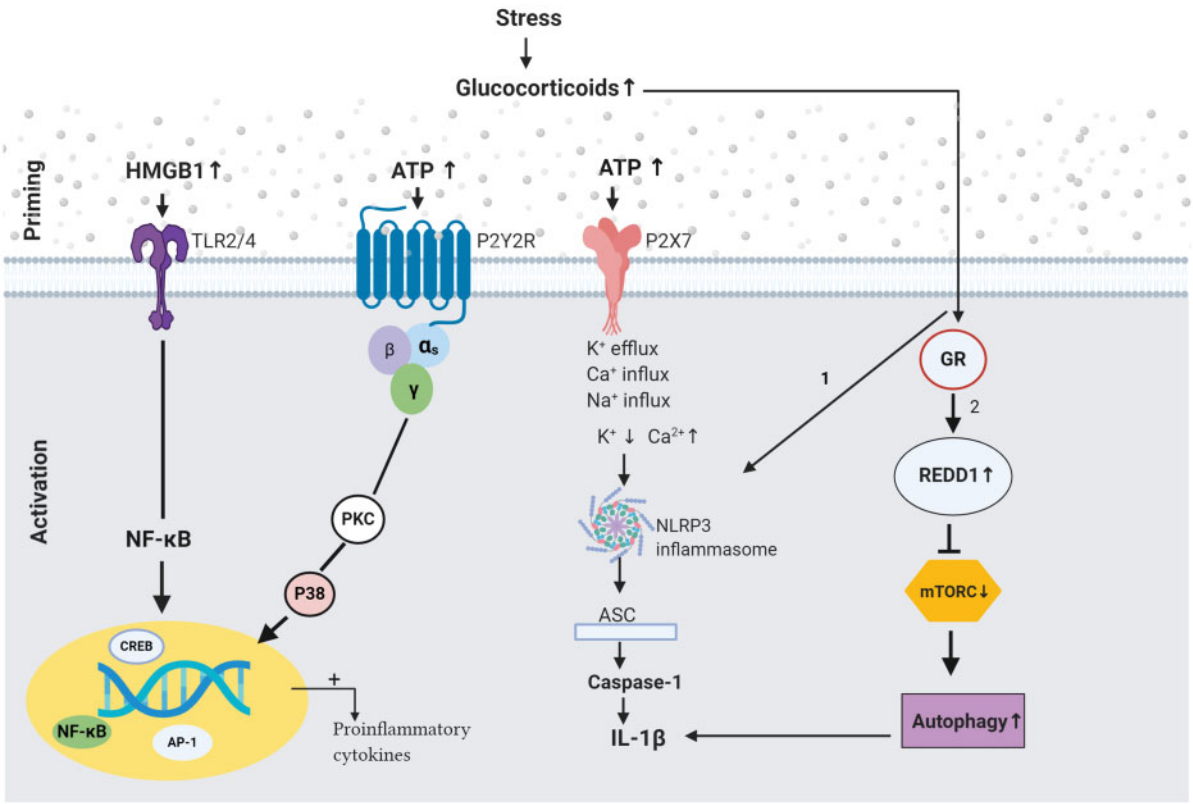
Considering the above-mentioned study results, increased GCs due to acute stress show both anti-inflammatory and proinflammatory effects by sensitizing innate immunity. This dual effect of GCs on the central and peripheral innate immune systems is called the 'opponent process model' [57]. In this model, the proinflammatory recuperative phase of GCs follows the anti-inflammatory effect that appears during the initial phase of the fight/flight response [58]. This effect of GCs reinforces the innate immune system, but also acts systemically to suppress the adaptive immune system in order to fix homeostasis [57].

GCs and inflammasome activation

In experimental neuroinflammation models, increased GCs in response to stress induce HMGB1 release, as a danger signal [80]. HMGB1 potentiates inflammation by activating NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) as a damage-associated molecular pattern (DAMP). In addition to this indirect effect, GCs can also activate NLRP3 directly [60]. GCs led to a significant induction of *NLRP3* mRNA in THP-MQ, and this induction was independent of the presence or absence of lipopolysaccharide. Interestingly, the induction of *NLRP3* mRNA and its protein were also observed in primary macrophages isolated from bone marrow of both human and wild-type C57BL/6 mice [60]. GCs specifically regulate NLRP3 but no other inflammasome component. It has been hypothesized that the rapid induction of NLRP3 by GCs was a primary effect of GR-dependent transcription rather than a secondary effect [60]. The GC-dependent induction of NLRP3 sensitizes the cells to extracellular ATP and significantly enhances the ATP-mediated release of proinflammatory molecules, including mature IL-1β, TNF-α and IL-6. Another preclinical study showing that GCs might lead to activation of the inflammasome was reported by Maturana *et al.* [81]. The authors showed that inflammasome components (NLRP3, Caspase 1) were increased in the offspring of mice exposed to high doses of dexamethasone during gestation. During this activation, they demonstrated an increase in P7X2 and Pannexin-1 along with TNF-α and IL-1β [81].

As noted above, the increase in REDD1 expression is caused by hypoxia and cellular stress, and by exposure to endogenous and exogenous GCs [82, 83]. Increased expression of REDD1 due to GCs leads to mTORC1 inhibition [70, 84] (Fig. 3). Britto *et al.* [85] demonstrated that muscle atrophy due to GCs developed in the context of REDD1-induced mTORC1 inhibition. REDD1 is responsible for an alteration of the protein synthesis/degradation balance and a reduction in skeletal muscle mass in stress conditions. REDD1 deletion prevents dexamethasone-induced skeletal muscle atrophy by

Fig. 3 The possible role of GCs on the development of inflammation.



