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The role of death receptors in neural injury

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1. ABSTRACT

Programmed cell death is an essential process in the development of the central nervous system (CNS) and is fundamental for the control of the final number of neurons and glial cells. Excessive cell death has been implicated in a growing number of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and multiple sclerosis as well as ischemic injury. We review the contribution of death receptors of the tumor necrosis factor (TNF)/nerve growth factor (NGF) family to cell death and survival in the context of CNS pathology, indicating the possible value of manipulating cell death induced by these receptors for the treatment of CNS diseases and injury.

2. INTRODUCTION

Programmed cell death is a key process during embryonic development and in the maintenance of tissue homeostasis. It is a mechanism that removes unwanted or damaged cells without triggering an inflammatory response. This highly conserved mechanism by which eukaryotic cells die follows a tightly regulated series of molecular events collectively called apoptosis. Any imbalance in the rate of apoptosis can result in disorders characterised by either excessive (e.g. neoplasia) or insufficient (e.g. neurodegenerative diseases) cell numbers.

In mammalian cells, apoptosis can be induced by the ligation of plasma membrane death receptors (the 'extrinsic' pathway) or by the perturbation of intracellular homeostasis (the 'intrinsic' pathway). In the latter case, cell organelles can act as sensors capable of detecting cell injury and activating the apoptotic machinery. Mitochondria are the best-characterised organelles known to trigger apoptosis (1) and not only participate in the initiation of cell death by the 'intrinsic' pathway, but also are required in some cell types to amplify the apoptotic signal triggered by death receptors (2, 3). Mitochondrial regulation of cell death involves the interaction among pro

and anti apoptotic Bcl-2 family members, release of cytochrome c to the cytosol and apoptosome formation. Eventually, both pathways culminate in the activation by cleavage of a cascade of proteases, called caspases that are central activators and effectors of apoptosis.

Apoptosis is an essential process in the development of the central nervous system (CNS) and is fundamental for the control of the final number of neurons and glial cells. About half of all the neurons produced during development die before the completion of CNS maturation by this process of naturally occurring cell death. Two waves of apoptotic cell death affect CNS neurons at different stages of embryonic life. The first wave consists of the death of proliferating precursors and young postmitotic neuroblasts that appears to be independent from synaptogenesis and is closely linked to cell cycle regulation (4, 5). The second wave affects postmitotic neurons and glia, and is largely due to competition for limiting amounts of survival signals. While the late apoptotic death of postmitotic neurons is triggered through the mitochondrial pathway, death receptor activation may also be involved (6).

3. APOPTOSIS AND CNS DISEASE

Excessive cell death has been implicated in a growing number of neurodegenerative diseases. For example, an excessive rate of apoptosis occurs in Alzheimer's disease, Parkinson's disease, and multiple sclerosis (7).

Alzheimer's disease (AD) is a neurodegenerative disorder resulting from the progressive loss of neurons in areas critical for learning and memory. It is the most common neurodegenerative disease in the developed world and affects 4 million people in the United States alone. It seems to be caused by abnormal protein deposits accumulating in the brain, although inflammatory cytokines have also been implicated as important factors in the progression of neuronal damage. Pathological signs of apoptosis such as DNA fragmentation and cleavage of caspases have been detected in post-mortem human AD brains (8-10). A small protein called amyloid beta (Aβ), which originates from the γ-secretase-mediated processing of amyloid precursor protein (APP), is the major component of pathological plaques found in the brains of AD patients and it is capable of inducing apoptosis in cultured neurons (11). Aβ accumulation triggers caspase activation, leading to caspase-cleavage of the cytoskeletal protein tau that accumulates during AD (12). Also, APP can be cleaved by caspases at sites different to the classic secretase-processing sites, releasing a carboxy-terminal peptide that is a potent inducer of apoptosis (13). These studies suggest that therapeutics aimed at inhibiting tau and APP caspase-cleavage may prove beneficial in slowing AD cognitive decline. APP itself functions as a cell surface receptor (14), and mutations of this protein found in familial AD or its over expression can cause APP to signal aberrant neuronal DNA synthesis and apoptosis (15).

