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The role of tumor necrosis factor receptor superfamily members in mammalian brain development, function and homeostasis

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Abstract

Tumor necrosis factor receptor superfamily (TNFRSF) members were initially identified as immunological mediators, and are still commonly perceived as immunological molecules. However, our understanding of the diversity of TNFRSF members' roles in mammalian physiology has grown significantly since the first discovery of TNFRp55 (TNFRSF1) in 1975. In particular, the last decade has provided evidence for important roles in brain development, function and the emergent field of neuronal homeostasis. Recent evidence suggests that TNFRSF members are expressed in an overlapping regulated pattern during neuronal development, participating in the regulation of neuronal expansion, growth, differentiation and regional pattern development. This review examines evidence for non-immunological roles of TNFRSF members in brain development, function and maintenance under normal physiological conditions. In addition, several aspects of brain function during inflammation will also be described, when illuminating and relevant to the non-immunological role of TNFRSF members. Finally, key questions in the field will be outlined.

Keywords

brain; cytokines; development; neuron; receptors; TNFRSF; TNFSF

Introduction

The tumor necrosis factor receptor superfamily (TNFRSF) is an ancient family of molecules which is present in both vertebrates (Su et al., 1992; Tan et al., 1997; Bridgham et al., 2001; Bridgham and Johnson, 2003; Tamura et al., 2004; Hosaka et al., 2005; Iha et al., 2009) and invertebrates (Ouwe-Missi-Oukem-Boyer et al., 1994; Kauppila et al., 2003; Wang et al., 2006; Kato et al., 2009; Li et al., 2009). For many years, the focus on the immunological and pathological role of TNFRSF members and their ligands (the TNFSF or tumor necrosis factor superfamily) has overshadowed research examining non-immunological functions for these proteins. However, important roles for TNFRSF members in the development, function and maintenance of brain function have recently been described. Collectively, these studies implicate TNFSF cytokines and their receptors as having profound and diverse neurological roles affecting aspects of neuronal function as diverse as sleep (Kapas et al., 2008), motor function (Twohig et al., 2010), pain (Peng et al., 2005), cognitive function

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(McAfoose et al., 2009), neuronal development/differentiation (Salama-Cohen et al., 2006) and the fine tuning of neuronal signaling and lifespan (Iosif et al., 2006). Whilst the impact of these ligands and receptors on brain function is becoming better appreciated, the underlying mechanisms through which they act remain to be elucidated. This review summarizes some of the current knowledge on the expression patterns and roles for TNFSFR/TNFSF members under normal physiological conditions. It begins by describing the TNFSFR/TNFSF families and their general expression in the brain. In the second half of the review, the roles individual TNFRSF members play in brain development and homeostasis are illustrated with evidence from studies of some of the most described members; Fas, TNFRp55 (TNFRSF1), $p75^{NTR}$, DR3 (TNFRSF25) and CD40.

The TNF superfamily

The TNFSF consists of more than 19 type II transmembrane (with the exception of LTα) proteins with high homology (20–30%) and a conserved extracellular C-terminal domain known as the TNF homology domain (THD), which is used for receptor binding (Bodmer et al., 2002). TNFSF members are primarily expressed as transmembrane proteins with soluble forms normally being generated by proteolysis and in some cases by alternative mRNA splicing. The THD domain is a conserved hydrophobic (aromatic) sequence of ~150 amino-acids (aa), which mediates trimerization of the TNFSF monomers into the active form of the ligand able to bind and activate receptors (Eck and Sprang, 1989; Jones et al., 1989; Banner et al., 1993; Karpusas et al., 1995; Hymowitz et al., 1999, 2000; Mongkolsapaya et al., 1999; Bodmer et al., 2000, 2002; Cha et al., 2000; Trabzuni et al., 2000). For many TNFSF ligands such as TNFα, multimeric ligand assembly and stability appear facilitated by high monomeric chain concentration, whereas low oligomeric concentration reduces trimeric ligand structural stability, favors dissociation, and leads to monomeric chain generation (Eck and Sprang, 1989; Corti et al., 1992). The exception appears to be human Glucocorticoid-induced TNF receptor ligand (GITRL), which structural analysis suggests may exist in both monomeric and trimeric states at equilibrium, each with different receptor binding affinities (Chattopadhyay et al., 2007, 2008).

The TNFR superfamily

Thus far, more than 29 different TNFRSF members have been isolated from multiple species, excluding splice and viral homologs that may have evolved by structural and functional duplication (Collette et al., 2003). TNFRSF members are predominantly type I transmembrane proteins with some exceptions (Bodmer et al., 2002), which are either type III proteins (BCMA, TACI, BAFFR and XEDAR), soluble proteins (DcR3 and OPG), or membrane proteins anchored via a glycolipid moiety (TRAIL-R3). Structurally, TNFRSF are characterized by the presence of 1–6 extracellular cysteine-rich domains (CRDs) (normally between 1 and 4 per receptor monomer chain), which are stabilized into an elongated structure by intermittent disulfide bridging (Bodmer et al., 2002). TNFRSF members are often further subdivided into two discrete families based on the presence or absence of a cytoplasmi ~180 aa interaction motif known as the death domain. Cell surface transmembrane bound TNFRSFs appear to be expressed as relatively stable homo-trimeric complexes, stabilized by light inter-chain binding and interaction (Chan, 2007). Depending on the scenario, the rate of TNFSFR oligomerization and the stability of receptor complexes has been suggested to be dependent on ligand concentration, receptor monomer availability, temperature and the ratio of ligand to receptor complex (Siegel et al., 2000; Locksley et al., 2001; MacEwan, 2002a, b; Chan, 2007; Chattopadhyay et al., 2007, 2008).

Many soluble receptor forms have also been identified, which appear capable of ligand binding (Lotz et al., 1996; Screaton et al., 1997a,b; Nocentini et al., 2000a). Soluble

TNFRSF can be generated by direct expression (e.g., DcR3 (Yu et al., 1999) and OPG (Khosla, 2001)), proteolytic cleavage and shedding of surface transmembrane forms (e.g., TNFR1, TNFR2, CD27, CD30 and CD40 (Gruss and Dower, 1995), and by alternative exon splicing of the transmembrane domain (e.g., Fas, 4-1BB and DR3 (Lotz et al., 1996; Screaton et al., 1997a; Wang et al., 2001). Alternative pre-mRNA splicing of TNFRSF members has also been suggested to generate multiple truncated receptor isoforms that have shortened or rearranged extracellular domains, alternative cytoplasmic domains with novel sequences (Screaton et al., 1997a, 1997b; Nocentini et al., 2000b) and soluble forms lacking either or both the transmembrane domain and intracellular cytoplasmic domain (Kitson et al., 1996; Bodmer et al., 1997; Wang et al., 2001). It has been speculated that the balance between different splicing products may regulate different physiological responses, by changing free ligand availability, and that different receptor isoforms may have different ligand binding affinities/sensitivities or may stimulate different intra cellular pathways (Screaton et al., 1997a; Nocentini et al., 2000a). Irrespective, alteration to TNFRSF isoform expression patterns has also been observed to be dependent on age (Hou et al., 2008), tissue of expression (Harrison et al., 2000; Wang et al., 2001) and activation state (Nocentini et al., 2000a, b). It is also worthy of note that viral open reading frames encoding TNFRSF homologs have been identified, including SVF-T2 in Shope-fibroma virus, Va53R in vaccinia, and (cytokine response modifiers) CrmB, CrmC and Crm D in orthopoxviruses and UL144 in human cytomegalovirus (Yano and Chao, 2000; Bodmer et al., 2002; Poole et al., 2006).

TNFRSF signaling

TNFSFs bind cognate TNFRSF to induce their various biological functions. Upon trimeric receptor complex activation by binding of either membrane or soluble ligand, receptor subunits undergo conformational changes, which facilitate the recruitment of cytoplasmic signaling/adaptor proteins to bind to their intracellular tail. Adaptor molecules can be broadly grouped into three classes: TNF receptor associated factors (TRAFs), death domain (DD)-containing proteins and non-TRAF/DD molecules with low homology, which can associate to form co-receptor complexes such as the Nogo-Lingo-1 receptor (NgR-Lingo1) (Mathis et al., 2010). Individual TNFRSF members have unique combinations of intracellular docking motifs that allow specific TRAFs (1–7) or DD binding proteins (TRADD, FADD) to attach (Dempsey et al., 2003; Watts, 2005). Receptors such as TNFR1, Fas, DR3, DR4, DR5 and DR6, which contain their own DDs, may also recruit and bind a cascade of smaller cytoplasmic DD-containing adaptor molecules (Wilson et al., 2009). This receptor-adaptor complex can then act as a recruitment scaffold for the attachment and autocleavage of immature procaspase subunits initiating death inducing signaling complex (DISC) formation, driving further caspase activation and ultimately inducing cell death (Ashkenazi and Dixit, 1998; Wilson et al., 2009). Alternatively, the DD-containing receptor-adaptor complex may act as a scaffold for the recruitment and attachment of TRAF molecules, which activate multiple signal transduction pathways (NF-κB, PI3K, JNK, ERK, p38MAPK) and induce changes to inflammatory/anti-apoptotic gene transcription promoting cell proliferation or survival (Dempsey et al., 2003). The receptor-adaptor complex may bind further DD-containing molecules, before initiating pro-caspase or TRAF binding, considerably enlarging the receptor-adaptor complex (Wilson et al., 2009). In the second category, DD-deficient receptors such as TNFR2, CD27, CD30, CD40, GITR, OX40, RANK, TROY, Fn14 (TweakR), LtbR and XEDER, utilize unique TRAF binding motifs known as TIMs (TRAF-interacting motifs) to directly recruit and bind specific combinations of TRAFs to activate intracellular signaling (Dempsey et al., 2003). The TNFSFR members DR5, $p75^{NTR}$, EDAR and TRAILR (10B) have both DD and TIM motifs. In the third category, $p75^{NTR}$ and TROY have both been shown to interchangeably bind NgR and Lingo-1, to form a specialized receptor complex allowing myelin inhibitory

protein binding and drive downstream RhoA and NFκB activation (Park et al., 2005, 2011; Mathis et al., 2010). Collectively, the intracellular signaling outcome of receptor ligation appears to be a product of ligand/receptor avidity and affinity, ligand and receptor expression levels, the presence or absence of competing ligands or receptors, the number and nature of the receptor proximal adaptor binding motifs present as well as the pre-existing balance and expression levels of intracellular signaling molecules within the cytoplasm. That TNFRSF members have such complex multilayer pathways, is thought to ensure the rapid generation and propagation of escalating and highly receptor-specific intracellular signaling which can be cross regulated at multiple points to ensure the appropriate cellular outcome.

