Autoimmunity Reviews 12 (2012) 38–43

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS): State of the art and future perspectives

Luca Cantarini [a,*,1], Orso Maria Lucherini [b,1], Isabella Muscari [a], Bruno Frediani [a], Mauro Galeazzi [a], Maria Giuseppina Brizi [a], Gabriele Simonini [b], Rolando Cimaz [b]

[a] Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Siena, Italy
[b] Department of Evolutionary Biology, University of Siena, Siena, Italy

ARTICLE INFO

Available online 2 August 2012

Keywords:
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
Autoinflammatory disorders
Amyloidosis
TNFRSF1A gene
Interleukin (IL)-1β inhibition

ABSTRACT

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder characterized by periodic fever episodes, arthralgia, myalgia, abdominal pain, serositis, and skin rash. TRAPS is caused by mutations in the gene encoding the TNF Receptor Super Family 1A (TNFRSF1A) on chromosome 12p13. The identification of *TNFRSF1A* mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF could potentially represent the primary therapeutic goal in TRAPS, thus disclosing new treatment choices for this complex disease. Anti-TNF therapy in TRAPS has been based on etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG_1 Fc fragment. However a decrease in responsiveness to etanercept over time has been described, and it may be due to a non-specific action of etanercept in TRAPS; its efficacy may reflect 'generic' anti-inflammatory properties. Long-term adherence to etanercept is poor and a significant number of patients need to switch to anti-interleukin (IL)-1β therapy. In fact, the IL-1 receptor antagonist anakinra has recently been shown to prevent disease relapses both in the short- and in the long-term, and to induce a prompt and stable disease remission.

Contents

1. Introduction

Tumor necrosis factor (TNF)-α receptor-associated periodic syndrome (TRAPS, MIM 142680) is an autosomal dominant autoinflammatory condition and is characterized by recurrent fever attacks lasting typically from 1 to 3 weeks; in addition to fever, its most common clinical manifestations include periorbital edema, conjunctivitis, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthralgia [1–3]; serosal membrane inflammation is also possible, often, but not only, in the form of polyserositis [1,4] (Fig. 1). TRAPS is caused by mutations in the gene *TNFRSF1A*, located on chromosome 12p13, encoding the 55-kD receptor for TNF-α (TNFRSF1A) [5]. TRAPS belongs to the group of hereditary systemic autoinflammatory diseases (SAIDs) - formerly known as hereditary periodic fever syndromes — an expanding list of diseases characterized

* Corresponding author at: Rheumatology Unit, Policlinico Le Scotte, University of Siena, Viale Bracci 1, 53100 Siena, Italy. Tel.: +39 577 233393; fax: +39 577 40450.
E-mail address: cantariniluca@hotmail.com (L. Cantarini).
[1] These authors contributed equally to the work.

1568-9972/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.autrev.2012.07.020