Parkinson's disease (PD) is the second most common neurodegenerative disease, after AD. Although the aetiology of PD is unknown, the clinical symptoms are attributed to a deficiency in the neurotransmitter dopamine resulting from the selective loss of dopamine-producing neurons from the substantia nigra area of the brain. Approximately 5% of PD cases are familial, while the rest are sporadic and age related. Morphological hallmarks for apoptosis have been reported in dopaminergic neurons in post-mortem PD tissue (16, 17). Similarly, the proportion of cleaved caspase 3-positive dopaminergic neurons is significantly higher in PD patients and cleavage of caspase 8 and caspase 9 has also been reported (18-21).

Multiple sclerosis (MS) is a progressive inflammatory demyelinating disease of the CNS that affects over a million patients worldwide. The aetiology of MS is unclear, although current evidence suggests that a combination of viral and autoimmune factors may be involved. MS is characterised by multifocal areas of demyelination within the CNS, and oligodendrocytes (the myelin forming cells of the CNS) appear to be the primary target. There is a component of axonal loss, which is likely to be secondary to loss of trophic support from the myelin and may be the pathological correlate of the progressive neurological impairment associated to this disease (22). Oligodendrocyte (OL) progenitors are present in the normal adult human CNS and in MS lesions but fail to repair demyelinated regions (23). OL loss in MS tissue has been ascribed to both apoptotic and necrotic cell death (24, 25).

Ischemic stroke is the third most common cause of death and disability in the Western world. During cerebral ischemia, there is a gradient in the severity of hypoperfusion and in cerebral energy failure. In the core region of the infarction, blood flow may be close to zero and cell death is mainly necrotic. In the areas surrounding the core, the so-called ischemic penumbra, where the injury is less severe, the neurons suffer transiently reversible damage, and then ultimately undergo death by apoptosis (26). There is evidence of caspase 3 activity in ischaemic brain tissue (27, 28). During the first few hours, reversible neuronal injury of the ischemic penumbra offers an opportunity for therapeutic intervention and, in this context, caspase inhibitors significantly attenuate neuronal loss following stroke (29-31). Cerebral ischemia in newborn infants is a major cause of cerebral palsy, epilepsy, and mental retardation. After the initial transient ischemic insult, cell death by apoptosis accumulates resulting in a permanent loss of neural cells (32). *In vivo* studies have shown that the point at which cells are committed to apoptosis has not been reached by 6 hours after ischemia, and up to this point, cell death can be reduced with mild hypothermia (33, 34). Indeed, the results of a recent clinical trial have shown that head cooling can improve both survival and neurodevelopmental outcome in infants with neonatal encephalopathy (34, 35).

4. ROLE OF DEATH RECEPTORS IN BRAIN INJURY AND DISEASE

A total of eight human death receptors have been identified (36) (Figure 1), but the ones that have been shown to be most relevant to the CNS are Fas (CD95 or