Homeostatic TNFRSF and TNFSF expression in the brain

Most TNFRSF members and their TNFSF ligands (TNFSF) have been found to be expressed in the mammalian brain or the nervous system during some stage of development under normal physiological conditions, with the exception of CD30/CD30L and CD27/CD27L, which have only been observed during specific neurological diseases (Held-Feindt and Mentlein 2002; Kodama et al., 2009). TNFRSF members that appear constitutively expressed in the brains of adult humans, rats and mice, include DR6, TROY, CD40, CD95, Fn14, p75 ^{NTFR}, TNFR1, TNFR2 and DR3 (Yan and Johnson, 1988; Lee et al., 1992; Pan et al., 1998; Eby et al., 2000; Kojima et al., 2000; Tan et al., 2002; Pispa et al., 2003; Shao et al., 2005; Hamill et al., 2007; Hou et al., 2008; O'Keeffe et al., 2008; Twohig et al., 2010). TNFSF members expressed in the brain include CD40L, TNFα, CD95L, EDA, TROY, TRAIL, GITRL and TL1A (French et al., 1996; Rieger et al., 1999; Pispa et al., 2003; Iosif et al., 2006; Zuliani et al., 2006; Harry et al., 2008; Corsini et al., 2009; Poulton et al., 2010). We define animals with normal physiological conditions as those which are apparently disease free and show no signs of inflammatory neurological or peripheral disease except where noted (eg adult Fas and FasL mutant mice). In this review, TNFSF/TNFRSF expression and function in the brain under normal conditions, will be referred to as homeostatic to delineate from TNFSF/TNFRSF expression and function occurring during inflammatory processes.

The neurological expression of the TNFSF/TNFRSF proteins is neither random nor immunological

Homeostatic TNFSF/TNFRSF expression in the brain of mammals appears to be important for multiple neurological functions, including promoting nerve growth (Hayashi et al., 2008; Mi, 2008), differentiation (Hou et al., 2008), innervations (O'Keeffe et al., 2008), sensitization (Czeschik et al., 2008), and dendrite formation (Shao et al., 2005), and is supported by several streams of evidence. Firstly, TNFSF/TNFRSF expression occurs in the normal brain of the fetus, neonate, adolescent and adult mammal in developmentally regulated patterns and does not appear to induce neurological disease or inflammation (Twohig et al., 2010). Secondly, many animals with abnormal TNFSF/TNFRSF function or expression have altered brain development, function and behavior in the absence of detectable immune responses (Peterson et al., 1999; Neumann et al., 2002; Tan et al., 2002; Golan et al., 2004; Zuliani et al., 2006). Thirdly, alterations to TNFSF/TNFRSF expression and/or signaling by neurons, glia and oligodendrocytes can induce changes in cell maturation, lifespan, morphology and function, leading to altered neurological functions *in vitro* (Rosch et al., 2005; Salama-Cohen et al., 2005; Zuliani et al., 2006; Bernardino et al., 2008; Keohane et al., 2010). Finally, inflammatory processes that do upregulate TNFSF/TNFRSF expression and signaling have also been associated with neurological change. For example, brain-dependent behavioral and neuro-functional changes can be noted in some individuals with altered TNFSF/TNFRSF activity or expression during neuroinflammation

(Chen et al., 2008) and immunosuppression (Krishnan et al., 2007; Feldman et al., 2008; Iglesias et al., 2009). Similarly, increased exposure to TNFSF during fetal development has also been suggested to correlate with changes to post-natal brain function and behavior (Romero et al., 2007; Fatemi et al., 2008, 2009; Burd et al., 2010).

Both the expression level and pattern of homeostatic TNFSF/TNFRSF expression vary with age, probably reflecting changing requirements for individual ligand/receptor function. In general, TNFSF/TNFRSF members are first expressed in the brain early during fetal development, decreased or downregulated prior to birth, upregulated and peak during neonatal development, rapidly decline during adolescence and are maintained at low levels in the adult, finally becoming variable in old age. In neonatal mice, for example, minimal Fas/FasL, CD40 (type I), and TROY expression are observed in the brain at birth, but they are quickly upregulated within 5 days, coincident with the induction of TNF [post-natal day (PD)6], DR3 (PD6-7) and the peripheral downregulation of GITR (PD5) (Yamasu et al., 1989; Probert et al., 1995; Hisaoka et al., 2006a; Zuliani et al., 2006; Hou et al., 2008; O'Keeffe et al., 2008; Twohig et al., 2010). The expression of TNFSF/TNFRSF members is detectable in the developing embryonic and fetal brain of many species (see Table 1). During this early stage of development, the emergent brain is formed through the emigration, expansion, differentiation and maturation of cells, which generate primary cell types such as endothelial cells, neurons, glia and oligodendrocytes. Following this, these cells and their progeny continue to differentiate and mature/migrate into select regions, specialize and/or send out processes to form a highly refined and supported neural network. During neonatal development, the brain undergoes its final primary developmental stages and undergoes structural and functional refinement, driven partly under the influence of environmentally driven neuronal stimulation encountered following birth. Indeed, more than 2500 genes in the neonatal murine brain appear to be developmentally regulated during the first month of postnatal development (Clinton et al., 2000). Commencement of TNFSF expression correlates closely with neuro- and synaptogenesis in most species, suggesting that this may be the primary role of this ligand-receptor family in the brain during embryonic development and early neonatal life. In the adult, primary brain development is complete, but continues with small-scale modifications as brain function and stimulation reaches a peak and thereafter declines in efficiency during old age (Patel and Brewer, 2008a, b), when TNFSF/TNFRSF expression is continued but low.

The requirement for neurological TNFSF/TNFRSF signaling in the brain also appears to be lifelong, irrespective of any change in specific expression pattern or function. In this regard, the neurological functions of many individual TNFSF/TNFRSF pairs also appear to change throughout mammalian life, responding to the needs of the changing brain. For example, in the neonate, Fas is primarily expressed by neurons and induces neuronal branching and synaptogenesis but in the adult, it is primarily expressed by neuronal stem cells and drives neurogenesis (Zuliani et al., 2006; Corsini et al., 2009). It should be noted, however, that many TNFSF/TNFRSF pairs have several partially overlapping and divergent neurological roles, as will be seen further in this review.

Within the brain, expression of TNFSF/TNFRSF pairs has been found in many different cell types under normal conditions including neurons (Twohig et al., 2010), astrocytes (Choi and Friedman, 2009), oligodendrocytes (Matysiak et al., 2002), and endothelial cells (Zuliani et al., 2006) *in vivo*. This homeostatic TNFSF/TNFRSF expression is tightly controlled and restricted throughout life, with different ligand and receptor proteins having unique developmental and geographical species-specific patterns. In neonatal mice, for example, $p75^{NTR}$ is prominently expressed by forebrain neurons, CD40 on most cortical neurons, and DR3 primarily by hippocampal neurons (Tan et al., 2002; Salama-Cohen et al., 2005; Twohig et al., 2010). Although not well documented, it is likely that many mammalian brain

cells express multiple TNFSF/TNFRSF members, as suggested by the overlapping expression patterns of these proteins found in mice. For example, individual murine hippocampal neuron responses to TNFα, appear strongly dependent on their relative ratio of TNFR1 and TNFR2 surface expression (Fontaine et al., 2002; Yang et al., 2002a). Intriguingly, no dedicated studies have yet been undertaken to establish the extent of TNFRSF overlap in terms of expression and function, or to establish the extent to which signaling by individual TNFRSFs can interact. However, it does appear that homeostatic TNFRSF expression can modulate the expression of other TNFSF/TNFRSF pairs in the brain under normal conditions in mice (Golan et al., 2004; Harry et al., 2008). For example, adult TNFR1/2^{KO} mice have constitutively higher Fas expression in the brain (Harry et al., 2008). In addition, TNFR1 and TNFR2 have also been suggested to have opposing and cooperative roles in modulating hippocampal development *in vivo* (Yang et al., 2002b).

Geographically, ligands and their receptors may also be generated by the same cell (TNFR1/2; Iosif et al., 2006), can have close proximity with adjacent cell types generating parallel expression patterns (Fas/FasL; Zuliani et al., 2006), or can be separated by significant distances (p75^{NTR}-Myelin; Park et al., 2010). Whilst TNFSF expression patterns are uniquely species-specific (as would be expected between species with structurally and functionally different brains generated by different developmental programs), the broad expression pattern and function of TNFSF/TNFRSF pairs appear generally preserved between different mammals with few differences. Regional brain expression of DR3, for example, appears similar in mice and humans, with the exception that human DR3, but not murine DR3, has been recorded in the cerebellum (Harrison et al., 2000; Twohig et al., 2010). In particular, the postnatal hippocampus appears to be a focal point of intensive TNFRSF expression. In neonatal mice, DR3 (Twohig et al., 2010), TNFR1 (Harry et al., 2008), TNFR2 (Harry et al., 2008), CD40 (Tan et al., 2002), p75^{NTR} (Salama-Cohen et al., 2006) and Fas (Park et al., 1998) are all highly expressed in the hippocampus.