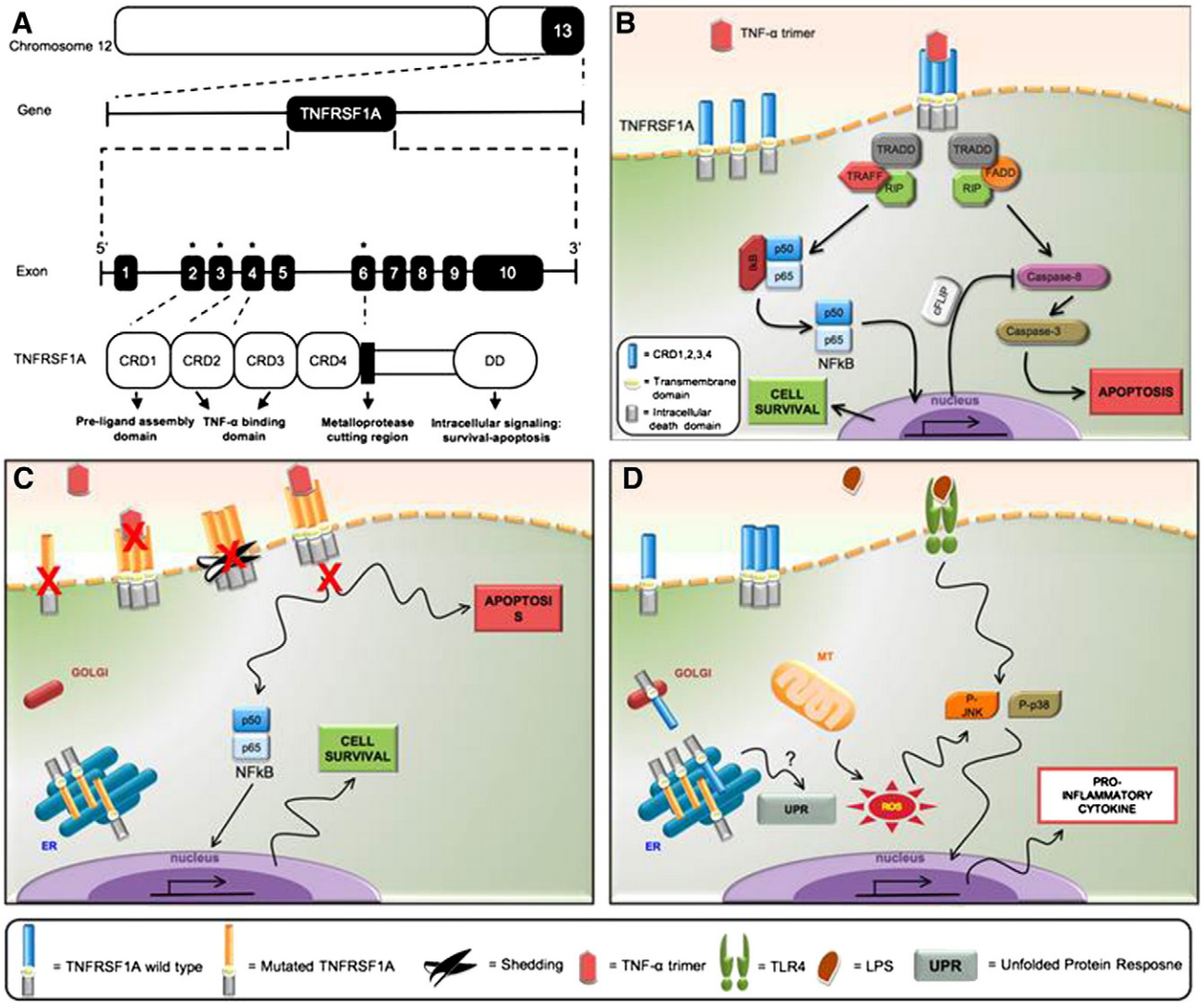

Fig. 1. Tumor necrosis factor (TNF)-α receptor-associated periodic syndrome (TRAPS): from *TNFRSF1A* gene to the pathogenic mechanism. A) *TNFRSF1A* gene is localized within distal chromosome 12p and consisting of ten exons. The majority of TRAPS disease related sequence variants are single-nucleotide *missense* mutations within exons 2, 3, 4, and 6. *TNFRSF1A* gene encodes the 55-kD receptor of tumor necrosis factor-α (TNF-α) (TNFRSF1A), that consists of an extracellular domain constituted by 4 tandem repeat cysteine-rich domains (CRD1-4), a transmembrane region and an intracellular death domain (DD). B) Binding of TNF-α trimer to TNFRSF1A receptor leads to either NF-κB activation, which induces several pro-inflammatory cytokines and survival signal or caspase-mediated apoptosis. Upon receptor activation TNFRSF1A intracellular death-domain promote TRAFF and RIP recruitment to the plasma membrane. This complex activates IKK pathway, which in turn allows the release and nuclear translocation of the NF-κB thus promoting cell survival and inflammatory signals. Moreover, activated TNFRSF1A recruits various adapter molecules including fas-associated death domain (FADD) and caspase-8 which leads to the induction of apoptosis. (C) The early investigation had demonstrated that TRAPS-associated TNFRSF1A mutations result in impaired i) TNFRSF1A trafficking to the cell surface; ii) TNF-α binding; iii) activation-induced shedding; iv) TNF-α induced activation of transcription factors or apoptosis. (D)Accumulation of mutated TNFRSF1A in the endoplasmic reticulum (ER) leads to both ER stress-signaling pathways activation a potential mechanism linked to enhanced ROS production by unfolded protein response (UPR) and mitochondrial (MT) reactive oxygen species (ROS) production that in turn potentiate pro-inflammatory cytokine production in response to lipopolysaccharide (LPS) by sustained MAPK activation (JNK and p38).

by unprovoked recurrent attacks of systemic inflammation with lack of autoantibodies or autoreactive T-cells [6]. In each of these syndromes a specific genetic defect which involves the regulation of innate immunity has been demonstrated, and the vast majority of these conditions is related to the activation of the interleukin-1 pathway, which results in or from a common unifying pathogenetic mechanism [7].

2. The genetic basis of TRAPS

TRAPS was initially called familial Hibernian fever, due to its first characterization in a single family of Irish/Scottish ancestry [8]. Since 1998, genome-wide searches and linkage analysis in the affected families have been used to map the susceptibility locus to chromosome 12p13 [5]. This chromosome region includes several candidate genes: *CD4*, *LAG-3*, *CD27*, *C1R*, *C1S* and *TNFRSF1A* [9]. The identification of several mutations in the *TNFRSF1A* gene and low levels of soluble TNFR observed in the serum of some TRAPS patients suggested a key role for TNFRSF1A in the development of symptoms related to TRAPS [10].