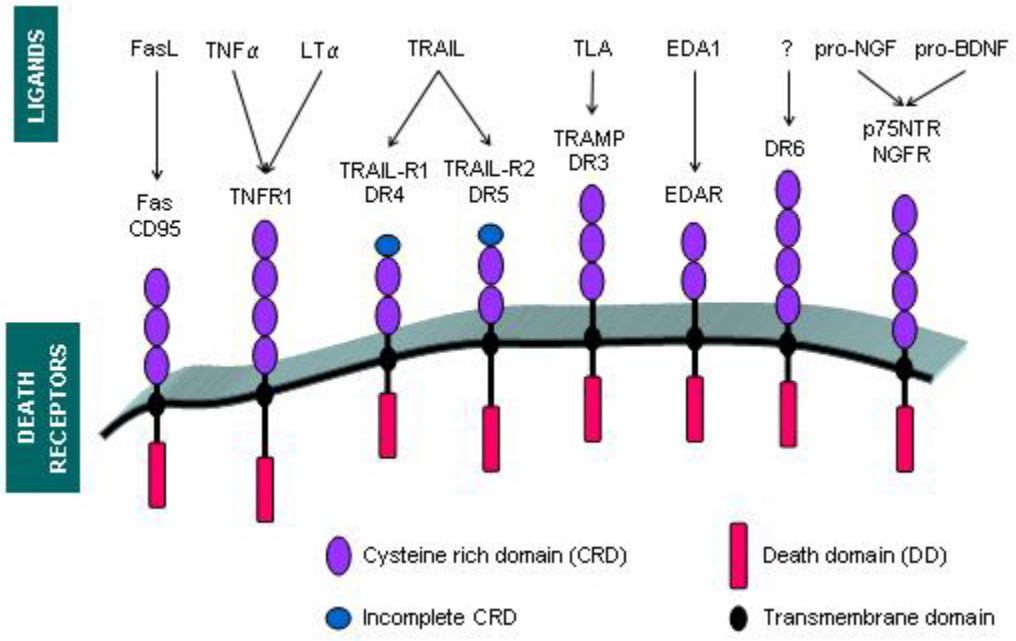

Figure 1. Apoptosis is induced by a subgroup of the tumor necrosis factor (TNF) receptor superfamily, the so called death receptors. Eight human death receptors are known to date. They are typically type I or type II transmembrane proteins that share a conserved 80 amino acid sequence, the death domain, in their cytoplasmic tail, and contain two to four cysteine rich extracellular domains that are involved in ligand binding. The known ligands for these receptors are denoted.

Apo-1), tumour necrosis factor receptor type 1 (TNFR1), the neurotrophin co-receptor p75 (p75NTR) and the TNF-related apoptosis-inducing ligand (TRAIL)-receptors 1 (TRAIL-R1 or DR4) and 2 (TRAIL-R2 or DR5). Death receptors are all type I or type II transmembrane proteins with a cytoplasmic 'Death Domain' (DD) motif that couples the cell surface protein to intracellular signalling cascades. They are generally activated by ligand-mediated oligomerisation and some members of the family, such as TNFR1 and p75NTR, elicit a broad spectrum of activities in addition to triggering apoptosis. These include cell survival, proliferation, differentiation, neurite outgrowth or immune activation depending on the cell type (37, 38). In this review, we will focus on the role of death receptors in the brain during development and injury/disease.

4.1. Fas (CD95)

Perhaps the best characterised death receptor signalling pathway to date is that of Fas/CD95. Binding of FasL to its receptor triggers a conformational change in Fas that recruits the adaptor molecule Fas-associated death-domain (FADD) to its intracellular death domain (DD). FADD recruits the death effector domain (DED)-containing caspases 8 and 10 to the receptor, forming the death-inducing signalling complex (DISC). Caspases recruited to the DISC proteolytically autoactivate themselves, initiating apoptosis by subsequent cleavage of downstream effector caspases (39) (Figure 2). Fas/CD95 can also induce cell death following recruitment of the receptor interacting protein (RIP) kinase to the DD of the receptor through a pathway that does not require apical caspase activation (40).

A crucial role for Fas on the developing CNS is unlikely, since Fas-deficient (lpr) mice and FasL-deficient (gld) mice show no neurological defects at birth (41, 42). Similarly, no developmental defects can be detected in genetically engineered $Fas^{-/-}$ mice (43). In the two mouse strains, lpr and gld, the most frequently reported neurological effects are attributed to an autoimmune response rather than endogenous defects in Fas-mediated apoptosis because they appear after the onset of autoimmune disease between the second and third months of life (44, 45). Moreover, despite the lack of Fas and FasL expression in neurons, the effect of the gld and lpr mutations on neuronal populations is not significant compared to wild type mice (46). However, defects in downstream apoptosis-related genes result in readily apparent neural defects, mice deficient in caspase 9 die perinatally with a markedly enlarged and malformed cerebrum caused by reduced apoptosis during brain development, and caspase 3 knockout mice display a similar phenotype (47, 48). These data strongly suggest that Fas-mediated apoptosis is either not involved, or can be replaced by alternate mechanisms in the control of neuronal populations during CNS development.