Homeostatic TNFSF/TNFRSF member expression in the brain is not generally lineage restricted, although trends are clearly observable. In general, TNFRSFs (DR3, Fas, TNFR1/2, CD40, p75^{NTR}) are normally expressed on neurons, whereas ligands (TNF, NGF, CD40L, TL1A) are expressed by surrounding cells, such as astrocytes and other glia, oligodendrocytes, and endothelial cells. Many exceptions can be found to these generalizations such as FasL, which is expressed by neurons in the neonatal murine hippocampus (Zuliani et al., 2006). That individual TNFSF/TNFRSF expression and function is geographically, and partly lineage restricted in the brain and dependent on age and species, suggests that it is highly regulated. The near simultaneous expression of several TNFSF/TNFRSF members in the fetus and neonate to within a few days in select murine brain cells supports pre-programmed triggered expression (Twohig et al., 2010). In addition, TNFSF/TNFRSF gene expression may also be controlled or modified by developmental or environmental signals, including immune responses. In the case of the developing fetus, it is possible that additional cues for gene expression may also be generated maternally and delivered transplacentally.

Neurological versus immunological signaling

Why does sustained homeostatic TNFSF/TNFRSF expression appear to not induce significant inflammation? For example, the embryonic mouse hippocampus appears bathed in soluble FasL (Zuliani et al., 2006), which might be expected to generate a significant immune response. There are a number of different mechanisms by which neurological TNFSF/TNFRSF signaling is distinguished from immunological signaling in the brain. These can be extrinsic or intrinsic to the neurological cells. Extrinsic mechanisms include the context of the TNFSF/TNFSFR signal. Firstly, homeostatic expression of TNFSF/

TNFRSF members in the brain is regulated, low and sustained. In contrast, TNFSF/TNFRSF expression during inflammation, undergoes rapid change, increases to high levels and appears dysregulated, in that expression can be noted in many more brain cell types than under normal conditions. Inflammation also generates other secondary signals such as multiple cytokines and chemokines in the brain, which facilitate the generation of an immune response. TNFSF/TNFRSF signaling in the brain may therefore have a neurological-immunological threshold that can be crossed by the right combination of early immunological signals, such as the generation of multiple cytokine (interleukins, interferons, TNFSFRLs) and chemokines. Providing such signals are absent, the brain responds in a neurological context to TNFSF signaling. Indeed, direct administration or increased vector-driven expression of several TNFSFs fails to generate an immunological response *in vivo*. As evidence of this, intracortical overexpression of murine FasL (by FasL lentivirus injection) at PD4 does not induce neuronal apoptosis over the next 5 days, despite extensive and dense Fas expression on cortical, hippocampal and neocortical neurons (Zuliani et al., 2006).

Intrinsic factors include neurological cell-type specific responses to the cytokines, which may differ dependent on the developmental stage of the brain. For example, neuroglia and neurons constitutively producing TNFSF members may view this expression as neurological if they are normally produced at low levels by self and have restricted local expression. Partially supporting this model, Akassoglou et al. (1997) have shown that mice, in which transmembrane-associated TNFα is overexpressed in neurons, appear normal whereas over-expression in astrocytes induces severe neurological disease. This response can change over time. In the Zuliani study (2006), isolated neonatal neurons became sensitive to FasL mediated apoptosis following 6 days of culture, suggesting that the internal signaling pathways responding to Fas ligation changed during that time. In the case of TNFSF with alternative receptors such as TNFα (TNFR1/TNFR2) and CD40L (CD40 type I/II), the ratio of receptors appears to be a primary determinant of cell death versus cell survival (Yang et al., 2002a; Hou et al., 2008). Finally, neurological and immunological TNFSF signaling might also be discriminated by differences in the structure of TNFSFR members. For example, several DR3 mRNAs are generated in the brain, whose alternative expression could potentially be utilized to discriminate neurological and immunological signaling (Harrison et al., 2000; Wang et al., 2001).

Together, this complex web of factors results in the brain utilizing TNFSF members to help regulate cellular responses, while restricting the inflammatory responses to those members in the brain. Individual TNFSF/TNFRSF thresholds are also likely to be modified by other factors, such as the age and stage of development and in the case of the fetus, maternal status. Such a process might allow the brain to respond in a neurological context in the fetus and newborn, where homeostatic TNFSF/TNFRSF signaling is higher, thus contributing to correct brain formation, whereas in the adult with sparse homeostatic TNFSF/TNFRSF expression, similar signaling might be viewed as inflammatory. The extent to which neurological and immunological TNFSF/TNFRSF signaling interact, remains unclear, but there is evidence that immunological elevation of inflammatory cytokines can induce altered neurological responses (Feldman et al., 2008; Boksa, 2010).

The neurological role of FasL and its receptor

FasL and Fas signaling in the brain provides an interesting example of how the role of these molecules is extremely tissue dependent. Within the peripheral immune system, FasL/Fas signaling is critically used to modify cell fate and drive contraction of peripheral lymphocyte populations following immune responses by triggering apoptosis (Green et al., 2003; Strasser et al., 2009). In the brain, however, FasL (CD95L) and Fas (CD95) facilitate

neuronal branching during early pre- and post-natal development and in the adult (Matsuyama et al., 1994; Bechmann et al., 1999) are important for the process of neuron renewal by facilitating immature neuron generation from neuronal stem/precursor cells (NSCs) (Zuliani et al., 2006; Ruan et al., 2008; Corsini et al., 2009). The number and complexity of neuronal (axonal and dendritic) branching of embryonic (ED15) hippocampal neurons is extensively increased following Leucine-Zipper (LZ)-CD95L treatment, which can also induce short bursts of neurite motility (Zuliani et al., 2006). Similarly, axonal branching of ED15 Wt hippocampal neurons can be increased by co-culture with sources of endogenous FasL, such as normal hippocampi (with high-density cortical cultures), but branching can be rapidly inhibited by addition of anti-FasL neutralizing mAb (Zuliani et al., 2006). Consistent with the mandatory requirement for FasL/Fas signaling for optimal neuronal branching, neonatal (PD5) Fas (lpr) or FasL (gld) deficient mice display notable reductions in neuronal synaptic density due to thinning and irregular simplification of dendritic pyramidal neuron branching throughout the brain (Sakic et al., 1998; Zuliani et al., 2006). Moreover, young Fas^{KO} mice have a smaller brain (primarily due to retarded cerebral cortex and cerebellum growth) before the onset of lymphoproliferative disease (Sled et al., 2009), supporting the notion that neurological Fas signaling drives brain neuronal network complexity. Importantly, these Fas and FasL dependent neuronal changes are likely to be immunologically-independent, as they are present within days of birth and occur in the absence of inflammation. That normal behavior requires a high degree of neuronal complexity driven by Fas signaling, is further highlighted by the reported behavioral deficits of young MRL-Fas^{KO} mice (pre-lymphoproliferative diseased), including poor taste aversion, reduced responsiveness to palatable stimulus, altered activity responses to novel-objects, altered motor skills, lower anxiety, depression-like behavior, and lower startle responses to acoustic and electric shock tests (Grota et al., 1987; Sakic et al., 1994a, b; Nielsen and Crnic, 2002; Gao et al., 2009).

Self-renewing NSCs/neural precursor cells (NPCs) are critical for the formation and maintenance of the brain throughout life and can alternatively differentiate into glial, oligodendrocyte and neuronal cell populations (Corsini et al., 2009; Landgren and Curtis, 2011). In the adult mouse brain, signaling by Fas also appears to impel and regulate immature neuron replacement from NSC/NPC populations, as Corsini et al. (2009) have reported that the majority of Fas^{+} cells within the adult SVZ and hippocampus mouse are phenotypically and functionally NSCs/NPCs, which undergo neurogenesis and differentiation following the reception of FasL signaling. Amongst several demonstrations, the authors forced lentiviral expression of FasL in the normal mouse brain, inducing the formation of new immature neurons in regions associated with vector delivery. Furthermore, neuronal regeneration and behavioral memory function following neuronal stem cell transplantation, is heavily impaired in the absence of stem cell Fas expression in a global ischemia mouse model, which suggests that the rate of neurological repair is limited by the number of Fas^{+} neuronal stem cells present in the brain (Corsini et al., 2009). This report follows on from earlier observations that adult rodent NSCs/NPCs express Fas but appear resistant to FasL mediated apoptosis (Ceccatelli et al., 2004; Tamm et al., 2004). In contrast, treatment of newborn murine NPCs (PD4) with FasL, does not appear to induce neurogenesis *in vitro*; rather FasL/Fas signaling induced expression of the anti-apoptotic gene Birc3 and facilitated precursor cell survival, suggesting that the neurological role of Fas changes with age, or might be dependent on cell source and culture differences (Knight et al., 2010). Irrespective, the loss of such Fas dependent repair processes may explain why aging adult FasL and Fas deficient mice suffer extreme neuropathology. In this regard, it would be interesting to examine whether the neuropathology of aging Fas deficient mice (*lpr*) could be significantly ameliorated by restoration of Fas expression to cells of the neuronal stem cell lineage and their progeny.

So how does the Fas signal enhance neuronal survival, neuronal branching and neuronal differentiation from the same receptor complex and why does one single function tend to dominate over others? Collated evidence from the few studies available suggests that Fas signals different functions through distinct intracellular signaling pathways in the brain although how this process is regulated to affect age and cell type specific effects remain unknown. For example, adult stem cell neurogenesis is induced by FasL/Fas induction of PI3-kinase and pp60-src kinase activation, in the absence of apparent FADD recruitment (Corsini et al., 2009), although such signaling has been reported to induce ERK activation (Tamm et al., 2004). Enhanced neuronal precursor survival induced by FasL/Fas signaling, results from upregulation of anti-apoptotic Birc3 (cIAP-2) protein expression following growth factor withdrawal *in vitro* (Knight et al., 2010). In comparison, induction of neuronal growth and branching by Fas is signaled through a unique cytoplasmic membrane proximal domain (MPD) which facilitates recruitment of ezrin, stimulates GTPase Rac1 activation, and drives cytoskeletal rearrangements in a process again independent of FADD or Fas-DD involvement (Ruan et al., 2008). In contrast, intracellular Fas signaling involving traditional FADD recruitment via the DD and DISC activation in the brain appears coupled with neurological cell death, which is evidenced in lysates from ischemic brains with apoptosis (Corsini et al., 2009).

