Open Access Library Journal

The Role of Death Domains Superfamily in Multiple Sclerosis Pathogenesis

Kabir M. Hamid[1], Abbas Mirshafiey[2*]

[1]Department of Immunology, School of Public Health, Tehran University of Medical Sciences—International Campus (TUMS-IC), Tehran, Iran
[2]Department of Immunology, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran
Email: kabiru20@yahoo.com, [*]mirshafiey@tums.ac.ir

Received 2 November 2014; revised 19 December 2014; accepted 7 January 2015

Abstract

Multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), are inflammatory diseases of the central nervous system (CNS), mediated by several immune cells. Oligodendrocytes are responsible for the formation and maintenance of myelin around multiple axons. In MS oligodendrocytes are the targets of inflammatory and immune attacks. Thus, the destruction of a single oligodendrocyte, possibly by apoptosis, results in the loss of myelin around several axons and the loss of many oligodendrocytes limiting the ability to repair or regenerate demyelinated areas. Apoptosis is mediated by an aggregation of various protein components, specifically death domains (DD) superfamily. This superfamily is composed of the death domain (DD), the death effector domain (DED), the caspase recruitment domain (CARD) and the pyrin domain (PYD) subfamilies. Within each subfamily, members form homotypic interactions and facilitate the assembly of oligomeric signaling complexes. Members of the death domain superfamily are critical components of apoptotic and inflammatory signaling. We summarize the structure and functions of the DD superfamily, and describe the role of the DD proteins in oligodendrocytes death and proinflammatory activation in MS pathogenesis.

Keywords

Multiple Sclerosis, Death Domain, Oligodendrocytes, Inflammation, Apoptosis

Subject Areas: **Immunology, Neurology, Pathology**

1. Introduction

Multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), are inflam-

[*]Corresponding author.

How to cite this paper: Hamid, K.M. and Mirshafiey, A. (2015) The Role of Death Domains Superfamily in Multiple Sclerosis Pathogenesis. *Open Access Library Journal*, **2**: e1210. http://dx.doi.org/10.4236/oalib.1101210

matory diseases of the central nervous system (CNS), considered as a multi-factorial disease depending on genetic and non-genetic factors [1], mediated by activated lymphocytes, macrophages, microglia, and complement [2], characterized by localized areas of demyelination, and being the leading cause of non-traumatic neurological disability in young adults [3]. In both MS and EAE, the myelin and the myelin-producing cells, the oligodendrocytes (OLGs), are targets of the autoimmune attack, and their loss is directly associated with neuronal dysfunction and damage leading to the clinical manifestations of the disease [4]. The cause of MS is still unknown and its pathogenic pathways are not fully understood. However, the pathological features of MS plaques are blood-brain barrier (BBB) leakage, destruction of myelin sheaths, OLG and axonal damage, axonal loss, glial scar formation and the presence of inflammatory cells infiltrates that mainly consist of lymphocytes and macrophages [5]. Inflammation is now known to include more than demyelination, as studies revealed significant axonal pathology. Once an axon is demyelinated, it is exposed and become available and susceptible to damage in the destructive inflammatory environment. In the established lesion, total depletion of OLGs is common [6], but depletion may be due to classic apoptosis or a cytotoxic mechanism (necrosis), but this remains unclear. Necrosis which is a form of cells injury occurs due to autolysis which results in premature death of cells in living tissue (Proskuryakov *et al*., 2003) [7]. However, this review is limited to apoptotic cell death. Apoptosis contributes to OLGs depletion in MS lesions and ultimately, increases demyelination. OLGs depletion increases potential for axonal injury and lack of remyelination [2]. Apoptosis is a coordinated and often energy-dependent process that involves the activation of a group of cysteine proteases called “caspases” and a complex cascade of events that link the initiating stimuli to the final death of the cell [8]. Moreover, apoptosis is mediated by the aggregation of the various protein components, specifically Death Domains (DD) containing proteins.

The DD superfamily is one of the largest and most studied domain superfamilies [9]. This superfamily is composed of the death domain (DD), the death effector domain (DED), the caspase recruitment domain (CARD) [10], and the pyrin domain (PYD) [11] subfamilies (**Table 1**); within each subfamily, members form homotypic interactions and facilitate the assembly of oligomeric signaling complexes [12]. Based on a genome analysis, there are 32 DDs, 7 DEDs, 28 CARDs and 19 PYDs in the human genome [13]. The DD mediates self-association of their receptors, thus giving the signal to downstream events that lead to apoptosis. Moreover, the DD-containing proteins involve in the regulation of apoptosis and inflammation, activate caspases and nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB). The review provides structural and functional overview of the death domains superfamily. Because OLGs destruction is crucial in MS pathology, we focused on the role of death domains superfamily in the death of OLGs and proinflammatory activation in MS pathogenesis. Though, considerable efforts have been made to elucidate the molecular mechanisms behind the process [4].

2. Death Domains Superfamily Structural Overview

DD are death fold found predominantly in the vertebrates, although represented throughout the animals [14].

Table 1. Summary of structural features and functional overview of DD subfamily.

Subfamily	Structure		Features	Activities
	NMR	Crystal		
DD	Fas DD FADD DD TNFR1 DD P75 DD	IRAK4 DD RAIDD DD	Variation exist in length and direction of helices Sequence homology low	Homotypic interactions Form homodimers Use to assemble signal complexes intracellularly for activation of caspase and NF-κB
DED	FADD DED PEA-15 DED	MC159 DED1 MC159 DED2	H2 residues form a hydrophobic patch E/D-RxDL motif form a conserved hydrogen-bonded charge	Found on caspases and adapters Induce apoptosis (DED containing caspase) NF-κB signalling Induce or inhibit caspase activation
CARD	RAIDD CARD ICEBERG CARD	Apaf-1	H1 either bent or broken into H1a and H1b helices Have polarized surface for interactions.	Apoptosis Cytokine processing Immune defense NF-κB activation
PYD	NALP1 PYD ASC PYD	NONE	H3 is altered replace by flexible loop	Probable caspase activation Function not really understood

The unifying feature of the DD superfamily is the six-helical bundle structural fold, which first revealed by nuclear magnetic resonance (NMR) structures [15]. Moreover, each subfamily within the DD superfamily has variations in sequence as well as the length and orientation of the helices (**Table 1**) that result in distinct structural characteristics [16].