Fas/CD95 has been implicated in protecting neural cells from autoimmune attack by immune privilege. The term "immune privilege" describes the lack of local immune responses within certain tissues. Local expression of FasL is essential for maintaining immune privilege in the eye and the placenta through the deletion of early

infiltrating inflammatory cells (49, 50), similarly, FasL has been reported to mediate immune privilege in the testis (51). It follows that any failure in immune privilege might

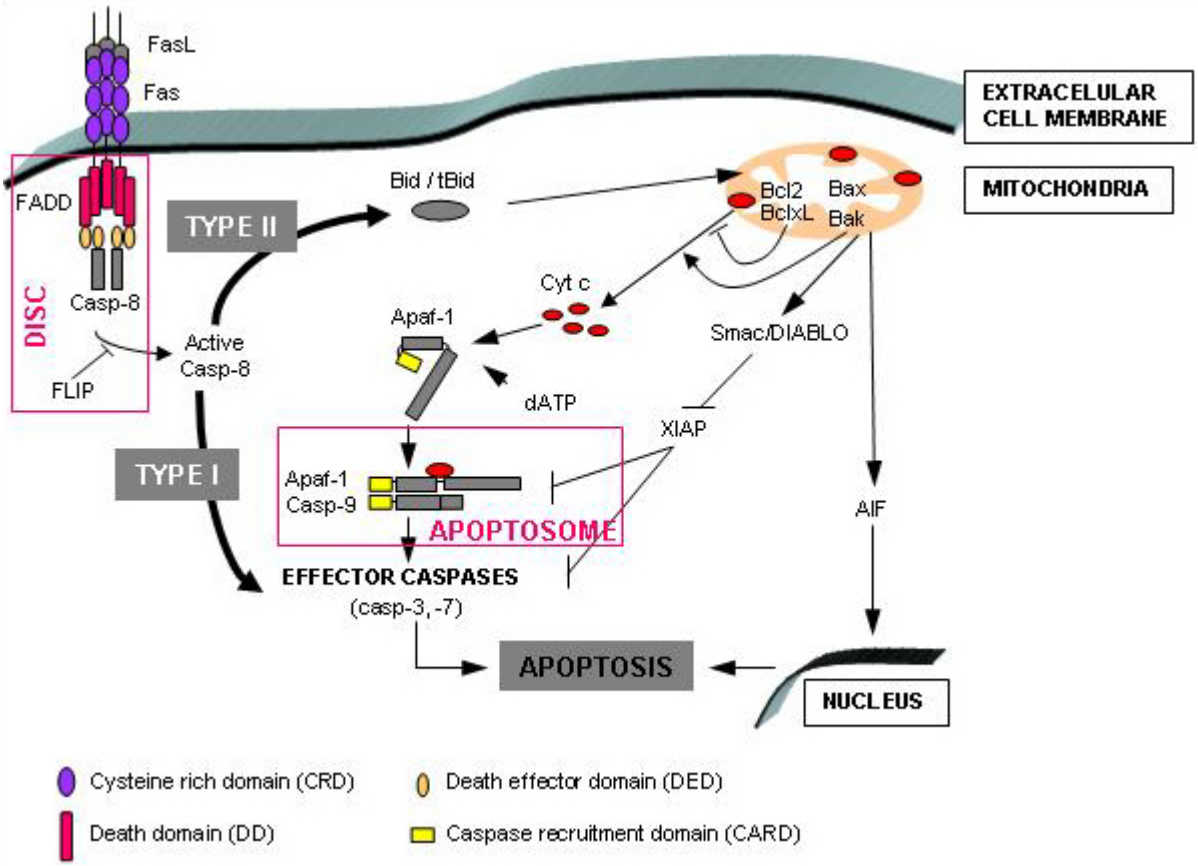

Figure 2. Fas/FasL-triggered apoptosis is the best characterised cell death receptor induced pathway. Upon Fas oligomerisation the adaptor molecule FADD and the pro-form of caspase 8 are sequentially recruited to the intracellular potion of the receptor via DD and DED interactions. The regulator c-FLIP can also be recruited to this complex named death-inducing signaling complex (DISC). The resulting oligomerisation of procaspase 8 results in its autoproteolytic processing and activation. The ensuing apoptotic program kills cells via two different pathways: either active caspase 8 directly cleaves and activates caspase 3 (type I) or caspase 3 cleavage is induced indirectly through cleavage of Bid and activation of the mitochondrial pathway (type II).

lead to inflammatory brain disease. For example, breakdown of the blood-brain barrier is a primary event in MS and other demyelinating diseases. This specialised endothelium is thought to be one of the factors responsible for the relative immune privilege of the CNS (52). In this context, the Fas-FasL system is a double-edge sword, acting as a protective and beneficial machinery against the endogenous immune responses, or as a destructive force *in situ*ations of aberrant immunity. FasL is expressed on oligodendrocytes, macrophages, microglia and lymphocytes in MS lesions (53, 54). Soluble FasL can also be recovered from cerebrospinal fluid (CSF) obtained from MS patients (55). Perhaps not surprisingly, it has been found that disruption of the Fas-FasL system improves clinical signs of experimental autoimmune encephalomyelitis (EAE), a widely studied animal model of MS. In both lpr and gld mutations the clinical signs of EAE are ameliorated while neutralisation of FasL during the progression phase of EAE significantly reduced the severity of the disease in wild type animals (56, 57). Paradoxically, when recombinant FasL was infused before EAE onset it suppressed acute EAE; however, injection of specific antibodies against FasL prevented spontaneous remission of EAE (57, 58). Thus, the Fas-FasL system may play a dual role in MS: a protective role against augmented immune responses to self antigens by triggering the (activation-induced) death of infiltrating inflammatory cells (59) and a cytotoxic role during the acute phase of the disease, causing the death of oligodendrocytes. In fact, mice lacking Fas expression in oligodendrocytes are partially protected from EAE (60).