It should be noted that neurological defects present in aged lpr (Fas^{KO}, only 10% normal expression) and gld ($FasL^{KO}$) mice, have both an immunological and neurological etiology. As they approach adulthood, Fas^{KO} and $FasL^{KO}$ mice develop extensive peripheral autoimmune disease, followed by the acquisition of neuropathy characterized by extensive inflammation (Ma et al., 2006), accelerating neuronal apoptosis and depletion, brain atrophy, and behavioral degeneration (Sakic et al., 1992, 2000a,b, 2002; Watanabe-Fukunaga et al., 1992; Takahashi et al., 1994; Ballok et al. 2003a, 2004a; Anderson et al., 2006; Ma et al., 2006; Sled et al., 2009). The neuronal effect of aberrant Fas/FasL expression has been predominantly studied on mice of the MRL-lpr background, which spontaneously develop age-dependent autoimmune disease similar to human autoimmune systemic lupus erythematosus (SLE) combined with lymphadenopathy (Sakic et al., 2002). This neurological decline, apparent in aging Fas^{KO} mice, is immunologically driven as peripheral inflammation and brain pathology are co-ordinately linked, and immunosuppressive therapy inhibits the progression of neurological and behavioral disorders (Sakic et al., 1995, 2000a; Farrell et al., 1997; Szechtman et al., 1997; Ballok et al., 2004b; Stanojcic et al., 2010; Williams et al., 2010). Behavioral disorders noted in these aged Fas^{KO} mice include: reduced movement, poor crossbeam travel, increased timidity, poor novelty environment exploration, reduced open field exploration, altered water maze responses, altered emotionality, altered motivation, impaired learning, reduced taste sensory function, reduced aggressiveness and spontaneous scratching behavior as well as other cognitive and sensorimotor deficits (Grota et al., 1987, 1989; Sakic et al., 1992, 1993, 1994a, 1996, 1997, 1998, 2002; Ballok et al., 2003b; Umeuchi et al., 2005). Apart from structural defects, aberrant neurotransmitter (e.g., serotonin, dopamine and norepinepherine) expression has been noted in the cortex and hippocampus of disease afflicted adult mice and is thought to be associated with behavioral change (Sakic et al., 2002). However, further experiments are required to assess the neurological role of FasL/Fas signaling in the adult brain in the absence of the peripheral inflammation present in Fas^{KO} and $FasL^{KO}$ mice. In this regard, Corsini et al. (2009) generated mice with normal immune system expression of Fas, but deficient in the neuronal expression of Fas (CD95floxNesCre+mice), and found that such animals had defective working memories and altered neurological behavior in the absence of inflammation. Not only does this evidence indicate that continued Fas expression is required for normal brain function in the adult rodent, but it also raises the possibility that some of the neurological defects observed in adult FasL/Fas^{KO} mice may be due to inherent neurological defects.

The neurological role of TNFα and its receptors

Of all TNFSF members known today, the neuronal functions of TNFα and its two receptors, TNFR1 (p55) and TNFR2 (p75), have been the most intensively studied due to their early discovery and potential role in brain pathology. To date, TNF receptor signaling has been implicated in neurological roles as diverse as regulating neuronal precursor development (Johansson et al., 2008), regulating neuronal lifespan (Yang et al., 2002b), modulating neuronal synapse strength (Stellwagen et al., 2005), and directly modulating neuron excitability (Cunningham et al., 1996).

Like Fas, TNFR signaling can drive neuronal precursor/stem and immature neurons to differentiate and proliferate *in vitro*, provided such cells are isolated from developmentally young animals. Not only does this suggest that TNFα plays a role in early brain development, but it implies that the renewal properties of such cells change with age. Both embryonic rat (hippocampal) and neonatal mouse (SVZ) NPCs stimulated with TNFα, undergo neurogenesis and maturation into immature neurons in response to TNFR1 signaling (Kajiwara et al., 2005; Bernardino et al., 2008). Similarly, TNFα treatment can induce the expansion of immature cerebellar Purkinje neurons, but only providing they are isolated from mice prior to ED17, with older neurons surprisingly refractory to this process (Oldreive and Doherty, 2010). Conflictingly however, TNFR signaling expression on neuronal stem/progenitor cells (Sheng et al., 2005) has also been shown to facilitate gliogenesis and suppress NPC proliferation and neurogenesis. For example, differentiation of human NPCs with TNFα, decreases neuronal differentiation and leads to increased astroglia generation *ex vivo* (Johansson et al., 2008). Furthermore, diminished striatal and hippocampal NPC proliferation *in vivo* is also observed following direct intra-brain perfusion of TNFα-specific blocking antibody after experimental stroke induction in the adult rat (Heldmann et al., 2005), and proliferation in the dentate gyrus of adult mice can also be reduced 7-fold by systemic administration of TNFα (Seguin et al., 2009). Certainly, TNFR signaling is redundant for gliogenesis as $TNFR1^{KO}$, $TNFR2^{KO}$ and $TNFR1/2^{KO}$ mice have normal numbers of brain microglia (Iosif et al., 2006), so why have such variable responses of NPCs to TNFα exposure been noted? Apart from differences in cell source, isolation and culture methods, Keohane et al. (2010) proposed that the timing of TNFα encountered by NPCs during their development, may be the key determinant of whether neurogenesis or gliagenesis is favored. Intriguingly, embryonic rat NPCs exposed to TNFα undergo neurogenesis normally, but if TNFα treatment is given when NPCs have finished proliferating during their differentiation phase, then the formation of new neurons is suppressed (by upregulated Hes-1 expression) and the generation of new astrocytes is favored (Keohane et al., 2010). Further experiments will be required to clarify these events in greater detail and how they are influenced by constitutive TNF production by other brain cell populations (Williams et al., 1995; Becher et al., 1996; Schwartz et al., 1998; Dziegielewska et al., 2000).

TNF/TNFR signaling may also regulate neuron migration, positional placement and modulate neurite outgrowth *in vivo*. TNFα treatment of newborn mouse neuronal SVZ cultures can induce growth-cone and neurite-like projections within hours in a process involving SAPK/JNK pathway (MAP-kinase) activation, triggered by TNFR1 despite TNFR2 expression (Bernardino et al., 2008). Consistent with this observation, pyramidal hippocampal neurons (CA1, CA3) in the newborn mouse have stunted apical dendrite growth and develop less complex dendritic branching in the absence of continued TNFα expression *in vivo* (Golan et al., 2004). In the periphery, sensory neuron axon growth in an experimental muscle innervation model in adult mice, also appears to be TNFα dependent (Hayashi et al., 2008). Intriguingly, Hattori et al. (1993) have also shown that TNFα can induce fibroblasts to produce several growth factors, including NGF, which can drive

neurite outgrowth and branching in embryonic chick sympathetic neurons. This is particularly interesting given that TNFα treatment of hippocampal neurons (and astrocytes) from the embryonic rat induces rapid surface upregulation of $p75^{NTR}$ NGF receptor (Choi and Friedman, 2009) raising the possibility of a TNFα-NGF-neurogenesis pathway. In contrast to these reports, Neumann et al. (2002) have shown that TNF-α can elicit reductions in the neurite length and branching of primary embryonic mouse hippocampal neurons in a process driven by TNFR activation of the GTPase RhoA signal pathway. Furthermore, in the same study, it was found that TNFα gene expression and secretion could be rapidly upregulated in astrocyte-enriched glia cultures *in vitro* following IFNγ treatment and that neurons cultured under these conditions also underwent neurite regression. Whether the reported differences in TNFα driven neurite growth reflect differences in cell source and culture conditions, remains unclear (Golan et al., 2004), although it would be interesting to examine whether the neurite regression observed by Neumann et al. (2002) was reflective of the induction of TNFα mediated neuronal apoptosis, as observed during inflammation. These collective data suggest that TNFα signaling is a key determinant of neuronal and glial cell differentiation, but that the relative effect of TNFα signaling is likely to be dependent on local cytokine concentrations, the relative expression of TNFR1 and TNFR2, the region of the brain the neuronal precursors are derived from and the age and species the precursors are isolated from.

Mature astrocyte differentiation and development can also be driven by TNF signaling, although this property appears to be age dependent. Low level TNFα stimulation of fetal astrocytes can induce adhesion molecule (E-selectin, VCAM-1 and IAM-1) and growth factor (CFS-1) expression, but does not affect their proliferation or apparent morphology (Hurwitz et al., 1992; Lee et al., 1993; Moretto et al., 1993). In contrast, TNFα treatment of adult human astrocytes can induce proliferation via TNFR1, indicating that TNF-mediated astrocyte proliferation may be age dependent (Barna et al., 1993; Lee et al., 1993; Moretto et al., 1993). Adult bovine astrocytes also proliferate in response to TNFα treatment *in vitro* (Selmaj et al., 1990). Primary rat astrocytes, moreover, express TNFR1 and low levels of TNFR2, which can be quickly upregulated by TNFα treatment in a positive feedback loop (Dopp et al., 1997; Lung et al., 2001). Such a feedback loop is likely to be operational at very early developmental stages in mammals, as newly formed astrocytes derived from murine embryonic NPCs upregulate and express both TNF receptors (Keohane et al., 2010).