2.1. DD Domain

The NMR structures of four isolated DD subfamily are Fas DD, Fas associated death domain (FADD) DD, Tumor necrosis factor receptor 1 (TNFR1) DD and p75 DD, while interleukin-1 receptor-associated kinase 4 (IRAK4) DD and RIP-associated ich-1/ced-3-homologue protein with a DD (RAIDD) DD are the two crystal structures [17]. They exhibit the six-helix bundle folds with existing variations in the length and direction of the helices. Due to low sequence homology among the DDs; their surface features are entirely different and may be responsible for their specificity in protein-protein interactions (**Table 1**). The only one structure of a DD: DD complex available is the crystal structure of the monomeric Pelle DD: Tube DD complex [18]. PIDDosome core complex composed of the DDs of p53-induced protein with a DD (PIDD) and RAIDD [16] and the Myddosome comprising the DDs of MyD88, IRAK2 and IRAK4 [19] are the common examples of the interfacial interactions between DDs.

2.2. DED Domain

There are two NMR structure of DED, these includes FADD DED [20] and phosphoprotein enriched in astrocytes 15-Kda DED (PEA-15 DED) [21], while the two crystal structure from the tandem DED of Molluscum contagiosum virus 159 (MC159) are DED1 and DED 2 [22]. FADD DED has a full-length structure which consisting of both DED and DD. FADD is a component of the death inducing signalling complex (DISC), while PEA-15 participates in mitogen activated protein kinase (MAPK) activation with the kinase extracellular signal regulated kinases (ERK). MC159 is a cellular FLICE-like inhibitory protein (c-FLIP) from a pox virus [22]. FADD DED, PEA-15 DED and MC159 DED2 structures show conserved six-helical bundle fold of the DD superfamily. They are more similar to each other than to other members of the DD superfamily [16]. However, MC159 structurally is more divergent from the other known DED structures [23]. In its helix structure H3 is replaced by a short loop connecting helices H2 and H4 and two helices, helix H0 at the N-terminus and helix H7 at the beginning of DED2 are added. DED was distinguished from other members of the DD superfamily by two conserved surface feature present on DEDs, the first is the conserved hydrogen-bonded charge triad formed by the E/D-RxDL motif [22] and hydrophobic patch formed by residues on H2 as the second feature (**Table 1**), it facilitates DED: DED interactions [20].

2.3. CARD Domain

The available NMR structures of CARD are RAIDD CARD [23] and ICEBERG CARD [24], while an available crystal structure of isolated CARD is Apaf-1 [25]. Although, CARD is identical with the conserved six-helical bundle fold of the DD superfamily, but it has a unique helix H1 which appears to be either bent or broken into H1a and H1b helices (**Table 1**). However, orientation and length of several helices may differ among the different CARDs. H1 of the CARD subfamily and H3 are both shortened and preceded by a long loop [26], or replaced by a loop entirely [27]. In the RAIDD CARD only six α-helices are present with Apaf-1 helices H1a and H1b combined into a single helix H1. The CARD domain of Apaf-1 is formed of a bundle of six (or seven) tightly packed α-helices [28], closely resembling the overall structure of the RAIDD CARD that interacts with caspases 2 and 9 [29]. Furthermore, the CARD structure of Apaf-1 is in complex with the caspase-9 CARD and found in the entire N-terminal fragment of Apaf-1 containing the CARD and the nucleotide-binding oligomerization domain (NOD). In the Apaf-1/procaspase-9 complex helices H2 and H3 of Apaf-1 CARD form a convex acidic surface that recognizes a complementary basic concave surface of caspase-9 CARD (formed by H1a, H1b, H4) with residues Y24, D27, S31, D32, Q40, N73, (Apaf-1) and R11, R13, R52, R56 (procaspase-9) [30] providing specificity in the interaction. CARDs have a polarized surface with both basic and acidic surfaces possibly used for protein-protein interactions. Besides these electrostatic interactions, additional hydrophobic contacts are present in the center of the interface, thus explaining why the association is refractory to high ionic strength [31].

2.4. PYD Domain

PYDs were considered to be subfamily of the DD superfamily based on their NMR structures of NALP1 [28] and Apoptosis-associated speck-like protein containing a CARD (ASC PYD) [32], which provides definitive evidence. They possess altered H3 apart from the classical six-helix bundle folds of the DD superfamily. H3 is completely replaced by a flexible loop in PYD from NALP1, while PYD from ASC remains only with a short helix of 4 residues and is coupled with a long, flexible loop preceding the helix (**Table 1**), these features appear to be a common in many PYD sequences. In structural comparisons among the homotypic interaction denotes that the Pelle DD: Tube DD complex [18], the Apaf-1 CARD: caspase-9 CARD complex [30] and the DED1: DED2 interaction in the tandem DED of MC159 [23], are the three homotypic complex structures in the DD superfamily. For non-homotypic interactions PEA-15 DED proteins interact heterotypically with non-DED proteins such as the MAP kinase ERK [22], also CARD-containing protein apoptosis repressor with caspase recruitment domain (ARC) interacts heterotypically with both the DDs of Fas and FADD and the C-terminus of Bcl-2 family protein Bax [33].

3. Death Domains Superfamily Function

The primary function of the death domains superfamily is to mediate protein-protein interaction by forming predominantly homotypic associations, thereby underpinning the formation of multi-subunit signaling complexes [34]. Most of the interactions observed in DD complexes seem to fall into one of three topologically similar arrangements as follows: type I, negatively charged residues of H2 and H3 of one DD interact with positively charged residues of H1 and H4 of another DD; type II, H4 and the H4-H5 loop of one DD interact with the N-terminal end of H6 of another DD; and type III, H3 of one DD interacts with the H1-H2 and H3-H4 loops of a second DD [35].