To date, more than 70 *TNFRSF1A* mutations have been associated with TRAPS, the majority of which are localised in the first two N-terminal cysteine-rich domains CRD1 and CRD2 (www.fmf.igh.cnrs.fr/infevers/) [11]. CRD1 is the pre-ligand binding assembly domain and is thought to mediate TNFRSF1A self-assembly [12], while CRD2 interacts with trimeric TNFα [13]. TRAPS associated mutations are mainly (about 94%) single-nucleotide missense variants within exons 2, 3, 4, and 6 encoding for the extracellular region of the receptor (Fig. 1A). Other variants have been reported: three deletions and one deletion/insertion, all in the extracellular domain. About 50% of the mutations described (known as “structural mutations”) involve cysteine residues and are associated with a higher disease penetrance [3]. Cysteine residues are known to be involved in intramolecular disulphide bonds that are critical for the three-dimensional structure of the receptor, thus

mutations that affect cysteine residues determine impaired conformation and stability of the TNFRSF1A extracellular portion. Other genetic variants that affect residues involved in the secondary structure of TNFRSF1A are also known. These mutations introduce or remove proline residues (P46L, L67P, S86P, R92P), or affect hydrogen-bond stabilization of the receptor (T50M, I170N) [14]. Moreover, several variants involving other residues, also called non-structural mutations, are associated with milder clinical manifestations [15]. Two of these are low-penetrance variants (R92Q and P46L) that occur in 1–5% of the general population and show distinctive clinical features [15,16].

There are currently no mutations that encode for a widely deleted receptor, suggesting that the synthesis of the mutated receptor is important for disease pathogenesis.

3. TRAPS pathogenesis

TNF-α is a type II transmembrane protein produced mainly by monocytes and macrophages but also by other cell types including lymphocytes, natural killer cells (NK) cells, polymorphonuclear leukocytes, keratinocytes and astrocytes. TNF is a major cytokine involved in systemic inflammation known to mediate a variety of biological processes including apoptosis, cell proliferation, immune modulation, inflammation, arthritis, autoimmune diseases and other pathological conditions [17].

TNF-α transmits its signal by binding to two different cell surface receptors, TNFRSF1A (or TNFR1, p55/p60-TNFR, CD120a) and TNFRSF1B (or TNFR2, p75/80-TNFR, CD120b), which belong to the superfamily of known receptors for TNF (Tumor Necrotic Factor Receptor Superfamily, TNFRSF). These receptors, through the recruitment of various signalling proteins, promote different signalling pathways leading to activation of transcription factors such as nuclear factor-kB (NF-kB) and c-Jun/activator protein 1 (AP-1), apoptosis and protein-kinase pathways activated by mitogens [18] (Fig. 1B).

TNFRSF1A is a member of the TNF receptor superfamily, a group of proteins known to be involved in numerous processes including inflammation, T-cell activation and B-cell homeostasis [19].

TNFRSF1A is a transmembrane protein characterized by an extracellular domain, consisting of the tandem repeat of four cysteine-rich subdomains (CRD1-4), a transmembrane region and an intracellular death domain (death domain, DD). The N-terminal region of CRD1, called the pre-ligand binding assembly domain (Pre-Ligand Assembly Domain or PLAD), is known to mediate homotypic receptor interactions, allowing efficient ligand binding and thus signal transduction [13]. The extracellular domain is characterized by the presence of intramolecular disulfide bridges, which constitute the binding site for TNF and also mediate self-assembly of TNFRSF1A. CRD3 and CRD2 domains interact with trimeric TNF, resulting in recruitment of the adaptor protein TRADD through the cytoplasmic death domain (DD) of TNFRSF1A [13,20]. TRADD in turn recruits other proteins to trigger the signal transduction cascade that leads to activation of NF-kB and subsequently to the production of proinflammatory cytokines, or alternatively the activation of caspase, resulting in apoptosis [21]. After TNFRSF1A receptor activation, the extracellular portion of the receptor is shed from the cell surface by metalloprotease cleavage (and released into the extracellular compartment, leading to the formation of a pool of soluble TNFRSF1A that binds circulating TNF, an important control strategy during acute inflammation [22].

The pathogenic mechanism by which *TNFRSF1A* mutations lead to the autoinflammatory phenotype of TRAPS is not well understood. Several pathogenic mechanisms have been proposed in recent years, but not all TNFRSF1A mutants shown similar defects in pathogenic mechanisms.

It was initially hypothesised that TRAPS mutations either constitutively determined activation of the TNFRSF1A or increased binding affinity of the receptor to TNF-α, but results obtained from controls and TRAPS patients' PBMCs disallowed these hypotheses [5]. It was then proposed that TRAPS mutations could be due to impaired metalloprotease-dependent cleavage of TNFRSF1A that produces soluble "shed" receptors [5]. In fact, it has been demonstrated that patients with structural mutations including C33Y, T50M, C52F and C88R demonstrated significantly reduced levels of soluble receptor in serum compared to healthy donors, suggesting a key role for TNFRSF1A in the development of symptoms related to TRAPS [2,3,5]. However, some TRAPS patients have normal receptor shedding [3]. Moreover, TNF- α blockage by means of the soluble p75 TNFR:Fc fusion protein Etanercept is not always effective in reducing TRAPS symptoms [23,24].