In contrast to the exacerbated immune response in MS, Alzheimer's disease might result from defective immune surveillance mechanisms. Activated T cells, neutrophils, and immunoglobulins are notably absent in the affected areas of the AD brain. Instead, activated microglia are associated with Aβ deposits in AD brains, but seem unable to clear them properly (61). FasL expression is significantly elevated in senile plaques and neurofilament-

positive dystrophic neurites in AD (62), which might explain the scarcity of T-cell infiltration. Increased levels of Fas have been detected in post-mortem AD brains and in the CSF of AD patients (63, 64). Disruption of Fas-FasL signalling by means of a fusion protein consisting of the ligand binding domain of Fas and the Fc domain of IgG (FasFc) has been found to protect primary cortical and cerebellar neurons against Aβ neurotoxicity (65). Moreover, neurons isolated from gld or lpr mice are also resistant to the apoptotic effects of Aβ (62). An intriguing finding came from Ethell *et al.* who observed that a broad-spectrum metalloproteinase inhibitor acted synergistically with Aβ to exacerbate neuronal cell death and this effect was mediated by FasL (66). Metalloproteinases facilitate the processing of APP to produce Aβ, and regulate the availability of FasL at the cell surface by shedding the Fas-binding ectodomain. While membrane-bound FasL is highly toxic, the released soluble form competes for Fas availability and has anti-apoptotic activity (67). The picture drawn by all these data is difficult to interpret; future research should elucidate the molecular mechanisms of AD and whether FasL plays a central role.

Soluble Fas and FasL have also emerged as candidates for prognostic markers of HIV-associated dementia (68, 69). Despite effective anti-retroviral therapy, about 11% of late-stage HIV-1 patients develop a syndrome of neurological deterioration known as HIV-associated dementia. Neurons are not productively infected by HIV-1, so neuronal injury most likely is the outcome of the microglial activation and the battery of pro-inflammatory and neurotoxic mediators released by activated mononuclear phagocytes. In this sense, activated astrocytes express FasL (70, 71). While neurons express Fas, they also depend on close contact with astrocytes for survival signals. Thus FasL expressed by activated astrocytes is likely to be deleterious to neurons.