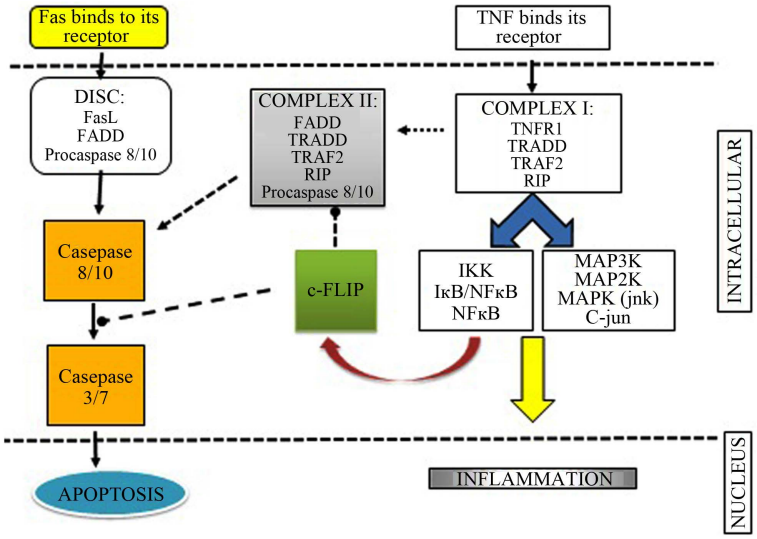
3.1. DD and DED Domains

DD proteins function in both apoptosis and NF-κB signaling in mammals. The TNFR family has several cytokine receptors containing DDs, among which are the death receptors (DR) 1, 2, 3 and the Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors (**Table 2**). Furthermore, through specific homotypic interactions these receptors are banded by adapter molecules bearing DDs for instance TNFR-associated death domain (TRADD) binds TNFR1; FADD binds DR2, DR3, and the TRAIL receptors. TRADD and FADD can bind to each other via DD-DD interaction, only when TRADD is bound to TNFR1. In Caspase-dependent apoptosis Fas and TNFR1 form homodimers upon ligand binding with both Fas and TNFR1, this can lead to an association of FADD and TRADD via a DD and recruitment of caspase 8 by a DED (**Figure 1**), resulting in activation of downstream effector caspases and apoptosis [36]. There are seven standard DED-containing proteins associated with the regulation of apoptosis and proliferation mediated by the TNF-α receptor family. These proteins are FADD, Caspase-8 and 10, c-FLIP, death effector domain containing DNA binding (DEDD) 1, DEDD2 and phosphoprotein enriched in astrocytes 15-Kda (PEA-15). DEDs are found on caspases and adapters. The DED-containing caspases (caspases-8, -10) function in death receptor-induced apoptosis in mammals, but appear to be involved in NF-κB signaling [14]. FADD may induce or inhibit caspase activation via its DED that interacts with a DED present on caspases-8 and 10 and on the regulatory molecule, c-FLIP (**Table 1**). The DR signalling pathways include the DISC, complex I and complex II (**Figure 1**). Members of TNF superfamily of ligands are mostly trimeric and can be either found attached to the membrane or soluble. They activate TNFR superfamily by ligand-induced receptor trimerization [37] and higher order oligomerization [38]. This DR contains DDs in their intracellular regions which use to assemble signal complexes for activating caspase and NF-κB. The three different types of complexes may assemble includes one of death receptor Fas and related receptors, and the other two by the death receptor TNFR1 and related receptors [16]. After ligand activation, Fas through its DD recruits FADD adapter protein, this homotypic interaction is through the C-terminal DD of the FADD. The FADD through its N-terminal DED interact homotypically with the tandem DED in the pro-domain of caspase-8 or 10 and this form a ternary DISC structure compose of Fas, FADD and caspase-8 or 10, this process leads to the activation of active caspase-8 or 10 into the cytoplasm to cleave and activate effector caspase-3 and 7 leading to a cascade of events in apoptotic cell death [39]. However, for the TNFR1, after ligand activation, it interacts with the DD of TRADD adapter protein through its DD. The TRADD binds to receptor interacting protein

Table 2. Members of DR family.

FAMILY NAME	OTHER NAMES	REMARKS
DR1	TNFR1, CD120a, P55, P60	Well characterized and studied previously in MS
DR2	CD95, APO-1, Fas	Well characterized and studied previously in MS
DR3	APO-3, LARD, TRAMP, WSL1	Expressed by lymphocytes and induce after T-cell activation
DR4	TRAILR1, APO-2	Cloned receptor
DR5	TRAILR2, KILLER, TRICK2	Cloned receptor
DR6	-	Expressed in human tissue
Ectodysplasin A receptor (EDAR)	-	-
Nerve growth factor receptor (NGFR)	-	-
Decoy receptor 1 (DcR1)*	TRAILR3, TRID, LIT	Protective
Decoy receptor 2 (DcR2)*	TRAILR4, TRUNDD	Protective

Note: *These are not members of DR family, DcR1 do not have DD and DcR2 have dysfunctional DD in their intracellular part.



Binding of TNF-α to TNF R1 results in trimerization and intracellular oligomerization of death domain; after the conformational change, TNFR1 recruits an adaptor protein TRADD via its DD. TRADD then recruits more different proteins such as downstream TRAF 2 and RIP via DD interaction to form complex I. The complex activates IKK to phosphorylates specific amino acids residues located in an IκB's protein regulatory domain, this action induce the degradation of IκB's protein to free NF-κB from IκB's/NF-κB complex which will enter into the nucleus where it will induce specific genes expression leading to inflammatory responses. In other way, MAP3K becomes activated after interaction with TRAF2. The activated MAP3K phosphorylates its substrate MAP2K which in turn will phosphorylate their substrate MAPK substrate. The MAPK (JNK) then binds and phosphorylates a transcription factor c-jun to induce inflammatory responses. C-jun serves as AP-1. Moreover, TRADD, TRAF2 and RIP complex can bind to FADD after dissociation from TNFR1 and recruit procaspase-8/10 via protein-protein interactions to form complex II (DISC complex). The complex, via procaspase-8/10 activate caspase-8/10 to cleave caspase 3/7 thus triggers downstream cascade reactions which subsequently cause apoptosis. The pathway by which ligands of Fas and TRAIL (not shown) activate apoptosis is similar to that of TNF. The binding of ligands accelerates aggregation of receptors, formation of DISC and activation of caspase cascade reactions. Adaptor protein FADD directly binds to death domain of FasL or TRAILR, without presence of TRADD. However, FADD apoptosis pathway can be inhibited by c-FLIP. FLIP activated by NF-κB, is analogous to caspase-8/10 and lack proteolytic activity. It can depress the apoptosis by inhibiting the interaction of FADD and procaspase-8/10 in complex II and activation of caspase 3/7 in Fas and TRAIL pathways. DISC (death-inducing signaling complex), TNF-α (Tumor necrosis factor), TNFR1 (Tumor necrosis factor receptor 1), TRADD (TNFR-associated death domain), TRAF 2 (TNF-associated factor 2), RIP (Receptor interacting protein kinase 1), IKK (IκB kinase), IκB (Inhibitor of κB), NF-kB (Nuclear factor kappa-light-chain-enhancer of activated B cells), FADD (Fas-associated death domain protein), MAP3K (Mitogen activated protein kinase 3), MAP2K (Mitogen activated protein kinase 2), MAPK (Mitogen activated protein kinase), JNK (c-jun N-terminal kinases), AP-1 (Activator protein 1), TRAILR (TNF-related apoptosis-inducing ligand receptor), c-FLIP (cellular Flice-inhibitory protein).

Figure 1. Signalling pathways.

kinase (RIP) and TNF-associated factors (TRAFs) through DD interaction to form a membrane bound complex I for activation of inhibitor of κ B kinase (IKK) and NF-κB. In order to form a cytoplasmic complex II for caspase activation, TRADD binds with FADD and caspase-8 after dissociation from TNRF1. Also for assembly of complex II both DD: DD and DED: DED interactions are necessary. The ability of TNF to induce either cell death or otherwise may depend on the assembly of complex I and complex II.