Apart from inducing complex morphological changes, TNFα can also directly modulate the lifespan of mature and adult neurons in a process dependent on ligand concentration and the relative balance between TNFR1 and TNFR2 expression (Fontaine et al., 2002; Yang et al., 2002a). Whereas low level TNFα concentration and signaling through both TNF receptors favors neurological responses, higher TNFα levels induce apoptosis primarily through TNFR1 activation (Yang et al., 2002b; Bernardino et al., 2008). In this regard, strong TNFR1 signaling appears to induce neuron apoptosis via downstream NF-κB activation, whereas strong TNFR2 signaling appears to promote cell survival via p38-MAP kinase expression (Yang et al., 2002a; Bernardino et al., 2008). Thus, murine embryonic hippocampal neurons deficient in TNFR1 are resistant to TNFα mediated apoptosis, whereas TNFR2 deficient neurons are more susceptible (Yang et al., 2002a). Consistent with this, Fontaine et al. (2002) have also reported that TNFR1 signaling can induce neuronal cell death, through upregulation of PI3 kinase and protein kinase B (Akt) activity, whereas neuronal TNFR2 signaling appears protective in a retinal ischemic model of neurological damage. Blockade of rat cortical neuron TNFR2 signaling has also been shown to promote NF-κB activation, decrease the neuronal Bcl-2/Bax ratio and promote cell death (Patel and Brewer, 2008a). Not surprisingly, high level expression of both TNF receptors or a failure to differentially upregulate TNF receptors in neurons, appears to increase neuronal sensitivity to apoptosis mediated directly by TNFα (Patel and Brewer, 2008b).

TNF stimulation can also serve to modulate neuronal excitability, increase synaptic strength and facilitate synaptic plasticity (Shibata and Blatteis, 1991; Beattie et al., 2002; Stellwagen et al., 2005). TNFα treatment of astrocytes (Koller et al., 1996) and hippocampal pyramidal neurons (Ogoshi et al., 2005) can also lead to a slow but sustained increase in intracellular Ca^{2+} and cell membrane depolarization, which may play a role in regulating local ion and neurotransmitter concentrations. TNFα, expressed by glial cells, can also enhance neuronal excitability and inter-neuronal synaptic strength by rapidly increasing neuronal synaptic AMPA receptor expression via TNFR1 signaling (Beattie et al., 2002; Ogoshi et al., 2005; Stellwagen et al., 2005). In addition, TNFα may also facilitate hippocampal neuron activity by downregulating GABA (A) receptors, which are the primary mediators of hippocampal fast inhibitory neuronal signaling (Stellwagen et al., 2005).

In contrast to these reports, high level or sustained TNFα signaling may serve to dampen neuronal signaling. Balosso et al. (1995) have shown that intra-hippocampal injection of TNFα can inhibit kainic acid induced seizures via TNFR2 signaling (Balosso et al., 2005). Similarly, long-term potentiation (LTP) in the rat hippocampus can be substantially inhibited by TNFα (Butler et al., 2004). While TNFR usage was not specifically examined in this process, the inhibition of neuronal LTP was associated with increased p38MAPK phosphorylation in the granule cells of the hippocampal dentate gyrus, suggesting that inhibition of neuronal signaling was also TNFR2-mediated. *Ex vivo* experiments have shown that TNFα can inhibit synaptic-transmission and LTP in hippocampal rat brain slices following sustained incubation (Tancredi et al., 1992; Cunningham et al., 1996) and can also induce long-term neuronal depression limiting neuronal signaling in murine hippocampal slice experiments (Albensi and Mattson, 2000). *In vitro* experiments, examining how TNF might be affecting neuronal signaling, have shown that it can modulate membrane Ca^{2+} channels and neurotransmitter receptor expression (Ogoshi et al., 2005) and modify voltage-gated calcium/sodium channel currents, indirectly affecting potassium membrane conductance (Diem et al., 2001; Czeschik et al., 2008). Morover, studies by Balosso et al. (2009) indicate that differential TNFR expression on hippocampal neurons is important for normal function of the hippocampal rat glutaminergic system, with TNFR1 signaling likely induced and TNFR2 signaling likely repressed (Balosso et al., 2009). Importantly, Balosso et al. (2009) also found hippocampal neuronal glutamate receptor expression was dependent on relative TNFR expression, as $TNFR1^{KO}$ mice were found to have decreased levels of GluR3 and NR1 glutamate subunits, whereas $TNFR2^{KO}$ mice have increased expression of the GluR2, GluR3, GluR6/7 and NR2A/B glutamate receptors.

Endogenous TNFα expression in the brain has been implicated in modulating slow-wave sleep in humans (Shoham et al., 1987). Similarly, TNFα can also induce non-rapid-eye-movement sleep (NREM) and decrease REM sleep following intracerebroventricular administration into rabbits at high doses (Kapas and Krueger, 1992). Consistent with this, $TNFR1^{KO}$ mice have shorter dark NREM and daylight REM sleep (Baracchi and Opp, 2008) and TNF expression in the adult rat brain appears diurnally regulated (Cearley et al., 2003). Furthermore, intracerebroventricular administration of anti-TNF mAb can also suppress NREM sleep in rats and rabbits (Takahashi et al., 1995a) and treatment of rabbits with a soluble TNF binding protein can impair NREM and REM sleep (Takahashi et al., 1995b, 1996a,b). In addition, intravenous administration of TNFα was found to disturb hippocampal theta wave patterns in cortical EEG monitored conscious rabbits and gallamine-immobilized cats (Kurumiya et al., 1990).

Mice with altered TNF/TNFR expression have been intensely studied and have been shown to have a variety of altered post-natal traits and behaviors, indicating that TNF and its receptors are essential for normal adult cognitive function in mammals (Baune et al., 2008). $TNFα^{KO}$ mice pups (P2-10) have normal locomotion and balance, but exhibit significantly

more rapid development of righting reflexes during the same period (Golan et al., 2004). Adult TNFα^{KO} mice exhibit altered open field test behavior, reduced learning/retention in novel object testing, reduced spatial learning and reduced cognitive function (Golan et al., 2004; Baune et al., 2008). Both TNFR1^{KO} and TNFR2^{KO} mice have altered forced swim test responses (Simen et al., 2006), increased exploration/activity in holeboard tests (Quintana et al., 2007), reduced spatial learning and partially reduced cognitive function (Baune et al., 2008) although they exhibit normal locomotor behavior (Kapas et al., 2008). More selectively, adult TNFR1^{KO} mice have normal anxiety but decreased fear conditioning responses (Simen et al., 2006) whereas TNFR2^{KO} mice have hedonistic sucrose consumption responses (Simen et al., 2006).

Several studies have also suggested that TNFα may be behaviorally depressive, consistent with the hypothesis that this ligand is neuromodulatory in humans (Simen et al., 2006) as suggested for rodents (Kurumiya et al., 1990). Consistent with this, depression associated with human disease, such as psoriasis and Crohns disease, is attenuated following administration of TNFα blocking medication such as etanercept (Feldman et al., 2005; Tyring et al., 2006; Krishnan et al., 2007) and infliximab (Lichtenstein et al., 2002; Feldman et al., 2008; Tookman et al., 2008; Iglesias et al., 2009). In mice, high dose TNFα administration in early trials have also been reported to reduce locomotion and induce behavioral change such as altered body position and eyelid droop which is associated with depression (Kurumiya et al., 1990).

The neurological role of TL1A and DR3

Amongst the TNFRSF, DR3 shows the highest homology to TNFR1, has a defined role in inflammatory disease models (Bull et al., 2008; Fang et al., 2008; Meylan et al., 2008; Pappu et al., 2008; Takedatsu et al., 2008) and utilizes much of the same downstream proximal signaling proteins to drive immunological signaling (Wang et al., 2001; Migone et al., 2002; Wen et al., 2003). In mice, TL1A has been identified as the sole DR3 ligand, whereas in humans, TL1A can also bind Decoy receptor 3 (DcR3) to potentially influence TL1A-DR3 signaling events (Migone et al., 2002; Bossen et al., 2006).

Although the high level of DR3 receptor mRNA expression in the mouse (Wang et al., 2001), rat (Harrison et al., 2000), and human brain (Harrison et al., 2000) initially suggested that DR3 may have a neurological function, this hypothesis was only confirmed when DR3^{KO} mice were generated, which displayed severe neurological disorder. Postnatal DR3^{KO} mice acquire a progressive neurological disease involving a rapid decline in motor control function and exhibit behavioral abnormalities (Twohig et al., 2010). This disorder is usually evident by 24 weeks of age, is sex-independent and 100% penetrant (Twohig et al., 2010). Apparent neurological disorder in DR3^{KO} mice is characterized by body tremor, dyskinesia, rapid and random head movement, disorientation, impaired balance, abnormal gait and panic responses, which can be augmented by environmental stimuli such as simple handling or bedding changes (Twohig et al., 2010).

The source of the abnormalities in DR3^{KO} mice, which provide evidence for the normal neurological function of DR3 in the brain, appear two-fold: aberrant neural pathway maintenance and altered neurotransmitter expression. Axonal retrograde tracing studies demonstrated that, in the absence of DR3, 25% of all neuronal connections between the striatum and cortex are progressively lost by old age (Twohig et al., 2010). It was hypothesized that cortical TL1A production by astrocytes stimulates the maintenance of interneuronal contact with adjoining striatal dopaminergic or serotonergic neurons (Twohig et al., 2010). Although the exact mechanism remains elusive and requires further investigation, TL1A/DR3 may contribute to neuronal axon growth, dendrite formation and/

or extension as found to variable extents for FasL/Fas (Zuliani et al., 2006), GITR/GITRL (O'Keeffe et al., 2008), TNF/TNFR (Golan et al., 2004), and p75NTR (Salama-Cohen et al., 2005). Another intriguing possibility is that TL1A/DR3 signaling may increase neuronal excitability, such as has been found for TNFα (Beattie et al., 2002; Stellwagen et al., 2005). As a by-product, TL1A may induce the formation of new dendrites and synapses, or contribute to the stabilizing of pre-existing neuronal networks. An absence of either process would be expected to result in cortical-striatal pathway decline. However, DR3 expression does not appear to be required for the generation of new neurons and does not appear to modify neuronal lifespan *in vivo* (such as is observed with Fas, TNFR1, TNFR2, CD40 and $p75^{NTR}$ deficient animals), as $DR3^{KO}$ mice have normal numbers of proliferating, non-proliferating and apoptotic neurons (Twohig et al., 2010).