Fas signalling has also been implicated in ischemic damage. Both Fas and FasL are up regulated following cerebral hypoxic-ischaemic injury to the developing and adult brain (26, 72). Studies using lpr and gld mice have shown that disruption of the Fas-FasL signalling pathway protects against cerebral ischemia (73). Inflammation plays an important role in brain damage progression after acute stroke, thus, one caveat of studies using gld or lpr mice is that the immune system is grossly dysregulated, and experimental data derived from these mice requires careful interpretation (74). Nevertheless, neutralisation of FasL protects primary cultures of cortical neurons from hypoxia-induced cell death, and FasL neutralising antibodies reduce infarct volume in mice subjected to focal ischaemic injury (75). These data suggest that Fas-FasL is implicated in ischemia-induced neuronal apoptosis, and that Fas-mediated neuronal apoptosis in this situation is deleterious. Similarly, detrimental effects of FasL have been recently described in a model of spinal cord injury, where neutralisation of FasL, but not TNF, promoted both axonal regeneration and functional improvement (76).

4.2. Tumour necrosis factor receptor (TNFR)

TNF exerts its effects through two distinct receptors, TNFR1 and TNFR2, but only TNFR1 has an intracellular death domain (36). Similar to Fas-FasL interaction, binding of trimeric TNFα to TNFR1 induces receptor cross linking. The first protein recruited to TNFR1 is TNFR1-associated death domain protein (TRADD), which serves as a platform to recruit additional mediators that trigger distinct biological responses. Recruitment of adaptor proteins such as FADD allows the binding and auto-activation of caspase 8, which leads to apoptosis. On the other hand, recruitment of TNFR associating factor 2 (TRAF2) and RIP leads to NF-κB and JNK activation. Once activated, JNKs can phosphorylate transcription factors (e.g. c-Jun) that then transactivate pro-inflammatory and anti-apoptotic genes. In the other arm of this protective pathway, TNFR1 suppression of apoptosis is largely dependent on NF-κB activation, which augments the inflammatory response to TNF (77).

TNF is readily detected in active MS lesions, largely produced by macrophages and microglia (78). TNFR1 expression has been found in OLs in the MS lesions (79) this might explain, at least in part, the demise of the OL lineage in MS pathology (60, 79). In accordance, transgenic over expression of TNF within the CNS results in chronic inflammation and demyelination and converts the acute phase of EAE into a more chronic phenotype (80-82); however, in the absence of TNF, myelin-specific T cells accumulate in the spleen of immunised animals that develop a chronic form of EAE (83). These findings point to a dual role of TNF: despite its harmful pro-inflammatory properties, it may also provide beneficial functions in autoimmune diseases by exerting immune-suppressive effects. This may provide an explanation for augmented immune activation and disease progression evidenced in clinical trials with MS patients treated with anti-TNF agents (84-86). Research using knockout mice for the different TNF receptors has revealed that demyelination and disease severity depend largely on TNFR1, while inmunosuppressive functions of TNF are exerted through both TNF receptors (82, 87-89). It is therefore likely that specific anti-TNFR1 strategies will be more advantageous in the treatment of human immunopathologies than therapies conducted to block TNF activity.

A different scenario may apply to stroke. It is well documented that following cerebral ischemia, TNF expression in the ischemic penumbra increases (90-92). Studies using TNF knockout mice or strategies that neutralise TNF after ischemia have been shown to reduce infarct volume (75, 93), while mice lacking TNFR1, TNFR2 or both, show enhanced ischemic damage (94), thus, an apparent paradox arises from these studies. Interestingly, increased levels of TNF prior to the ischemic insult significantly reduced infarct size in mice (95, 96). This notion is strengthened by data obtained in humans where it has been found that ischemic tolerance in acute stroke is associated with increased plasma TNF levels (97). In summary, there appears to be a protective effect of TNF, possibly mediated by TNFR1 (98), if present before the ischemic injury and a deleterious one after the insult. This has clear implications in the development of TNF-based strategies for stroke treatment.