3.2. CARD Domain

CARD containing proteins may be prodomains of caspases or adapters in the assembly of apoptotic and inflammatory signaling complexes. In mammals, CARD domain-containing proteins have a wide range of functions (apoptosis, cytokine processing, immune defense, NF-κB activation). CARD domains are found on several mammalian procaspases (caspase-1, -2, -4, -5, -9, -12, -13), and on adapter molecules involved in caspase activation (RAIDD-caspase-2, Apaf-1-procaspase-9, CED-4-CED-3, ARK-Dronc) [14]. CARD-containing proteins that may inhibit or perhaps activate caspases (in particular, caspase-1) include Cardiak [40], ICEBERG [24], Pseudo-ICE [41] and Cop. Apaf-1 forms the central platform of a molecular complex known as apoptosome for caspase activation in intrinsic apoptosis pathway [42]. The apoptosome then recruits caspase-9 via the CARD domain interaction between Apaf-1 and caspase-9 [16].

3.3. PYRIN Domain

The PYRIN domain proteins are the least understood in terms of possible roles in apoptosis, and no PYRIN-PYRIN interactions have been clearly elucidated or their functions established in death signaling. Nevertheless, there is an example of a PYRIN domain protein with a recognizable action: one of the zebra fish caspases carries a PYRIN domain. Therefore, it is likely that the PYRIN, DED, and CARD domains on caspases all have similar roles in caspase activation [14]. In the formation of inflammasome for activation of caspase-1, NALP1 interacts with ASC through the PYD and with caspase-5 through the CARD. Other DD-containing proteins, such as ankyrin, MyD88 and Pelle, are probably not directly involved in cell death signalling. DD-containing proteins also have links to innate immunity, communicating with Toll-like receptors through bipartite adapter proteins such as MyD88 [43].

4. Role of Death Domains Superfamily in MS Pathogenesis

MS is characterized by activated autoreactive myelin-specific lymphocytes that home to the CNS where they initiate a vicious cycle of inflammation and tissue damage [4]. In this regard, both subgroups of T helper cells (Th1 and Th2) are involved in pathogenesis of MS, although it is evident that the role of Th1 is more prominent in comparison to Th2 [44] [45]. The presence of CD8+ T cells in pathogenesis of MS has also been reported [44] [46]. However, other cells, such as B cells, macrophages and natural killer (NK) cells also contribute to the pathogenesis [47]. In addition, CD8+ T cells are more prevalent in the MS lesions than the CD4+ T cells, and CD8+ cells can recognize antigen presented on major histocompatibility I (MHC I) on neurons and oligodendrocytes and kill the target cells [48]. Again, both CD4+ and CD8+ T cells can express ligands for DR [49]. Th17 cells, which generate inflammatory cytokines such as IL-17 and IL-21, are also involved in neuroinflammation [44] [49]. Studies of EAE have indicated the role of myelin specific CD4+ Th1 and Th17 [50]. The myelin specific CD4+ Th1 and Th17 cells serve as driving force in the autoimmune processes [47]. It was suggested that the selective loss of oligodendrocytes and their myelin sheaths occurs through a variety of mechanisms. These may involve direct interaction with cellular immune mediators, demyelination antibodies as well as cytokines, such as TNF superfamily [51].

This is because TNF-α and its receptors are part of a large and complex superfamily of homologous ligands and receptors, whose show many biological functions overlap; bear an intracellular death domain and are able to mediate apoptosis directly. Furthermore, investigations have demonstrated the effects of TNF-α at various stages of pathology in MS, including oligodendrocyte death, demyelination, immune cell trafficking, cellular proliferation and MHC antigen expression [52]. Apart from direct OLG damage, TNF-α has been shown to mediate indirect excitotoxic damage to OLGs and neurons by modulating the accumulation and release of glutamate from astrocytes [53]. In humans, eight of the over 30 known TNF receptors contain DD in their cytoplasmic tails; several of these TNF receptors use caspase activation as a signaling mechanism [54]. The ligands for DD con-

taining receptors belonging to the TNFR superfamily present in MS lesions include FasL, TRAIL and TNF itself; are up-regulated in response to pro-inflammatory cytokines [55] and have been described to mediate neuronal and OLGs damage [56]. More important to note, FADD protein mediates apoptosis by coupling DR (such as Fas, TNFRI, and TRAIL receptors) (**Figure 1**) with the caspase cascade [57]. Again, Mc Guire and his colleagues show that FADD is critical for OLGs apoptosis and the development of autoimmune demyelinating disease [4].

TRAIL and its receptors are constitutively expressed in a variety of normal tissues, tumor cells [58] and human brain tissue [59]. Furthermore, the elevated TRAIL expression in blood mononuclear phagocytes of MS patients has been reported [51]. Moreover, OLGs have been shown to be one of TRAIL's targets; thus TRAIL and OLG interaction may potentially be the cause of the demyelination. In this regard, a study using a primary culture of OLGs revealed that ligation of TRAIL-R1 induces OLGs death in the presence of protein synthesis inhibitor or pre-treatment with IFN-γ [60]. Because, IFN-γ is produced by lymphocytes in MS lesions, and systemic administration of IFN-γ exacerbates MS [55]. IFN-γ can also be cytotoxic to OLGs in culture by modulating the cellular response to injury; these responses involve up-regulation of Fas expression [61]. Another study suggests that p53 mediated OLGs cell death is at least partially through the TRAIL receptor signaling pathway [62]. However, the susceptibility to TRAIL-induced death is dependent on low expression of decoy TRAIL-R3 (**Table 2**). A study in EAE has shown that rather than direct interaction, TRAIL may act through an indirect mechanism [63]. Again, mice expressing the viral caspase inhibitor p35 selectively in OLGs are protected against myelin oligodendrocyte glycoprotein (MOG) 35-55-induced EAE [64], this show that caspase dependent apoptosis of OLGs play an important role in the pathology of EAE [4]. Similarly, specific deletion of Fas in OLGs partially protects mice from MOG35-55-induced EAE [65]. Furthermore, when mice crossed to TNFR-1-deficient mice, could acquire protection against EAE induction [4]. However, the role of TNFR-1 in EAE pathogenesis is not only based on its expression in OLGs; rather, it may also be based on its role in mediating astrocytic, microglial, and endothelial responses as well as peripheral immune responses [66]. Moreover, the protective effect of TNFR-1 is yet to be clear, but may be due to the lack of TNFR-1 signaling in OLGs or other cell types [4].