In vitro studies suggest that TRAPS-associated *TNFRSF1A* mutations are responsible for impaired TNF-α binding [10], abnormal apoptosis [25] and altered NF-κB pathway [10,26] as well as defective TNFR trafficking to the cell surface [27] (Fig. 1C). Some of these impaired mechanisms could be associated with the anti-inflammatory effect (e.g. less binding of TNF-α to the mutated receptor, less cell-surface expression and decreased TNF-induced NF-kB activation). On the other hand, several studies have shown characteristics of the mutated TNFRSF1A pro-inflammatory effect, such as defective TNF-induced apoptosis. Indeed, neutrophils and fibroblast from TRAPS patients who have mutations of cysteine residues or interstitial deletion show decreased TNF-alpha-induced apoptosis [28].

To date, some TRAPS-associated mutations – in particular those linked to intramolecular disulphide bond alteration – have been associated with defective TNFRSF1A trafficking. *In vitro* experiments, in combination with the molecular modelling of TNFRSF1A mutants, have demonstrated that abnormal oligomerization of mutant receptors results in their intracellular retention in the endoplasmic reticulum (ER) [27]. Lobito et al in fact demonstrated that misfolding and abnormal oligomerization of TNFRSF1A mutants result in retention in the endoplasmic reticulum (ER), as well as inability to form soluble receptors, and altered signaling.

Recently, the intracellular retention of TNFRSF1A mutant has/also been confirmed in peripheral blood mononuclear cells of TRAPS patients and in multiple cell types from two independent lines of knock-in mice harbouring TRAPS-associated *TNFRSF1A* mutations [29]. In fact, in a recent paper, Simon et al demonstrated that TRAPS-associated *TNFRSF1A* mutations determined intracellular TNFRSF1A receptor accumulation, which sensitized cells to the effects of other innate stimuli such as LPS (due to spontaneously increased activation of MAPK), resulting in an excessive pro-inflammatory response dependent on autocrine TNF-α secretion [29]. These results suggest that the enhanced production of inflammatory cytokines and chemokines secondary to low concentration of pro-inflammatory stimuli (e.g. TNF-α and lipopolysaccharide, LPS) may play a central role in triggering the inflammatory attacks associated with TRAPS [29,30]. Moreover, Bulua et al demonstrated that mitochondrial ROS are an important component of the inflammatory response, both in normal cells and in the hyper-responsive TRAPS cells. They studied blood mononuclear cells from TRAPS patients and mouse embryonic fibroblasts (MEFs) from knock-in mice harboring TRAPS-associated TNFRSF1A mutations [30]. In particular, Bulua et al found that TRAPS cells showed altered mitochondrial function with enhanced oxidative capacity and mitochondrial ROS generation, which in turn potentiated pro-inflammatory cytokine production in response to LPS by means of sustained MAPK activation [30] (Fig. 1D).

4. TRAPS clinical features

TRAPS is characterized by recurrent fever episodes which typically last 1 to 3 weeks on average; fever attacks recur at varying intervals, generally longer than those seen in other SAIDs, and initiate with muscle cramps or myalgia that migrates in a centrifugal pattern, followed by fever with skin, joint, abdominal and ocular manifestations [1–3]. Recurrent inflammatory episodes occur either spontaneously or after minor triggers, such as local injury, minor infection, stress, exercise and hormonal changes. The most common skin manifestation

is centrifugal migratory erythematous rash, which overlies an area affected by myalgia; this type of lesion is painful and warm to the touch. Skin lesions may also include erysepela-like erythema, edematous plaques and urticarial lesions. TRAPS skin lesions are characterized by a dermal perivascular lymphocytic and monocytic infiltrate [31]. Early lesions consist of erythematous macules and papules, individual or in groups. As these lesions progress, they expand at the periphery, coalescing into large patches or plaques. Myalgia also displays centrifugal migration and is due to a monocytic fasciitis [32]. Eye involvement can manifest in the form of conjunctivitis, periorbital edema or uveitis [3]. Abdominal pain may occur and is due to inflammation of the peritoneal cavity and abdominal wall muscles. Arthralgias are common, and in rare cases non-erosive arthritis may be present, mainly affecting single large joints.

About 25% of TRAPS patients carrying mutations involving cysteine residues may, over time, develop kidney amyloidosis (versus 2% of patients carrying low-penetrance mutations), usually manifesting with proteinuria [33].

The average age at disease onset is around 3, but many diagnoses have been made in adolescents or adults [1,4,16,34]. The low-penetrance *TNFRSF1A* variants may contribute to the development of the disease during adulthood [15]. Adult-onset TRAPS patients may present a phenotype that mimics other autoinflammatory disorders such as familial Mediterranean fever (FMF,) even in terms of the duration of inflammatory attacks, which can be short, frequently leading to misdiagnosis and improper management [34]. Low-penetrance TNFRSF1A variants may also cause oligosymptomatic TRAPS and atypical inflammatory responses, including cardiac diseases such as myocarditis and pericarditis as the only clinical manifestation [1]. We recently identified low penetrance TNFRSF1A mutations in about 6% of unselected patients affected with idiopathic recurrent pericarditis (IRAP). We therefore suggested possible clues to detect TRAPS among IRAP patients [35].