4.3. The p75 Neurotrophin Receptor (p75NTR)

The low affinity neurotrophin receptor p75 (p75NTR) is involved in several different biological pathways including cell death, survival, proliferation, differentiation, axonal elongation and synaptic transmission. Although p75NTR was among the earliest identified neurotrophin receptors, its biological role and mode of action have proved elusive. Much of the controversy about the role of this receptor stems from the fact that it binds all of the known neurotrophins with similar affinity (therefore its early name low-affinity nerve growth factor receptor). The association of p75NTR with receptors of the trk family (tropomyosin related receptor tyrosine kinases), TrkA, TrkB or TrkC, modulates its binding affinity for neurotrophins (99-101). The p75NTR also associates with the Nogo receptor complex, signalling responses to Nogo, myelin associated glycoprotein (MAG) and myelin oligodendrocyte glycoprotein (MOG) (102,103). In the context of apoptosis, p75NTR seems to mediate cell death in response to neurotrophin binding rather than ligand withdrawal, as suggested by initial p75NTR over expression experiments (104-106). Pro-NGF and pro-BDNF are the most effective inducers of apoptosis via the activation of a receptor complex of p75NTR and sortilin (107-109).

There are two isoforms of the p75NTR, full-length p75NTR (FL-p75NTR) and a short isoform (s-p75NTR) that differ in the number of extracellular cysteine-rich repeats but both contain an intracellular death domain. Recently, a relative of p75NTR designated PLAIDD (p75-like apoptosis-inducing death domain) was also identified (110). Unlike Fas or TNFR, the p75NTR death domain exhibits a type II structure. Multiple adaptor proteins can be recruited to the intracellular domain of p75NTR being responsible for its different biological activities (111). Among these are TNF receptor associated factor 6 (TRAF6), neurotrophin receptor interacting factors 1 and 2 (NRIF 1 and NRIF2), melanoma associated antigen (MAGE), neurotrophin-interacting MAGE homologue (NRAGE or MAGE-D1), Schwann cell factor 1 (SC-1), RhoGDI, protein kinases such as the interleukin-1 receptor associated kinase (IRAK) and the mitogen-activated protein kinases ERK1 and ERK2 and others.

Developmental studies have established a role for p75NTR in programmed cell death associated with neurogenesis. Studies in mice carrying mutations in the NGF and p75NTR genes indicate that a significant amount of the early cell death observed in the developing retina and in the spinal cord is mediated by NGF acting through p75NTR (112). Under certain pathological conditions such as traumatic brain damage, cerebral ischemia, axotomy, AD, and epileptic seizures, p75NTR is re-expressed by CNS cells at levels comparable to those present in early development (113, 114). p75NTR re-expression under pathological conditions, when Trk receptors may be down regulated, suggests that an imbalance of neurotrophin receptor signalling may be involved in some diseases of the nervous system. The fact that p75NTR induces cell death upon binding toxic peptides, such as the neurotoxic prion protein fragment PrP (aa 26-106) and the Aβ peptide (115, 116), reinforce this idea and suggest that research in p75NTR signalling may identify promising drug targets for preventing cell death in some CNS pathologies.