Like Fas^{KO} (MRL-lpr) mice (Sakic et al., 2002), $DR3^{KO}$ mice also exhibit dysregulated expression of the neurotransmitters dopamine and serotonin (Twohig et al., 2010). Relative to controls, aged $DR3^{KO}$ mice had increased levels of striatal dopamine (160%), DOPAC (168%, dopamine metabolite), HVA (150%, dopamine metabolite) and reduced levels of serotonin (24%) (Twohig et al., 2010). In the hippocampus, aged $DR3^{KO}$ mice also exhibited increased DOPAC (130%) and reduced noradrenaline (85%, NA) expression. Furthermore, the altered dopamine expression in these mice did not appear to be a failure of striatal dopamine metabolism, as the ratio of dopamine to dopamine metabolites and the expression of tyrosine hydroxylase (required for dopamine, DOPAC and HVA and NA production) appeared normal. Thus, the exact relationship between abnormal neuronal pathways, defective neurotransmitter expression and behavior still remains to be clarified in $DR3^{KO}$ mice. Nevertheless, $dopamine^{KO}$ and $serotonin\ receptor^{KO}$ mice also exhibit motor control and locomotion defects (Zhou and Palmiter, 1995; Lesch et al., 2003; Palmiter, 2008) implicating dysregulated striatal neurotransmitter expression as being a primary causative factor in the $DR3^{KO}$ mouse behavioral phenotype (Twohig et al., 2010).

Two papers have also suggested that changes to DR3 expression may have implications for neurological disease, as has been found for many other TNFSF receptors. Grenet et al. (1998) reported that DR3 protein expression was generally absent or low on human neuroblastoma lines due to simultaneous deletions of DR3 and TL1A coding sequence, and/or DR3 gene translocations to other chromosomes (Grenet et al., 1998). In addition, Newman et al. (2000) noted that increased neuronal expression of DR3 can be observed in the brains of aged humans with Alzheimer's disease, suggesting that it may be involved in disease pathogenesis (Newman et al., 2000).

The neurological role of $p75^{NTR}$

$P75^{NTR}$ was one of the first TNFSFR members without a DD demonstrated to be expressed by neurons and acts as a receptor for several non-TNFSF ligands such as the nerve growth factors NGF, brain-derived neurotrophic factor (BDNF) NT-3 and NT-4 (Johnson et al., 1986; Misko et al., 1987; Radeke et al., 1987; Ernfors et al., 1990; Hallbook et al., 1991; Lee et al., 1992; Rodriguez-Tebar et al., 1992). In the mammalian brain, $P75^{NTR}$ is expressed throughout life primarily on neurons (Hefti et al., 1986; Kordower et al., 1988; Mufson et al., 1989; Pioro and Cuello, 1990a, b; Mufson and Kordower, 1992; Chen et al., 1996; Hartig et al., 1998). $P75^{NTR}$ signaling is complex and has been shown to drive several opposing processes in neurons that are dependent on the cell context such as age, species and type. Understanding the various normal neurological roles of the low-affinity NGF receptor $p75^{NTR}$ has also been complicated by both the high number of $p75^{NTR}$ ligands and cross-talk from other receptors such as the high-affinity NGF receptor TrkA (Park et al., 2010).

Following activation, the P75^{NTR} may signal directly or indirectly via association with several proteins, to form the p75^{NTR}-NgR-Lingo-1 receptor complex, which binds the myelin inhibitory proteins Nogo-A, MAG (myelin-associated protein) and OMgp (oligodendrocyte myelin glycoprotein) with high affinity (Mathis et al., 2010), in effect making these *de facto* p75^{NTR} ligands (Liu et al., 2002; Wang et al., 2002; Yamashita et al., 2002; Park et al., 2005; Cafferty et al., 2010; Mathis et al., 2010). Intriguingly, myelin inhibitory protein binding by the p75^{NTR}-NgR complex does not prevent direct p75^{NTR} ligand binding (Wang et al., 2002; Yamashita et al., 2002). To further complicate this, most p75^{NTR} ligands can also mediate their effects through several additional non-TNFSF receptors, which have neurological effects; NGF for example can signal neurological events through both the p75^{NTR} and TrKA tyrosine kinase receptor (Casaccia-Bonnefil et al., 1999). Similarly, the myelin inhibitory proteins can bind and activate the high affinity PirB receptor to induce further neurological events (Atwal et al., 2008). Such complex signaling diversity is thought to explain the diversity of neuronal and cellular responses generated by p75^{NTR} apparent in the literature.

In brief, a primary neurological role of P75^{NTR} *in vivo* appears to be in suppressing neurite outgrowth signaled by myelin inhibitory proteins through the p75^{NTR}-NgR-Lingo-1 complex (Wang et al., 2002). Additionally in mice, NGF binding to P75^{NTR} can also inhibit the generation of new neuronal dendrites and facilitate the formation of inhibitory synapses by activating Notch and NFκB and suppressing the expression of the dendrite forming protein neurogenin 3 (Salama-Cohen et al., 2005, 2006). The studies by Salama-Cohen et al. (2006) also suggested P75^{NTR} signaling increased and supported the formation of hippocampal inhibitory GABAergic synapses, raising the possibility that P75^{NTR} may facilitate inhibition of synaptic activity in refractive neurons. This would be consistent with the report showing that long-term depression of synaptic firing in hippocampal slices of 2 weeks old mice is inhibited in the absence of functional P75^{NTR} signaling expression (Rosch et al., 2005).

Strong data supporting a role for p75^{NTR}-dependent axonal degeneration in determining and maintaining normal adult brain pathways *in vivo* have been provided by recent experiments in mice indicating that P75^{NTR} activation is an important mediator of inter-neuronal contact (Park et al., 2010). Elegantly, they demonstrate that inappropriate neural sprouting onto myelinated tracts results in myelin-mediated degeneration in the adult mouse brain *in vivo*. Examining basal forebrain ChAT^{+} neurons in adult mice, they found that axonal projections normally terminate at the myelin corpus callosum boundary. However, loss of p75^{NTR} expression resulted in significant axonal projection into the corpus callosum, as myelin contact failed to act as a regional elongation barrier by induction of axonal degeneration (Park et al., 2010). This process, therefore, explains the observations from Naumann et al. (2002) and others, which noted significantly dysregulated forebrain neuronal fiber positioning in several different strains and ages of p75^{NTR}mutant mice.

The p75^{NTR}-reliant neural degeneration noted by Park et al. (2010) was also found to occur through p75^{NTR} activation of the RhoA-pathway and caspase-6, which is consistent with p75^{NTR}-NgR-Lingo-1 receptor complex activation via myelin inhibitory ligands (Yamashita et al., 2005). Consistent with this hypothesis, NogoA/MAG/OMgp deficient mice have greater axon growth and locomotor activity following spinal injury (Cafferty et al., 2010). In addition, OMgp^{KO} mice have altered thalamo-cortical neural connectivity evidenced by extensive axon projection beyond the normal layer IV into layers II-III, although the behavioral significance of this remains unclear (Gil et al., 2010).

Myelin-dependent degeneration of p75^{NTR} expressing sympathetic neurons can also be rescued by increasing TrkA signaling or increasing intracellular cAMP, further

demonstrating the high degree of intracellular regulation (Park et al., 2010). Myelin-dependent septal neuron degeneration could be inhibited *in vitro* by BDNF under low-NGF conditions, supporting the hypothesis that $p75^{NTR}$ ligand binding also facilitates axon degeneration (Park et al., 2010). More distal to the brain, $p75^{exonIV}$ (complete $P75NTR^{KO}$) mice have also been shown to have aberrant anterior shifts in retinal axon termination in the anterior colliculus, indicating that this receptor is involved in axon guidance at a more refined level in the periphery (Lim et al., 2008). $P75^{NTR}$ signaling appears to be mandatory for maintenance of the peripheral sensory nervous system, as p75exonIVmice have abrogated skin sensory nerve fiber development and sympathetic innervation of the atria and subendocardium is largely abolished (Lee et al., 1992; Habecker et al., 2008; Lorentz et al., 2010). Similarly, p75exonIV have aberrant sympathetic and sensory innervations to the meningeal arteries, suggesting that the receptor is important for normal peripheral neuron axon target guidance (Kawaja, 1998).

$P75^{NTR}$ signaling can also promote the survival of injured neurons by activating TrKA and NF-κB pathways and stimulating expression of the anti-apoptotic proteins bcl-2 and bcl-xl (Bui et al., 2002; Culmsee et al., 2002). This may explain why $p75^{NTR}$ deficient mice have significantly impaired peripheral nerve regeneration and axon growth following injury (Song et al., 2009). Numerous studies have also demonstrated that neuronal NGF signaling sustains $p75^{NTR+}$ neuron survival in the adult forebrain, although whether this is due to either $p75^{NTR}$ signaling and/or TRK signaling remains unresolved. In this regard, some $p75^{NTR}$ signaling following NGF or BDNF binding appears to require independent co-signaling by TRK, suggesting that both pathways may act cooperatively (Ceni et al., 2010). Irrespective, intraventricular transplant of fibroblasts constitutively expressing human NGF can promote $p75^{NTR+}$ neuronal survival and drive cholinergic fiber extension in adult Rhesus monkeys following experimental forebrain injury (Emerich et al., 1994; Kordower et al., 1994). Similarly, intraparenchymal human NGF administration in unilateral-transacted rats prevented forebrain neuronal loss and triggered vigorous axonal cholinergic neuronal axonal sprouting (Tuszynski, 2000). Importantly, $P75^{NTR}$ cholinergic neurons numbers, which are lost during aging (~17%), can be restored by long-term lentivirus NGF gene delivery (Nagahara et al., 2009). To date, these $p75^{NTR}$-dependent neurological functions have not been reported to involve $p75^{NTR}$-NgR-Lin-go-1 receptor complex activity and the role of $P75^{NTR}$ in these processes remains unclear and requires further study.