TRAPS patients have also been reported to have an increased risk of cardiovascular diseases such as atherosclerosis and acute myocardial infarction [24].

In recent years, scientific interest has increased dramatically, since several mediators secreted by adipose tissue known as adipokines, such as leptin and adiponectin, have been described to have proinflammatory properties and also to be associated with increased cardiovascular risk in patients affected with chronic inflammatory disorders [36]. We recently showed that serum leptin levels significantly correlate with TRAPS severity, and in addition, that serum adiponectin levels are significantly increased in TRAPS patients with reactive amyloidosis (unpublished, manuscript submitted).

However, whether leptin and adiponectin are responsible for increased cardiovascular risk in TRAPS patients still remains to be investigated.

5. Laboratory investigations

In TRAPS, laboratory tests commonly reveal increases in indicators of inflammation during each acute inflammatory episode; in particular, marked increases are observed for erythro-sedimentation rate and C-reactive protein, as well as fibrinogen and haptoglobin, which characteristically return to normal levels during non-acute intervals. These increases can also be associated with abnormalities in blood cell count, such as neutrophil leukocytosis, thrombocytosis and hypo- or normochromic anemia, which is typical of chronic inflammatory diseases. Also fairly frequent are findings of polyclonal hyper-gammaglobulinemia due to stimulation of immunoglobulin synthesis by numerous proinflammatory cytokines, such as IL-6.

Acute-phase reactants are often elevated in patients with TRAPS even between fever attacks, although at a lower level than during attacks, but the most determinant laboratory element of the quiescent phase is the finding of low serum levels of the soluble TNF receptor (<1 ng/ml), as the illness is linked to a defective release of the receptor from cell membranes [2]. Serum amyloid-A (SAA) is an acute-phase protein, synthesized and secreted by the liver upon stimulation by proinflammatory cytokines as IL-1, IL-6 and TNF-α. Its amino-terminal fragment may be deposited in various organs in the form of amyloid fibrils, leading to the development of AA-amyloidosis. The measurement of serum SAA is a useful diagnostic aid: elevated concentrations are associated with a risk of progressive amyloid-fibril deposits in various parenchymas. SAA has been shown to be a useful parameter in the evaluation of clinical activity in response to treatment [37].

Like that of SAA in inflammatory processes of various origins, the role of the protein S100A12 (or calgranulin C) has also been clarified [38]: it is a calcium-binding protein expressed and secreted by neutrophil granulocytes which, through the NF-κB pathway, activates the inflammatory response in the endothelial cells and leukocytes of patients with CAPS. It has been demonstrated that determination of serum S100A12 levels is closely correlated not only with the disease activity, but also with the clinical efficacy of therapy, providing a reliable new marker for future utilization [38].

6. TRAPS treatment

TRAPS treatment proves more challenging than that of other autoinflammatory syndromes due to the wide-ranging genetic heterogeneity and to the protean clinical phenotype: some patients experience significant disability over time or develop signs of renal amyloidosis, requiring novel treatment strategies with the aim of better long-term disease control. Goals of therapy for TRAPS are: i) to control symptoms, ii) to improve patients' quality of life, iii) to prevent long-term complications.

There are patients who gain some symptomatic relief from high-dose non-steroidal anti-inflammatory drugs, whilst colchicine or immunomodulators such as methotrexate, cyclosporine and thalidomide produce little benefit. Inflammatory attacks usually respond to corticosteroid administration, but often require increasing doses, especially in patients with frequent relapses or continuous symptoms, who become prone to metasteroidal co-morbidities [5,37].

The identification of *TNFRSF1A* mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF – even though TNF is not increased in most patients – [39] could potentially represent the primary therapeutic goal in TRAPS, thus suggesting new treatment choices for this complex disease.

Anti-TNF therapy in TRAPS has been based on etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG_1 Fc fragment.

In contrast, the administration of other anti-TNF agents, such as infliximab, a mouse-human chimeric monoclonal IgG_1 antibody to TNF, or adalimumab, a fully humanized anti-TNF monoclonal antibody, may lead to enhanced anti-apoptotic activity, over-secretion of pro-inflammatory cytokines (IL-1, IL-1R, IL-6, IL-8, and IL-12) [10] and paradoxical exacerbation of the TRAPS clinical picture [40,41]. Differences in response to treatment with different TNF-inhibitors seem to be related to the more stable binding complexes with soluble TNF and to their much higher binding avidity to transmembrane TNF of monoclonal antibodies than etanercept [42]. Moreover, it has been hypothesized that mutations altering the extracellular conformation of TNFRSF1A fail to shed infliximab-bound TNF/TNFRSF1A from the cell surface, thus leading to the induction of inflammatory responses [40].