4.4. TNF-related apoptosis-inducing ligand receptors (TRAIL-R)

The TNF-related apoptosis-inducing ligand, TRAIL, is capable of binding four homologous receptor molecules with comparable affinities (117). Two of them, TRAIL-R1 (DR4) and TRAIL-R2 (DR5), induce apoptosis upon ligand binding (118-120). In contrast, the other two receptors are unable to transduce a death signal; TRAIL-R3 (DcR1) lacks the intracellular portion, and TRAIL-R4 (DcR2) has a truncated cytoplasmic DD. These receptors are preferentially expressed on healthy cells and act as "decoys", protecting normal tissues against TRAIL-induced apoptosis (121, 122). The absence of these decoy receptors on tumour cells, together with the expression of functional TRAIL-R1 or -R2 (123), may represent the underlying basis for the sensitivity of many cancer cells to TRAIL-mediated apoptosis. This has triggered a flurry of research into the use of TRAIL as a chemotherapeutic adjunct molecule. TRAIL itself is not constitutively expressed in adult human brain (124), while the healthy brain and the majority of brain tumours and glioma cell lines co-express TRAIL-R1 and -R2, and the "decoy" TRAIL-R3, suggesting that there might not be a significant role for this system in the apoptotic regulation of brain tumours (125). However, recent studies suggest that brain tumours may be more susceptible to TRAIL-induced apoptosis than was first thought (126-128). Resistance of some neural tumours to TRAIL therapy might be due to the loss of activity of some downstream TRAIL effectors (129, 130). TRAIL-based strategies aiming at enhanced apoptosis of chemotherapy-resistant brain cancer cells have been proposed as new therapeutic alternatives for the treatment of primary brain tumours (131).

The fact that TRAIL selectively induces death of human oligodendrocytes isolated from adult brain and in MS lesions (132, 133), suggests a putative role for TRAIL as an effector molecule in inflammatory or demyelinating diseases such as MS (134). In fact, very recently it has been shown that this is exactly the case. Aktas and co-workers found that TRAIL-deficient myelin-specific lymphocytes induced less severe EAE when transferred to wild-type mice, while intracerebral delivery of TRAIL to animals with EAE increased the clinical deficits (135). These findings suggest that an anti-TRAIL approaches may be useful in the treatment of MS (136).

5. PERPECTIVES

Death receptors of the TNF superfamily are capable of eliciting multiple cell responses that range from proliferation, differentiation, and inflammation to cell death. Since they are differentially expressed during brain development their role in neurogenesis might be expected to differ, and this is indeed the case. So, while mutations in Fas/CD95, or the TNF and TRAIL receptors do not have an overt neural phenotype, p75NTR has been implicated in the NGF-dependent elimination of spinal cord motor neurons.

In contrast to a lack of function in normal brain development, Fas/CD95 and the TNF and TRAIL receptors are strongly implicated in a number of CNS pathologies. The most promising strategies aimed to block the Fas-FasL system are in the context of cerebral ischemia and spinal cord injury. The benefit of blocking TNF in CNS injury is not so straightforward. TNF, through its two receptors, has been implicated in protective immune responses as well as cell death. Because of this dual role, blocking TNF can be either beneficial or harmful depending on the type or stage of injury. In this context, the most promising therapeutic strategies might be those aimed at interfering specifically with one or other of the TNF receptors, especially TNFR1. The study of TRAIL in brain development and pathology is in its infancy and results obtained using TRAIL as an anti-tumour agent have yielded mixed results in gliomas and neuroblastomas. On the other hand, there is a growing body of evidence for the involvement of TRAIL and other death receptors in CNS inflammation and in demyelinating diseases in particular. Clearly, this is an area or research where further investigation is warranted.

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Abbreviations: Ab: Amyloid beta, AD: Alzheimer's disease, APP: Amyloid precursor protein, BDNF: Brain derived neurotrophic factor, CNS: Central nervous system, CSF: Cerebrospinal fluid, DD: Death domain, DED: Death effector domain, DISC: Death-inducing signalling complex, EAE: Experimental autoimmune encephalomyelitis, FADD: Fas-associated death domain, MS: Multiple sclerosis, NF-kB: Nuclear factor kappa B, NGF: Nerve growth factor, OL: Oligodendrocyte, PD: Parkinson's disease, p75NTR: Neurotrophin receptor p75 , TNF: Tumour necrosis factor, TNFR1: TNF receptor type 1, TNFR2: TNF receptor type 2, TRAIL: TNF-related apoptosis-inducing ligand, TRAIL-R (1 to 4): TRAIL receptor (1 to 4)

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