Inflammation and OLGs injury are characteristic of MS and EAE. Inflammatory process often relies following the activation of protein kinases, for instance IκB kinase, a proinflammatory kinase, which phosphorylates IκB result to its degradation [67]. The degradation liberates NF-κB transcriptional factors which subsequently induce the transcription of genes for immune and inflammatory responses (**Figure 1**) [68]. Moreover, some protein families such as caspases are involved in both apoptotic and inflammatory signalling; the identified caspases are broadly categorized into initiators (caspase-2, -8, -9, -10), effector or executioners (caspase-3, -6, -7) and inflammatory caspases (caspase-1, -4, -5) [69]. The caspase activation may be regulated to signal cell death and the kinase activation to signal inflammation. Moreover, caspase-1 a subclass of caspase involved in proinflammatory responses cleave pro-IL-1β to IL-1β leading to NF-κB activation and elicitation of proinflammatory responses [70] and innate immunity [16]. On the other hand, IL-1β, as a proinflammatory cytokine initiates differentiation of Th17, thus IL-1RI-deficient mice are resistant to EAE induction [71]. Furthermore, like the IL-17 and IL-22, IL-1β can enhance BBB disruption; promote microglia and astrocyte activation and stimulate the demyelination process [72].

Caspase-11 is an apical caspase that activates caspase 3 and 1; highly expressed in both OLGs and infiltrating cells, such as T lymphocytes in EAE lesions and shows to play significant role in both inflammation and apoptosis in certain pathological conditions [73]. Because, in vitro study shows that cell death induced by TNF-α, IFN-γ, or anti-Fas antibody, and the activation of caspase-3 by TNF-α and IFN-γ were all reduced in caspase-11-deficient OLGs, indicating that caspase-11 functions in a cell-autonomous manner to regulate cell death; thus suggest that caspase-11 plays a vital role in the execution of OLGs death and the neurological manifestations of MS and EAE [73]. Moreover, both TNF and FasL, two cytotoxic cytokines acting through the prototypical DRs TNFR-1 and Fas, respectively, are highly expressed in MS and EAE [74] and can induce OLGs apoptosis in vitro [75].

Many data showed that caspase-2 acts upstream of the mitochondria to initiate apoptosis [76]. In response to DNA damage caspase-2 becomes activated by PIDDosome and NF-κB activation was mediated by RIP. The PIDDosome consist of RAIDD, PIDD and caspase-2, formed through DD interaction between PIDD and RAIDD and CARD interaction between RAIDD and caspase-2. In RIP mediated activation of NF-κB, PIDD binds kinase RIP through DD interaction which this in turn interacts with the IKK complex for the activation. In addition to the IKK complex, RIP2 can also interact with caspase-1 via its CARD domain, resulting in the cleavage and activation of pro-IL-1β [55] to IL-1β thus activates the inflammatory response.

5. Conclusion

Inflammation and demyelination are characteristic features of multiple sclerosis. The inflammation is associated with inflammatory responses triggered mainly by proinflammatory cytokines; while the demyelination is due to oligodendrocytes destruction via apoptosis or necrosis. OLGs express death receptors; corresponding ligands binding to these receptors may trigger apoptosis that may lead to its depletion; the OLGs are responsible for secretion of myelin sheath needed for neurons in order to transmit the action potential. The DD superfamily mediates apoptosis and inflammation through protein-protein interaction of its subfamilies. The DD superfamily proteins can also interact to form a complex for activation of proinflammatory cytokines which likely exacerbate the pathogenesis of multiple sclerosis. However, determining triggers for these death receptors is likely to be unclear as such more effort is required to clarify the factors responsible for this.

References

[1] Mirshafiey, A., Matsuo, H., Nakane, S., Rehm, B.H., Koh, C.S. and Miyoshi, S. (2005) Novel Immunosuppressive Therapy by M2000 in Experimental Multiple Sclerosis. *Immunopharmacology and Immunotoxicology*, **27**, 255-265. http://dx.doi.org/10.1081/IPH-200067751

[2] Cudrici, C., Niculescu, T., Niculescu, F., Shin, M.L. and Rus, H. (2006) Oligodendrocyte Cell Death in Pathogenesis of Multiple Sclerosis: Protection of Oligodendrocytes from Apoptosis by Complement. *Journal of Rehabilitation Research and Development*, **43**, 123-132. http://dx.doi.org/10.1682/JRRD.2004.08.0111

[3] Korn, T. (2008) Pathophysiology of Multiple Sclerosis. *Journal of Neurology*, **225**, 2-6. http://dx.doi.org/10.1007/s00415-008-6001-2

[4] Mc Guire, C., Volckaert, T., Wolke, U., Sze, M., de Rycke, R., Waisman, A., *et al*. (2010) Oligodendrocyte-Specific FADD Deletion Protects Mice from Autoimmune-Mediated Demyelination. *Journal of Immunology*, **185**, 7646-7653. http://dx.doi.org/10.4049/jimmunol.1000930

[5] Mirshafiey, A. (2007) Novel Promising Therapeutic Agents in Multiple Sclerosis. *Recent Patents on Inflammation and Allergy Drug Discovery*, **1**, 218-224. http://dx.doi.org/10.2174/187221307782418856

[6] Raine, C.S. (1997) The Neuropathology of Multiple Sclerosis. In: Raine, C.S., McFarland, H.F. and Tourtellotte, W.W., Eds., *Multiple Sclerosis Clinical and Pathogenetic Basis*, Chapman & Hall Medical, London, 151-171.

[7] Proskuryakov, S.Y., Konoplyannikov, A.G. and Gabai, V.L. (2003) Necrosis: A Specific Form of Programmed Cell Death? *Experimental Cell Research*, **283**, 1-16. http://dx.doi.org/10.1016/S0014-4827(02)00027-7

[8] Elmore, S. (2007) Apoptosis: A Review of Programmed Cell Death. *Toxicologic Pathology*, **35**, 495-516. http://dx.doi.org/10.1080/01926230701320337

[9] McEntyre, J.R. and Gibson, T.J. (2004) Patterns and Clusters within the PSM Column in TiBS, 1992-2004. *Trends in Biochemical Sciences*, **29**, 627-633. http://dx.doi.org/10.1016/j.tibs.2004.10.006

[10] Valmiki, M.G. and Ramos, J.W. (2009) Death Effector Domain-Containing Proteins. *Cellular and Molecular Life Sciences*, **66**, 814-830. http://dx.doi.org/10.1007/s00018-008-8489-0

[11] Kohl, A. and Grütter, M.G. (2004) Fire and Death: The Pyrin Domain Joins the Death-Domain Superfamily. *Comptes Rendus Biologies*, **327**, 1077-1086. http://dx.doi.org/10.1016/j.crvi.2004.08.006

[12] Ferrao, R. and Wu, H. (2012) Helical Assembly in the Death Domain (DD) Superfamily. *Current Opinion in Structural Biology*, **22**, 241-247. http://dx.doi.org/10.1016/j.sbi.2012.02.006

[13] Reed, J.C., Doctor, K.S. and Godzik, A. (2004) The Domains of Apoptosis: A Genomics Perspective. *Science's Signal Transduction Knowledge Environment*, **2004**, re9.