The efficacy of etanercept has been shown in single patients and/or in case-series of patients of different ages with fully penetrant TRAPS phenotypes, as evidenced by decreased frequency of attacks and/or decreased severity of disease [43–45]. In a recently reported case series of 7 patients affected with TRAPS who were treated with etanercept for 24 weeks, although the drug did not completely eliminate inflammatory attacks, it was able to reduce disease activity, in terms of acute-phase response as well, and allowed for reduction of corticosteroid dose administration in all cases [45].

However a decrease in responsiveness to etanercept over time has been described, and it may be due to a non-specific action of etanercept in TRAPS; its efficacy may reflect 'generic' anti-inflammatory properties [2,46]. Etanercept-resistant patients have also been reported [47].

Bulua et al recently showed that etanercept reduces symptoms and serum inflammatory markers of TRAPS in a dose-dependent manner, but does not completely normalize symptoms or acute-phase reactants [41]. Long-term adherence to etanercept is poor, since a significant number of patients need to switch to anti-IL-1β therapy; however, remaining on etanercept may provide continued symptomatic benefit [41].

Since IL-6 levels may be elevated in TRAPS [39], it has been hypothesized that tocilizumab, a humanized monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 receptor–mediated signalling, might be effective [48]. Recently, a 52-year-old TRAPS patient resistant to etanercept and anakinra, was administered tocilizumab for 6 months. The treatment aborted an evolving acute attack and also prevented further attacks. Moreover, the acute-phase response diminished significantly during treatment. However, cytokine levels were not reduced. This case supports the notion of a prominent role for IL-6 in mediating inflammatory attacks in TRAPS, but blockage of IL-6 does not seem to affect the underlying pathogenesis.

There are promising results deriving from the use of anakinra, a recombinant interleukin-1 receptor antagonist; in etanercept-resistant patients, anakinra has recently been shown to prevent disease relapses in the short-term, and to induce a prompt and stable disease remission [49,50]; its long-term efficacy and safety in patients with and without AA amyloidosis have also been recently described [50]. However, refractoriness to anakinra has also been described in a patient carrying the T50M mutation [51].

Long-lasting drugs targeting IL-1 such as canakinumab, a human IgG1 anti-IL-1β monoclonal antibody, and rilonacept, dimeric glycoprotein, consisting of human IL-1 receptor extracellular domains and the Fc portion of human IgG1, might overcome the need for daily injections.

7. Conclusions

Our understanding of the pathogenic mechanism underlying TRAPS continues to grow thanks to recent studies of mouse models. The mechanisms underlying this disease seem to be complex because the underlying biology of impaired TNFRSF1A function in TRAPS may be ligand-independent [29]. In fact, there is a growing consensus among researchers that the hyper inflammation shown in TRAPS cells is primarily independent of its TNF-α signalling function, which may be due to enhanced production of inflammatory cytokines and chemokines secondary to low concentration of pro-inflammatory stimuli [29]. This condition could result in a positive feedback loop through the cytokines produced by TRAPS cells, which could explain the inflammatory response observed in TRAPS. The condition of cellular stress detected in TRAPS cells involves enhanced oxygen consumption and ROS production [30]. Moreover, activation of ER stress signalling pathways is another potential mechanism linked to enhanced ROS production by means of unfolded protein response (UPR). Simon et al did not observe activation or alteration of the classic UPR in heterozygous TNFRSF1A-mutant cells or in monocyte-derived macrophages from TRAPS patients [29]. However, an alternative UPR signalling that involves low-level activation of ER stress signaling engaging XBP-1 could be implicated in TRAPS. This unconventional UPR activation was described by Martinon et al in mouse macrophages, where TLR activation was associated with XBP-1 activation without activation of classic ER stress–induced genes [52]. Hyper responsiveness to LPS has been reported in TRAPS cells, indicating that unconventional UPR activation could be involved in TRAPS.

To date, despite in the lack of literature on inflammasome activation in TRAPS, TRAPS patients treated with recombinant IL-1 receptor antagonist (IL-Ra) have been shown to elicit a beneficial response [49,50]. The link between inflammasome activation and TRAPS is still unknown, however it is conceivable that an inflammasome activation stimuli such us ROS derived from mitochondrial or ER-stress signals may be involved.

Take-home messages

- TRAPS is an autosomal dominant disorder caused by TNFRSF1A gene mutations (12p13)
- TRAPS is the most variable and multifaceted autoinflammatory syndrome
- TRAPS diagnosis relies on mutational analysis and a compatible clinical picture
- Etanercept has been shown to be efficacious in most TRAPS cases
- Etanercept efficacy might be non-specific; resistant patients have been described
- Interleukin-1 inhibition has been shown to induce a stable disease remission.