Studies examining the structure of the brain in $p75^{III}$ mice, having only a partial $p75^{NTR}$ gene deletion, initially led to conflicting reports about the relative importance of this receptor in brain development and function, as results appeared to depend on the age, background strain, and the methodology employed (Van der Zee et al., 1996; Peterson et al., 1997, 1999; Yeo et al., 1997; Hagg, 1999; Ward and Hagg, 1999; Greferath et al., 2000a; 2000b; Naumann et al., 2002). For example, adult $p75^{NTRexonIII}$ mice have been reported to have altered inter-hemisphere neuronal fiber positioning, higher dentate granule and dentate molecular layer ChAT fibre density, but exhibit a 40% reduction in basal forebrain neuron numbers, 25% less basal forebrain volume, and significantly increased numbers of striatal neurons (Peterson et al., 1999). In contrast, early neonatal $p75^{NTRexonIII}$ (P6) have also been reported to have higher numbers of $ChAT^{+}$ medial septum basal forebrain neurons in the absence of normal $p75^{NTR}$ expression, but normal numbers of forebrain neurons and normal hippocampal cholinergic innervation in contrast to other reports (Ward and Hagg, 1999). However, it was later found that $p75^{NTRexonIII}$ deficient mice continue to express a shorter functional $p75^{NTR}$ isoform generated via alternative splicing as well. This, combined with inter-study differences in anatomical delineation of brain-regions and the discovery of considerable inter-strain variation in neuron number (von Schack et al., 2001; Naumann et al., 2002), explains many of the apparent conflicts between studies. More recently, mice have been generated, which are completely deficient in $p75^{NTR}$ receptor isoform expression

($p75^{exonIV}$). These mice have been shown to have 28% greater numbers of cholinergic medial septum neurons and altered neuronal fiber positioning at 2 weeks of age, indicating that $p75^{NTR}$ is a key regulator of forebrain neuron survival, as well as positioning, during development although this changes with age (Naumann et al., 2002). By 4 months of age, $p75^{exonIV}$ mice have fewer cholinergic forebrain neurons, although this difference becomes obscured in very late age (15 months) by the level of significant and variable forebrain neuronal loss in normal mice as well (Greferath et al., 2000a). Intriguingly, such age-dependent neuronal forebrain neuron loss in aged rats and humans has been suggested to be due to a progressive declining in NGF-$p75^{NGF}$ signaling with age (Greferath et al., 2000b; Tuszynski, 2000). Noticeably, cholinergic forebrain neurons also have diminished size in the absence of continued $p75^{NTR}$ expression in the adult mouse (Greferath et al., 2000).

Behaviorally, young adult $p75^{exonIII}$ mutant mice were demonstrated to have impaired spatial memory performance on the hidden water maze, inhibitory avoidance, altered motor activity, and aberrant habituation task performance associated with impaired cognitive sensorimotor activity and other neurological defects (Yeo et al., 1997; Peterson et al., 1999). Adult $p75^{exonIII}$ mice also display poor cage grasping skills and impaired thermal withdrawal reflex consistent with absent cutaneous sensory innervation (Lee et al., 1992). More recently, however, older completely $P75^{NTR}$ deficient ($p75^{exonIII/IV}$) mice have been shown to have superior spatial learning in the Barnes maze and exhibit greater behavioral stress responses in open field tests (Greferath et al., 2000; Barrett et al., 2010). The improved memory responses of $p75^{NTRexonIII/\ IV}$ have been suggested to reflect enhanced hippocampal function resulting from improved cholinergic basal forebrain neuron activity as evidenced by elevated hippocampal choline acetyltransferase (Barrett et al., 2010). In addition, Barret et al. (2010) have also suggested that the low hippocampal $p75^{NTR}$ expression in normal adult mice is likely to have only limited signaling influence relative to strong forebrain input, although this hypothesis remains to be formally examined.

The neurological role of TROY

Although recently discovered, TROY, like $p75^{NTR}$, appears to be most strongly expressed in the developing and adult mammalian brain and can inducing neuronal signaling via TRAF mediated NF-κB activation (Kojima et al., 2000; Hisaoka et al., 2003, 2006a,b; Shao et al., 2005; Trifunovski et al., 2006; Satoh et al., 2007). Importantly, TROY can also act as a co-receptor in the myelin-inhibitory protein receptor complex involving NgR and Lingo-1 to mediate multiple neuronal effects (Park et al., 2005; Mathis et al., 2010). In this regard, $p75^{NTR}$ and TROY appear to function as competing homologous proteins for the same receptor complex and are unique amongst TNFRSF members in that they appear to be responsible for mediating myelininhibition, although their primary cellular expression patterns in mice appear to be relatively differentially restricted (Park et al., 2005; Mathis et al., 2010). Indeed, the TROY/NgR/Lingo-1 complex is also capable of binding Nogo-A, MAG, or OMgp to induce downstream RhoA activation and myelin-dependent neuronal out-growth inhibition (Hisaoka et al., 1996; Park et al., 2005). In a neuronal differentiation model, TROY overexpression can also inhibit neurite outgrowth and may in part inhibit neuronal differentiation, possibly via NF-κB and JNK pathway modulation (Hisaoka et al., 2006a). Furthermore, Mathis et al. (2010) have reported that both TROY and $P75^{NTR}$ are expressed by embryonic neuronal precursors migrating to the cortical plate, suggesting either one or both receptors may be involved in controlling their subsequent final distribution in the brain, as this process is severely perturbed in Nogo-A deficient mice (Mathis et al., 2010).

No behavioral abnormalities have been reported in TROY deficient mice (Pispa et al., 2008), although extensive studies have not yet been conducted to examine brain

development, function and behavior. However, transgenic mice with NgR1 overexpression in forebrain neurons have normal motor control, but impaired locomotor learning skills as demonstrated in extended rotarod tests and impaired long-term special memory demonstrated by Morris water maze studies (Karlen et al., 2009). Whether the altered behavior of these mice reflects loss of TROY- or $p75^{NTR}$-dependent signaling in the brain, will require further investigation.

The neurological role of CD40L and CD40

Like many TNFSFRs, CD40 and its ligand, CD40L (CD154), have been proposed to be involved in several neuro-inflammatory processes (Calingasan et al., 2002; Shibata et al., 2003), but more recent data indicates that CD40/CD40L has homeostatic neurological functions by promoting adult neuron survival *in vivo*, which may have important implications for postnatal human brain function. In support of this, ligation of CD40 on primary murine neurons, can prevent neuronal apoptosis induced by serum withdrawal by activating the p44/32 MAPK and Ras pathways, maintaining anti-apoptotic Bcl-x_b expression, and inhibiting pro-apoptotic c-Jun N-terminal kinase (JNK) pathway activation *in vitro* (Tan et al., 2002). CD40 ligation can also prevent neuronal apoptosis following NGFβ withdrawal via similar pathways and promote the differentiation of medulla PC12 cells into neuron-like cells with enhanced neurofilament expression (Tan et al., 2002). More importantly, and as with $DR3^{KO}$ (Twohig et al., 2010) and Fas^{KO} (Ballok et al., 2003a) mice, $CD40^{KO}$ mice also exhibit progressive age-dependent neuronal changes in the structure of the brain, suggesting that continued CD40 expression is required for maintenance of normal adult brain structure and function (Tan et al., 2002). During adulthood, $CD40^{KO}$ mice exhibit increased numbers of apoptotic and dysmorphologic neurons in the hippocampus (particularly the dentate gyrus and pyramidal cell layer) and neocortex (particularly the focal areas) (Tan et al., 2002). Extensive neuronal cell loss is also evidenced by a dramatic 16% reduction in brain weight and a corresponding 185% increase in the size of the ventricle area between 6–16 months of age, decreased neurofilament expression and increased pro-apoptotic Bax protein expression (Tan et al., 2002).

Neurological deficits, including progressive neurological disease with an unexplained 80% mortality rate, have also been reported in select CD40L deficient humans (Bishu et al., 2009). However, these CD40L deficient patients were noted to have a variety of different ongoing complications derived from the X-linked hyper-IgM syndrome from which they suffer, complicating the interpretation of these results (Bishu et al., 2009). Behaviorally, the role of CD40L-CD40 signaling has not been well studied except during inflammation. Of interest, treatment of β-amyloid peptide overproducing transgenic mice (which suffer progressive Alzheimer's-like neuropathology) with anti-CD40L, improves spatial and non-spatial memory as assessed by standard water maze, radial arm maze and object recognition tests, suggesting that CD40 signaling may affect hippocampal function (Todd Roach et al., 2004).

Pretreatment of rat cortical neurons with CD40L has also been shown to enhance neurite outgrowth and synaptic function driven by macrophage-conditioned media (Shibata et al., 2003). More intriguingly, Tan and colleagues suggested that CD40 signaling might facilitate neuronal differentiation in postnatal mice in a process regulated in part by changes to CD40 isoform expression (Hou et al., 2008). In humans and mice, three CD40 isoforms are expressed in the adult brain, corresponding with a signal-transducing CD40 (type I), a C-terminal truncated isoform, non-signal-transducing CD40 (type II) and a soluble CD40 variant, the last two of which are thought to act as CD40 pathway antagonists (Tone et al., 2001; Hou et al., 2008). CD40 type I protein appears progressively upregulated in the brain (especially in the CA1 and cortical regions), whereas antagonist CD40 type II and soluble

CD40 decreased in the first few weeks following birth, corresponding with upregulation of neonatal brain development (Hou et al., 2008). Furthermore, similar CD40 protein expression changes can be noted in neuron-like N2a cells induced to neuronally differentiate by CD40L *in vitro* (Hou et al., 2008).