[14] Lahm, A., Paradisi, A., Green, D.R. and Melino, G. (2003) Death Fold Domain Interaction in Apoptosis. *Cell Death and Differentiation*, **10**, 10-12. http://dx.doi.org/10.1038/sj.cdd.4401203

[15] Huang, B., Eberstadt, M., Olejniczak, E.T., Meadows, R.P. and Fesik, S.W. (1996) NMR Structure and Mutagenesis of the Fas (APO-1/CD95) Death Domain. *Nature*, **384**, 638-641. http://dx.doi.org/10.1038/384638a0

[16] Park, H.H., Lo, Y., Lin, S., Wang, L., Yang, J.K. and Wu, H. (2007) The Death Domain Superfamily in Intracellular Signaling of Apoptosis and Inflammation. *Annual Review of Immunology*, **25**, 561-586. http://dx.doi.org/10.1146/annurev.immunol.25.022106.141656

[17] Park, H.H. and Wu, H. (2006) Crystal Structure of RAIDD Death Domain Implicates Potential Mechanism of PIDDosome Assembly. *Journal of Molecular Biology*, **357**, 358-364. http://dx.doi.org/10.1016/j.jmb.2005.12.082

[18] Xiao, T., Towb, P., Wasserman, S.A and Sprang, S.R. (1999) Three-Dimensional Structure of a Complex between the Death Domains of Pelle and Tube. *Cell*, **99**, 545-555. http://dx.doi.org/10.1016/S0092-8674(00)81542-1

[19] Lin, S.C., Lo, Y.C. and Wu, H. (2010) Helical Assembly in the MyD88-IRAK4-IRAK2 Complex in TLR/IL-1R Signalling. *Nature*, **465**, 885-890. http://dx.doi.org/10.1038/nature09121

[20] Eberstadt, M., Huang, B., Chen, Z., Meadows, R.P., Ng, S-C., Zheng, L., *et al*. (1998) NMR Structure and Mutagenesis of the FADD (Mort1) Death-Effector Domain. *Nature*, **392**, 941-945. http://dx.doi.org/10.1038/31972

[21] Hill, J.M., Vaidyanathan, H., Ramos, J.W., Ginsberg, M.H. and Werner, M.H. (2002) Recognition of ERK MAP Kinase by PEA-15 Reveals a Common Docking Site within the Death Domain and the Death Effector Domain. *The EMBO Journal*, **21**, 6494-6504. http://dx.doi.org/10.1093/emboj/cdf641

[22] Yang, J.K., Wang, L., Zheng, L., Wan, F., Ahmed, M., Lenardo, M.J. and Wu, H. (2005) Crystal Structure of MC159 Reveals Molecular Mechanism of DISC Assembly and FLIP Inhibition. *Molecular Cell*, **20**, 939-949. http://dx.doi.org/10.1016/j.molcel.2005.10.023

[23] Li, F.Y., Jeffrey, P.D., Yu, J.W. and Shi, Y. (2006) Crystal Structure of a Viral FLIP: Insights into FLIP-Mediated Inhibition of Death Receptor Signaling. *Journal of Biological Chemistry*, **281**, 2960-2968. http://dx.doi.org/10.1074/jbc.M511074200

[24] Humke, E.W., Shriver, S.K., Starovasnik, M.A., Fairbrother, W.J. and Dixit, V.M. (2000) ICEBERG: A Novel Inhibitor of Interleukin-1β Generation. *Cell*, **103**, 99-111. http://dx.doi.org/10.1016/S0092-8674(00)00108-2

[25] Vaughn, D.E., Rodriguez, J., Lazebnik, Y. and Joshua-Tor, L. (1999) Crystal Structure of the Apaf-1 Caspase Recruitment Domain: An α-Helical Greek Key Fold for Apoptotic Signaling. *Journal of Molecular Biology*, **293**, 439-447. http://dx.doi.org/10.1006/jmbi.1999.3177

[26] Bae, J.Y. and Park, H.H. (2011) Crystal Structure of NALP3 Protein Pyrin Domain (PYD) and Its Implications in Inflammasome Assembly. *Journal of Biological Chemistry*, **286**, 39528-39536. http://dx.doi.org/10.1074/jbc.M111.278812

[27] Hiller, S., Kohl, A., Fiorito, F., Herrmann, T., Wider, G., Tschopp, J., *et al*. (2003) NMR Structure of the Apoptosis- and Inflammation-Related NALP1 Pyrin Domain. *Structure*, **11**, 1199-1205. http://dx.doi.org/10.1016/j.str.2003.08.009

[28] Day, C.L., Dupont, C., Lackmann, M., Vaux, D.L. and Hinds, M.G. (1999) Solution Structure and Mutagenesis of the Caspase Recruitment Domain (CARD) from Apaf-1. *Cell Death & Differentiation*, **6**, 1125-1132. http://dx.doi.org/10.1038/sj.cdd.4400584

[29] Chou, J.J., Matsuo, H., Duan, H. and Wagner, G. (1998) Solution Structure of the RAIDD CARD and Model for CARD/CARD Interaction in Caspase-2 and Caspase-9 Recruitment. *Cell*, **94**, 171-180. http://dx.doi.org/10.1016/S0092-8674(00)81417-8

[30] Qin, H., Srinivasula, S.M., Wu, G., Fernandes-Alnemri, T., Alnemri, E.S. and Shi, Y. (1999) Structural Basis of Procaspase-9 Recruitment by the Apoptotic Protease-Activating Factor 1. *Nature*, **399**, 549-557. http://dx.doi.org/10.1038/21124

[31] Kumar, S. (1999) Mechanisms Mediating Caspase Activation in Cell Death. *Cell Death & Differentiation*, **6**, 1060-1066. http://dx.doi.org/10.1038/sj.cdd.4400600

[32] Liepinsh, E., Barbals, R., Dahl, E., Sharipo, A., Staub, E. and Otting, G. (2003) The Death-Domain Fold of the ASC PYRIN Domain, Presenting a Basis for PYRIN/PYRIN Recognition. *Journal of Molecular Biology*, **332**, 1155-1163. http://dx.doi.org/10.1016/j.jmb.2003.07.007

[33] Nam, Y.J., Mani, K., Ashton, A.W., Peng, C.F., Krishnamurthy, B., Hayakawa, Y., *et al*. (2004) Inhibition of Both the Extrinsic and Intrinsic Death Pathways through Nonhomotypic Death-Fold Interactions. *Molecular Cell*, **15**, 901-912. http://dx.doi.org/10.1016/j.molcel.2004.08.020

[34] Dioletis, E., Dingley, A.J. and Driscoll, P.C. (2013) Structural and Functional Characterization of the Recombinant Death Domain from Death-Associated Protein Kinase. *PLoS ONE*, **8**, e70095. http://dx.doi.org/10.1371/journal.pone.0070095

[35] Ferrao, R. and Wu, H. (2012) Helical Assembly in the Death Domain (DD) Superfamily. *Current Opinion in Structural Biology*, **22**, 241-247. http://dx.doi.org/10.1016/j.sbi.2012.02.006

[36] Kay, W.H.T, Darwiche, R., Irawaty, W., Chong, M.M.W., Pennington, H.L. and Thomas, H.E. (2003) The Role of Cytokines as Effectors of Tissue Destruction in Autoimmunity Cytokines and Chemokines in Autoimmune Disease. Kluwer Academic/Plenum Publishers, Dordrecht, 73-86.