References

[1] Dodé C, André M, Bienvenu T, Hausfater P, Pêcheux C, Bienvenu J, et al. French Hereditary Recurrent Inflammatory Disorder Study Group. The enlarging clinical, genetic, and population spectrum of tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2002;46:2181-8.
[2] Aganna E, Hammond L, Hawkins PN, Aldea A, McKee SA, van Amstel HK, et al. Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. Arthritis Rheum 2003;48:2632-44.
[3] Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, Oh HH, et al. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in *TNFRSF1A*, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. Am J Hum Genet 2001;69:301-14.
[4] Cantarini L, Imazio M, Brucato A, Lucherini OM, Galeazzi M. Innate versus acquired immune response in the pathogenesis of recurrent idiopathic pericarditis. Autoimmun Rev 2010;9:436-40.
[5] McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999;97:133-44.
[6] Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621-68.
[7] Dinarello CA. Blocking interleukin-1β in acute and chronic autoinflammatory diseases. J Intern Med 2011;269:16-28.
[8] Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghill PJ. Familial Hibernian fever. Q J Med 1982;51:469-80.
[9] McDermott MF, Ogunkolade BW, McDermott EM, Jones LC, Wan Y, Quane KA, et al. Linkage of familial Hibernian fever to chromosome 12p13. Am J Hum Genet 1998;62:1446-51.
[10] Nedjai B, Hitman GA, Yousaf N, Chernajovsky Y, Stjernberg-Salmela S, Pettersson T, et al. Abnormal tumor necrosis factor receptor I cell surface expression and NF-kappaB activation in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008;58:273-83.
[11] Sarrauste de Menthière C, Terrière S, Pugnère D, Ruiz M, Demaille J, et al. INFEVERS: the Registry for FMF and hereditary inflammatory disorders mutations. Nucleic Acids Res 2003;31:282-5.
[12] Chan FK, Chun HJ, Zheng L, Siegel RM, Bui KL, Lenardo MJ. A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling. Science 2000;288:2351-4.
[13] Banner DW, D'Arcy A, Janes W, Gentz R, Schoenfeld HJ, Broger C, et al. Crystal structure of the soluble human 55 kd TNF receptor-human TNF beta complex: implications for TNF receptor activation. Cell 1993;73:431-45.
[14] Rebelo SL, Bainbridge SE, Amel-Kashipaz MR, Radford PM, Powell RJ, Todd I, et al. Modeling of tumor necrosis factor receptor superfamily 1A mutants associated with tumor necrosis factor receptor-associated periodic syndrome indicates misfolding consistent with abnormal function. Arthritis Rheum 2006;54:2674-87.
[15] Ravet N, Rouaghe S, Dodé C, Bienvenu J, Stirnemann J, Lévy P, et al. Clinical significance of P46L and R92Q substitutions in the tumor necrosis factor superfamily 1A gene. Ann Rheum Dis 2006;65:1158-62.
[16] Tchernitchko D, Chiminqgi M, Galactéros F, Préhu C, Segbena Y, Coulibaly H, et al. Unexpected high frequency of P46L TNFRSF1A allele in sub-Saharan West African populations. Eur J Hum Genet 2005;13:513-5.
[17] Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. N Engl J Med 1996;334:1717-25.