Stress-induced GCs prime innate immune cells by stimulating damage-associated molecular patterns such as ATP and HMGB1. They also upregulate TLRs 2/4 on innate immune cells. HMGB1 can directly interact with TLRs. Activation of TLRs leads to activation of the transcription factors (NF-κB) and subsequent induction of proinflammatory cytokines. ATP binds to the P2X7 receptor. The efflux of potassium (K^+) caused by ATP induces NLRP3 activation and recruits the adaptor protein ASC and pro-caspase 1. Mature caspase 1 is cleaved from pro-caspase 1, which cleaves pro-IL-1β to make mature IL-1β. Stimulation of P2Y2R leads to the activation of PKC and results in the induction of second messenger and enzyme cascades system such as p38 MAPK. These reactions induce the activity of transcription factors such as NF-κB, CREB and AP-1, which up-regulate the expression of proinflammatory genes. GCs induce a rapid and sustained increase in *NLRP3* mRNA and protein and sensitize the NLRP3 inflammasome to extracellular ATP (1). GCs increase REDD1 expression and mTORC1 inhibition (2). This may lead to autophagy activation. **Abbreviations:** ATP: adenosine triphosphate; GCs: glucocorticoids; TLRs: Toll-like receptors; NF-κB: nuclear factor-kappa B; MAPK: mitogen-activated protein kinase; Ca: calcium; GR: glucocorticoid receptor; Na: sodium; HMGB1: high-mobility group box 1; AP-1: activating protein 1; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; PKC: protein kinase C.

suppressing mTORC1 and protein synthesis inhibition by a mechanism involving Akt and PRAS40 [86]. That is, GCs, as well as catecholamines, are also effective in the activation of REDD1 *in vivo*.

Conclusions and future directions

This review has potential limitations. There is a limited number of studies into the role of stress in FMF patients developing attacks; these few studies have been conducted with a heterogeneous method, and there are hardly any studies into measuring stress mediator levels during FMF attacks. Added to that, the presence of an insufficient number of studies in terms of stress mediators and their actions on inflammasome activation may be considered to be a limiting factor for this review. However, we know that stress mediators have a wide range of effects on the cell membrane and intracellular signalling system (Table 1). In patients with FMF with hypermorphic mutation with a low activation threshold, these effects can be claimed to lead to the development of pyrin inflammasome activation and attacks [87]. It has been claimed that for activation of the pyrin inflammasome, both a priming step and RhoA inactivation are required [5]. GCs may contribute to priming of innate immune cells and to the activation of inflammation by increasing DAMP products such as ATP and HMGB1, as well as enhancing REDD1 expression, and

Table 1 Sympathoadrenal system mediators and their roles in inflammation and inflammasome activation

Mediators	Target	Reported actions of mediators on inflammation and inflammasome activation	Reference
Epinephrine	Transcription factors	NF-κB cascade activation and proinflammatory cytokines stimulation	[35, 36]
	Stress response proteins	Increases REDD1 expression, and leads to mTORC1 inhibition and then autophagy induction	[41, 42, 44, 45, 46]
Norepinephrine	Rho family proteins and inflammasome	Inhibits Rho GTPase activity similar to C3 transferase of *Clostridium botulinum* by increasing cAMP and leads to pyrin inflammasome activation	[48]
Glucocorticoid	Innate immune system (priming effects)	Sensitizes the innate immune system against potential dangers	[60]
		Stimulates TLR level when combined with inflammatory cytokines	[61, 62]
		Amplifies cell signaling initiated by ATP and increases IL-6 production	[67]
		Increases catecholamine release from adrenal glands	[74]
		Amplifies immune cell mobilization to the injury site	[76]
		Increases the expression of cytokine receptors	[78]
	Nuclear protein	Induces HMGB1 release as a DAMP; HMGB1 activates NLRP3	[80]
	Inflammasome	Activates NLRP3 directly	[60]
	Stress response protein	Increases REDD1 expression, and leads to mTORC1 inhibition	[70, 84]

ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; DAMP: damage-associated molecular pattern; HMGB1: high-mobility group box-1 protein; NF-κB: nuclear factor-kappa B; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; mTORC1: mammalian target of rapamycin inhibitor complex 1; REDD1: regulated in development and DNA damage responses 1; Rho GTPase: Ras homologous protein guanosine triphosphate; TLR: Toll-like receptors.

subsequently leading to the formation of NET-mediated IL-1β release. The ability of catecholamines to produce RhoA inactivation by acting as C-transferase of *C. botulinum* via increased cAMP may contribute to the activation of the inflammasome. Catecholamine-induced cAMP inhibits the NLRP3 inflammasome but activates the pyrin inflammasome [88]. Taken together, stress mediators may have multiple roles in the activation of the inflammasome and inflammation pathways, rather than a single pathway. Inflammasome activation may also be responsible for the development of the inflammation in autoimmune diseases [89–92]. Studies investigating the relationship between stress and inflammation may also clarify the mechanism of stress-related exacerbations in the course of autoimmune and autoinflammatory diseases. The use of epinephrine, norepinephrine and GCs as activators in studies investigating inflammasome activation will reveal the stress–inflammation relationship more clearly. If stress-induced inflammasome activation and inflammation networks play a role in the development of FMF attacks with the mechanisms outlined above, other questions need to be answered. Is it worth investigating whether mutation differences in patients with FMF make a difference in response to stress? Does the role of stress and stress mediators differ in colchicine-resistant patients from colchicine-sensitive patients? Do stress modifications and stress management lead to changes in disease phenotype? Can the feedback relationship between REDD1 and mTORC1 be an explanation for the self-limited attacks of FMF? Further studies on these subjects will provide a better understanding of the mechanisms of attacks and will contribute to the development of new treatment options for the treatment of this disease.

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