[37] Banner, D.W., D'Arcy, A., Janes, W., Gentz, R., Schoenfeld, H.J., Broger, C., *et al*. (1993) Crystal Structure of the Soluble Human 55 kd TNF Receptor-Human TNF Beta Complex: Implications for TNF Receptor Activation. *Cell*, **73**, 431-445. http://dx.doi.org/10.1016/0092-8674(93)90132-A

[38] Kischkel, F.C., Hellbardt, S., Behrmann, I., Germer, M., Pawlita, M., Krammer, P.H., *et al*. (1995) Cytotoxicity Dependent APO-1 (Fas/CD95)-Associated Proteins form a Death-Inducing Signaling Complex (DISC) with the Receptor. *The EMBO Journal*, **14**, 5579-5588.

[39] Salvesen, G.S. (2002) Caspases and Apoptosis. *Essays in Biochemistry*, **38**, 9-19.

[40] Thome, M., Hofmann, K., Burns, K., Martinon, F., Bodmer, J.L., Mattmann, C., *et al*. (1998) Identification of CARDIAK, a RIP-Like Kinase That Associates with Caspase-1. *Current Biology*, **8**, 885-888. http://dx.doi.org/10.1016/S0960-9822(07)00352-1

[41] Druilhe, A., Srinivasula, S.M., Razmara, M., Ahmad, M. and Alnemri, E.S. (2001) Regulation of IL-1β Generation by Pseudo-ICE and ICEBERG, Two Dominant Negative Caspase Recruitment Domain Proteins. *Cell Death & Differentiation*, **8**, 649-657. http://dx.doi.org/10.1038/sj.cdd.4400881

[42] Zou, H., Henzel, W.J., Liu, X., Lutschg, A. and Wang, X. (1997) Apaf-1, a Human Protein Homologous to C. Elegans CED-4, Participates in Cytochrome c-Dependent Activation of Caspase-3. *Cell*, **90**, 405-413. http://dx.doi.org/10.1016/S0092-8674(00)80501-2

[43] O'Neill, L.A., Dunne, A., Edjeback, M., Gray, P., Jefferies, C. and Wietek, C. (2003) Mal and MyD88: Adapter Proteins Involved in Signal Transduction by Toll-Like Receptors. *Innate Immunity*, **9**, 55-59. http://dx.doi.org/10.1177/0968051930090010701

[44] Jadidi-Niaragh, F. and Mirshafiey, A. (2010) Histamine and Histamine Receptors in Pathogenesis and Treatment of Multiple Sclerosis. *Neuropharmacology*, **59**, 180-189. http://dx.doi.org/10.1016/j.neuropharm.2010.05.005

[45] Nicot, A. (2009) Gender and Sex Hormones in Multiple Sclerosis Pathology and Therapy. *Frontiers in Bioscience*, **14**, 4477-4515. http://dx.doi.org/10.2741/3543

[46] Neumann, H., Medana, I.M., Bauer, J. and Lassmann, H. (2002) Cytotoxic T Lymphocytes in Autoimmune and Degenerative CNS Diseases. *Trends in Neurosciences*, **25**, 313-319. http://dx.doi.org/10.1016/S0166-2236(02)02154-9

[47] Kasper, L.H. and Shoemaker, J. (2010) Multiple Sclerosis Immunology: The Healthy Immune System vs the MS Immune System. *Neurology*, **74**, 2-8. http://dx.doi.org/10.1212/WNL.0b013e3181c97c8f

[48] Friese, M.A. and Fugger, L. (2009) Pathogenic $CD8^+$ T Cells in Multiple Sclerosis. *Annals of Neurology*, **66**, 132-141. http://dx.doi.org/10.1002/ana.21744

[49] Bettelli, E., Oukka, M. and Kuchroo, V.K. (2007) T_H-17 Cells in the Circle of Immunity and Autoimmunity. *Nature Immunology*, **8**, 345-350. http://dx.doi.org/10.1038/ni0407-345

[50] Batoulis, H., Addicks, K. and Kuerten, S. (2010) Emerging Concepts in Autoimmune Encephalomyelitis beyond the CD4/T_H1 Paradigm. *Annals of Anatomy—Anatomischer Anzeiger*, **192**, 179-193. http://dx.doi.org/10.1016/j.aanat.2010.06.006

[51] Huang, W.X., Huang, M.P., Gomes, M.A. and Hillert, J. (2000) Apoptosis Mediators FasL and TRAIL Are Upregulated in Peripheral Blood Mononuclear Cells in MS. *Neurology*, **55**, 928-934. http://dx.doi.org/10.1212/WNL.55.7.928

[52] Su-Yin, L. and Constantinescu, C.S. (2010) TNF-α: A Paradigm of Paradox and Complexity in Multiple Sclerosis and its Animal Models. *The Open Autoimmunity Journal*, **2**, 160-170. http://dx.doi.org/10.2174/1876894601002040160

[53] Korn, T., Magnus, T. and Jung, S. (2005) Autoantigen Specific T Cells Inhibit Glutamate Uptake in Astrocytes by Decreasing Expression of Astrocytic Glutamate Transporter GLAST: A Mechanism Mediated by Tumor Necrosis Factor-Alpha. *The FASEB Journal*, **19**, 1878-1880.

[54] Jurewicz, A., Matysiak, M., Tybor, K., Kilianek, L., Raine, C.S. and Selmaj, K. (2005) Tumor Necrosis Factor-Induced Death of Adult Human Oligodendrocytes Is Mediated by Apoptosis Inducing Factor. *Brain*, **128**, 2675-2688. http://dx.doi.org/10.1093/brain/awh627

[55] Pouly, S., Becher, B., Blain, M. and Antel, J.P. (2000) Interferon-Gamma Modulates Human Oligodendrocyte Susceptibility to Fas-Mediated Apoptosis. *Journal of Neuropathology & Experimental Neurology*, **59**, 280-286.