[18] Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death Differ 2003;10:45-65.
[19] Kimberley FC, Lobito AA, Siegel RM, Screaton GR. Falling into TRAPS-receptor misfolding in the TNF receptor 1-associated periodic fever syndrome. Arthritis Res Ther 2007;9:217.
[20] Naismith JH, Devine TQ, Brandhuber BJ, Sprang SR. Crystallographic evidence for dimerization of unliganded tumor necrosis factor receptor. J Biol Chem 1995;270:13303-7.
[21] Baud V, Karin M. Signal transduction by tumor necrosis factor and its relatives. Trends Cell Biol 2001;11:372-7.
[22] Porteu F, Nathan C. Shedding of tumor necrosis factor receptors by activated human neutrophilis. J Exp Med 1990;172:599-607.
[23] Kallinich T, Briese S, Roesler J, Rudolph B, Sarioglu N, Blankenstein O, et al. Two familial cases with tumor necrosis factor receptor-associated periodic syndrome caused by a non-cysteine mutation (T50M) in the TNFRSF1A gene associated with severe multiorganic amyloidosis. J Rheumatol 2004;31:2519-22.
[24] Stojanov S, Dejaco C, Lohse P, Huss K, Duftner C, Belohradsky BH, et al. Clinical and functional characterisation of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. Ann Rheum Dis 2008;67:1292-8.
[25] D'Osualdo A, Ferlito F, Prigione I, Obici L, Meini A, Zulian F, et al. Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. Arthritis Rheum 2006;54:998–1008.
[26] Churchman SM, Church LD, Savic S, Coulthard LR, Hayward B, Nedjai B, et al. A novel TNFRSF1A splice mutation associated with increased nuclear factor kappaB (NF- kappaB) transcription factor activation in patients with tumour necrosis factor receptor associated periodic syndrome (TRAPS). Ann Rheum Dis 2008;67: 1589-95.
[27] Lobito AA, Kimberley FC, Muppidi JR, Komarow H, Jackson AJ, Hull KM, et al. Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). Blood 2006;108:1320-7.
[28] Siebert S, Fielding CA, Williams BD, Brennan P. Mutations of the extracellular domain of tumour necrosis factor receptor I causes reduced NF-κB activation due to decreased surface expression. FEBS Lett 2005;579:5193-8.
[29] Simon A, Park H, Maddipati R, Lobito AA, Bulua AC, Jackson AJ, et al. Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. Proc Natl Acad Sci U S A 2010;107: 9801-6.
[30] Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, Kim KY, et al. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). J Exp Med 2011;208:519-33.
[31] Schmaltz R, Vogt T, Reichrath J. Skin manifestations in tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Dermatoendocrinol 2010;2: 26-9.
[32] Hull KM, Wong K, Wood GM, Chu WS, Kastner DL. Monocytic fasciitis: a newly recognized clinical feature of tumor necrosis factor receptor dysfunction. Arthritis Rheum 2002;46:2189-94.
[33] Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, et al. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with abroad phenotype including recurrent fever, cold sensitivity, sensorineural, deafness, and AA amyloidosis. Arthritis Rheum 2002;46:2445-52.
[34] Cantarini L, Iacoponi F, Lucherini OM, Obici L, Brizi MG, Cimaz R, et al. Validation of a diagnostic score for the diagnosis of autoinflammatory diseases in adults. Int J Immunopathol Pharmacol 2011;24:695-702.
[35] Cantarini L, Lucherini OM, Brucato A, Barone L, Cumetti D, Iacoponi F, et al. Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. Clin Res Cardiol 2012 [Epub ahead of print].
[36] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716-24.
[37] Cantarini L, Rigante D, Lucherini OM, Cimaz R, Laghi Pasini F, Baldari CT, et al. Role of etanercept in the treatment of tumor necrosis factor receptor-associated periodic syndrome: personal experience and review of the literature. Int J Immunopathol Pharmacol 2010;23:701-7.
[38] Cantarini L, Rigante D, Brizi MG, Lucherini OM, Sebastiani GD, Vitale A, et al. Clinical and biochemical landmarks in systemic autoinflammatory diseases. Ann Med 2011 [Epub ahead of print].
[39] Nowlan ML, Drewe E, Bulsara H, Esposito N, Robins RA, Tighe PJ, et al. Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A. Rheumatology (Oxford) 2006;45:31-7.
[40] Nedjai B, Hitman GA, Quillinan N, Coughlan RJ, Church L, McDermott MF, et al. Proinflammatory action of the antiinflammatory drug infliximab in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2009;60: 619-25.
[41] Bulua AC, Mogul DB, Aksentijevich I, Singh H, He D, Muenz L, et al. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Arthritis Rheum 2011 [Epub ahead of print].
[42] Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparison of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301:418-26.
[43] Arostegui JI, Solis P, Aldea A, Cantero T, Rius J, Bahíllo P, et al. Etanercept plus colchicine treatment in a child with tumour necrosis factor receptor-associated periodic syndrome abolishes auto-inflammatory episodes without normalizing the subclinical acute phase response. Eur J Pediatr 2005;164:13-6.
[44] Stojanov S, Dejaco C, Lohse P, Huss K, Duftner C, Belohradsky BH, et al. Clinical and functional characterization of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. Ann Rheum Dis 2008;67:1292-8.
[45] Drewe E, McDermott EM, Powell PT, Isaacs JD, Powell RJ. Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. Rheumatology (Oxford) 2003;42: 235-9.
[46] Jesus AA, Oliveira JB, Aksentijevich I, Fujihira E, Carneiro-Sampaio MM, Duarte AJ, et al. TNF receptor-associated periodic syndrome (TRAPS): description of a novel TNFRSF1A mutation and response to etanercept. Eur J Pediatr 2008;167:1421-5.
[47] Jacobelli S, André M, Alexandra JF, Dodé C, Papo T. Failure of anti-TNFtherapy in TNF Receptor 1-Associated Periodic Syndrome (TRAPS). Rheumatology (Oxford) 2007;46:1211-2.
[48] Vaitla PM, Radford PM, Tighe PJ, Powell RJ, McDermott EM, Todd I, et al. Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the anti-interleukin-6 receptor monoclonal antibody tocilizumab. Arthritis Rheum 2011;63:1151-5.
[49] Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008;58:1516-20.
[50] Obici L, Meini A, Cattalini M, Chicca S, Galliani M, Donadei S, et al. Favourable and sustained response to anakinra in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) with or without AA amyloidosis. Ann Rheum Dis 2011;70:1511-2.
[51] Quillianan N, Mannion G, Mohammad A, Coughlan R, Dickie LJ, McDermott MF, et al. Failure of sustained response to etanercept and refractoriness to anakinra in patients with T50M TNF-receptor-associated periodic syndrome. Ann Rheum Dis 2011;70:1692-3.
[52] Martinon F, Chen X, Lee AH, Glimcher LH. TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. Nat Immunol 2010;11: 411-8.