[56] Aktas, O., Prozorovski, T. and Zipp, F. (2006) Death Ligands and Autoimmune Demyelination. *Neuroscientist*, **12**, 305-316. http://dx.doi.org/10.1177/1073858405285208

[57] Sun, J., Hilliard, B., Xu, L. and Chen, Y.H. (2005) Essential Roles of the Fas-Associated Death Domain in Autoimmune Encephalomyelitis. *The Journal of Immunology*, **175**, 4783-4788. http://dx.doi.org/10.4049/jimmunol.175.7.4783

[58] Schneider, P., Bodmer, J.L, Thome, M., Hofmann, K., Holler, N. and Tschopp, J. (1997) Characterization of Two Receptors for TRAIL. *FEBS Letters*, **416**, 329-334. http://dx.doi.org/10.1016/S0014-5793(97)01231-3

[59] Dorr, J., Bechmann, I., Waiczies, S., Aktas, O., Walczak, H., Krammer, P.H., *et al*. (2002) Lack of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand but Presence of Its Receptors in the Human Brain. *Journal of Neuroscience*, **22**, RC209 1 of 5.

[60] Matysiak, M., Jurewicz, A., Jaskolski, D. and Selmaj, K. (2002) TRAIL Induces Death of Human Oligodendrocytes Isolated from Adult Brain. *Brain*, **125**, 2469-2480. http://dx.doi.org/10.1093/brain/awf254

[61] Panitch, H.S., Hirsch, R.L., Schindler, J. and Johnson, K.P. (1987) Treatment of Multiple Sclerosis with Gamma Interferon: Exacerbations Associated with Activation of the Immune System. *Neurology*, **37**, 1097-1102. http://dx.doi.org/10.1212/WNL.37.7.1097

[62] Wosik, K., Antel, J., Kuhlmann, T., Bruck, W., Massie, B. and Nalbantoglu, J. (2003) Oligodendrocyte Injury in Multiple Sclerosis: A Role for p53. *Journal of Neurochemistry*, **85**, 635-644. http://dx.doi.org/10.1046/j.1471-4159.2003.01674.x

[63] Huang, Y., Erdmann, N., Peng, H., Zhao, Y. and Zheng, J. (2005) The Role of TNF Related Apoptosis-Inducing Ligand in Neurodegenerative Diseases. *Cellular Molecular Immunology*, **2**, 113-122.

[64] Hisahara, S., Araki, T., Sugiyama, F., Yagami, K., Suzuki, M., Abe, K., *et al*. (2000) Targeted Expression of Baculovirus p35 Caspase Inhibitor in Oligodendrocytes Protects Mice against Autoimmune Mediated Demyelination. *The EMBO Journal*, **19**, 341-348. http://dx.doi.org/10.1093/emboj/19.3.341

[65] Hovelmeyer, N., Hao, Z., Kranidioti, K., Kassiotis, G., Buch, T., Frommer, F., *et al*. (2005) Apoptosis of Oligodendrocytes via Fas and TNF-R1 Is a Key Event in the Induction of Experimental Autoimmune Encephalomyelitis. *Journal of Immunology*, **175**, 5875-5884. http://dx.doi.org/10.4049/jimmunol.175.9.5875

[66] van Loo, G., De Lorenzi, R., Schmidt, H., Huth, M., Mildner, A., Schmidt-Supprian, M., *et al*. (2006) Inhibition of Transcription Factor NF-kB in the Central Nervous System Ameliorates Autoimmune Encephalomyelitis in Mice. *Nature Immunology*, **7**, 954-961. http://dx.doi.org/10.1038/ni1372

[67] Stancovski, I. and Baltimore, D. (1997) NF-kB Activation: The IkB Kinase Revealed? *Cell*, **91**, 299-302. http://dx.doi.org/10.1016/S0092-8674(00)80413-4

[68] Liu, Z.G., Hsu, H., Goeddel, D.V. and Karin, M. (1996) Dissection of TNF Receptor 1 Effector Functions: JNK Activation Is Not Linked to Apoptosis While NF-kB Activation Prevents Cell Death. *Cel1*, **87**, 565-576. http://dx.doi.org/10.1016/S0092-8674(00)81375-6

[69] Rai, N.K., Tripathi, K., Sharma, D. and Shukla, V.K. (2005) Apoptosis: A Basic Physiologic Process in Wound Healing. *International Journal of Lower Extremity Wounds*, **4**, 138-144. http://dx.doi.org/10.1177/1534734605280018

[70] Martinon, F. and Tschopp, J. (2004) Inflammatory Caspases: Linking an Intracellular Innate Immune System to Autoinflammatory Diseases. *Cell*, **117**, 561-574. http://dx.doi.org/10.1016/j.cell.2004.05.004

[71] Sutton, C., Brereton, C., Keogh, B., Mills, K.H.G. and Lavelle, E.C. (2006) A Crucial Role for Interleukin (IL)-1 in the Induction of IL-17-Producing T Cells That Mediate Autoimmune Encephalomyelitis. *Journal of Experimental Medicine*, **203**, 1685-1691. http://dx.doi.org/10.1084/jem.20060285

[72] Ferrari, C.C., Depino, A.M., Prada, F., Muraro, N. and Campbell, S. (2004) Reversible Demyelination, Blood-Brain Barrier Breakdown, and Pronounced Neutrophil Recruitment Induced by Chronic IL-$_1$ Expression in the Brain. *American Journal of Pathology*, **165**, 1827-1837. http://dx.doi.org/10.1016/S0002-9440(10)63438-4

[73] Hisahara, S., Yuan, J., Momoi, T., Okano, I.H. and Miura, M. (2001) Caspase-11 Mediates Oligodendrocyte Cell Death and Pathogenesis of Autoimmune-Mediated Demyelination. *Journal of Experimental Medicine*, **193**, 111-122. http://dx.doi.org/10.1084/jem.193.1.111

[74] D'Souza, S.D., Bonetti, B., Balasingam, V., Cashman, N.R., Barker, P.A., Troutt, A.B., *et al*. (1996) Multiple Sclerosis: Fas Signaling in Oligodendrocyte Cell Death. *Journal of Experimental Medicine*, **184**, 2361-2370. http://dx.doi.org/10.1084/jem.184.6.2361

[75] Li, W.Y., Maeda, Y., Ming, X., Cook, S., Chapin, J., Husar, W. and Dowling, P. (2002) Apoptotic Death Following Fas Activation in Human Oligodendrocyte Hybrid Cultures. *Journal of Neuroscience Research*, **69**, 189-196. http://dx.doi.org/10.1002/jnr.10285

[76] Lassus, P., Opitz-Araya, X. and Lazebnik, Y. (2002) Requirement for Caspase-2 in Stress-Induced Apoptosis before Mitochondrial Permeabilization. *Science*, **297**, 1352-1354. http://dx.doi.org/10.1126/science.1074721