The neurological role of GITRL and GITR

Very little is known about the expression and functional role of GITR and GITRL in the mammalian brain, although neuronal signaling shall be discussed in this review in light of the revealing paper by O'Keeffe et al. (2008), indicating that GITR is neurologically functional in the peripheral nervous system. These investigators demonstrated that GITR signaling appears to be important for the promotion of NGF-induced neurite growth and ERK-1/ERK-2 activation in mice. Impairment of GITR/GITL signaling in cultured murine neonatal neurons (SCG-superior cervical ganglion), either by transgenic GITR deficiency or GITR-decoy fusion protein, leads to inhibition of NGF-promoted neurite growth characterized by reduced neurite length and branching (O'Keeffe et al., 2008). Furthermore, neuronal activation induced by GITRL overexpression in normal SCG neurons, or addition of soluble GITRL-IgG to NGF treated cultures, resulted in promotion in the size and complexity of neurite arbors. GITRL promotion of SCG neurite growth also appeared to be operational in a strictly defined developmental window, with neurons from PD1-3 mice being sensitive and ED18/PD5 cultures being refractory (O'Keeffe et al., 2008). Indeed, alteration to GITR and GITRL expression levels in ED18 and PD5 SCG neurons failed to reverse this apparent developmental insensitivity to axon extension, suggesting that the developmental window was determined by differences in downstream intracellular signaling pathways (O'Keeffe et al., 2008). As the final proof, $GITR^{KO}$ mice have a significantly reduced sympathetic SCG axonal innervation density directed towards the iris and nasal mucosa at birth (O'Keeffe et al., 2008). Furthermore, innervation failure appears to be due to defective axonal growth and branching, as $GITR^{KO}$ mice have normal numbers of SCG neurons when examined (O'Keeffe et al., 2008). Additional studies will be required to assess the neurological role of GITR expression in the human brain (Gurney et al., 1999).

The neurological role of other TNFSFR/L members

Several other TNFSFR/L members have been identified as being expressed in the mammalian brain, however the functional significance of this expression remains unknown. For example, mRNA of both ectodysplasin (EDA) and its receptor (EDAR) have been shown to be expressed in the brain of developing mouse embryos (ED10-12) by *in situ* hybridization (Pispa et al., 2003). EDA expression is found diffusely in the head mesenchyme, in the developing diencephalon, lateral ventricles, the hindbrain and the mid-hindbrain margin neuro-epithelium by immunohistochemistry (Pispa et al., 2003). Similarly, primary EDAR expression was found in the thalamus, mid-brain and lateral ventricles overlapping or adjacent to EDA expression (Pispa et al., 2003). EDA and EDAR are the first TNFSF/TNFSFR pairing for which an immunological role has not been described and appear to have a primary role in early tooth and hair formation (Kere and Elomaa, 2002; Laurikkala et al., 2002). EDAR signaling has been shown to regulate embryonic morphogenesis (Thesleff and Mikkola, 2002) with abnormal EDA/EDAR expression or loss-of-function mutations during embryonic development, leading to ectodermal dysplasia syndromes in both humans and mice (Srivastava et al., 1997).

Of interest, Rieger et al. (1999) have also reported that TRAIL expression can be found in human brain astrocytes, but not in neurons and non-neoplastic glia (Rieger et al., 1999). The expression of the TRAIL receptors DR5 and Trail-R3 (thought to be a DR5 decoy receptor) have been detected by northern blot in adult human brain tissue (MacFarlane et al., 1997). In

contrast, the expression of DR5 and MK (a TRAIL binding DR5 homolog) appear absent in the adult mouse brain (Screaton et al., 1997a; Wu et al., 1999). However, it will be important to generate and examine the brain development and function of TRAIL and TRAIL receptor deficient animals before a neurological role for these molecules can be ruled out.

Conclusions

Substantial evidence now exists of neurological roles for many TNFSF/TNFRSF members in the mammalian brain, but many important questions remain to be addressed. What are the mechanisms by which the brain delineates neurological and immunological signaling and to what extent do they influence each other? Can inflammatory TNFSF/TNFRSF signaling be altered to induce neurological signaling? What are all the neurological roles of newly identified TNFSF/TNFRSF members in the brain? What are the exact geographical and lineage expression patterns of the TNFSF/TNFRSF members and what is the mechanism by which this is regulated? Can TNFRSF signaling by individual members interact with others to modify or regulate different neurological processes? In this regard, it will be particularly important to examine brain development and function in mice with multiple TNFSF/TNFRSF gene disruptions. In addition, the generation of brain maps showing the geographical and lineage specific expression patterns of multiple TNFSF/TNFRSF members throughout development would also greatly assist in our understanding of the functional roles of these molecules in the brain. Finally, a greater knowledge of homeostatic TNFSF/TNFRSF expression and function is ultimately likely to benefit our understanding of human brain development, function and neurological disease especially where these processes occur in the absence of significant inflammatory processes.

Biography

From 1992–1996, Jason P. Twohig studied at the Australian National University and the John Curtin School of Medicine completing a BSc Hons (Immunology/Cytokine engineering) which explored the potential role of TNF family members in mammalian anti-viral vaccines. Between 1997 and 2001, he studied at Melbourne University completing a PhD (Veterinary Science) examining the dynamics of early T cell pool formation in mammals. In 2001, he joined the Sir William Dunn School of Pathology at Oxford University examining the role of dendritic cells in inflammatory bowel disease. From 2003, he have worked at the Cardiff University School of Medicine examining the role of DR3, and other TNF family receptor members, in brain function and adaptive immune responses.

Simone M. Cuff received her PhD in Immunology and Virology from the Australian National University before researching the immune response to cancer in the Institut Curie, Oxford University and Cardiff University. She is currently studying how the immune responses to vaccine vectors can affect the vaccination response at the School of Medicine, Cardiff University.

Dr. Audrey A. Yong graduated in medicine from St. Bartholomew’s Hospital, London in 1991. She began her postgraduate training in surgery at St. Mary, Hospital, London, achieving FRCS in 1996. She then trained in Radiology at St. Mary’s Hospital, London, and

was awarded FRCR in 1999. Her Consultant Appointment came in 2002 at the University Hospital of Wales, Cardiff, UK, where she remains a Consultant Radiologist.

Dr. Eddie C.Y. Wang was awarded a BA in Natural Sciences from the University of Cambridge in 1989 and a PhD in Immunology studying T cell responses to human cytomegalovirus from the same university in 1993. He spent the following 4 years as a Beit Memorial Fellow at the Imperial Cancer Research Fund, London, investigating the role of Death Receptor 3 (DR3) in T cell development. He was appointed a Lecturer at the University of Wales College of Medicine, Cardiff, Wales, UK in 2000, where he has remained until the present day. Currently, he is a Reader in the Department of Infection, Immunity & Biochemistry at the School of Medicine, Cardiff with two broad research interests: (i) immune modulation by herpesviruses and, (ii) the biology of DR3.

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Table 1

Expression patterns of select TNFSF/TNFRSF members in neuronal tissue in healthy mammals.

TNFRSF/TNFSF member	Species	Period of development[a]	Cell type	Region	Reference
Fas and Fas L	Mouse	ED15-18	Non-endothelial	Hippocampus, cortex, ventricular zone	French et al. (1996); Zuliani et al. (2006)
					Choi et al. (1999)
Fas and Fas L	Human	Fts 20-25 weeks	Astrocytes		Zuliani et al. (2006)
Fas and Fas L	Mouse	PD1	Neurons, oligodendrocytes	Hippocampus, cortical layers II, III and V	Knight et al. (2010)
Fas and Fas L	Mouse	PD4	Neural progenitors		Zuliani et al. (2006)
Fas and Fas L	Mouse	PD5 (peak)	Neurons	Hippocampus, CA2 and CA3	Zuliani et al. (2006)
Fas	Mouse	PD14	Endothelial	dentate gyrus, CA1	Park et al. (1998)
	Mouse		Neurons		Harry et al. (2008)
FasL	Mouse	PD21 (low)	Neurons	Scattered throughout	French et al. (1996)
Fas and Fas L	Mouse				Matsuyama et al. (1994)
Fas and Fas L	Mouse				Corsini et al. (2009)
Fas	Mouse	Ad (low)	Neural progenitors	Dentate gyrus, SVZ	Knight et al. (2010)
Fas and Fas L	Mouse	Ad (high)	Neural progenitors	Scattered throughout	Choi et al. (1999)
FasL	Human	Ad (high)	Astrocytes		Bechmann et al. (1999)
FasL	Rat	Ad (high)	Astrocytes		Bechmann et al. (1999)
FasL	Human	Ad	Neurons	Associated with blood vasculature	Bechmann et al. (1999)
FasL	Human	Ad	Astrocytes	Associated with blood vasculature	
TNF	Mouse	ED10-19			Yamasu et al. (1989)
TNF	Human	Fts 18 weeks	Astrocytes		Lee et al. (1993)
TNF	Sheep	ED30-lst trimester		Ventricular & Marginal zone, white matter	Dziegielewska et al. (1994)
TNF	Human	Fts	Astrocytes		Lee et al. (1993)
TNF	Human	Fts	Microglia		Williams et al. (1995)
	Rat	Fts	Glia		Schwartz et al. (1998)
TNF	Mouse	PD7 (Peak)			Yamasu et al. (1989)
TNF	Human	Ad	Microglia		Becher et al. (1996)
TNF	Rat	Ad		Throughout including cortex, hippocampus	Cearly et al. (2003)
TNFR1/TNFR2	Mouse	ED10-19		throughout including hippocampus and cerebellum	Neumann et al. (2002); Yang et al. (2002); Oldrieve et al. (2010)

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TNFRSF/TNFSF member	Species	Period of development[a]	Cell type	Region	Reference
					Keohane et al. (2010)
TNFR1/TNFR2	Rat	Fts	Neural progenitor cells	(reported to be TNF sensitive)	Hurwitz et al. (1992)
TNFR?	Human	Fts	Astrocytes	(reported to be TNF sensitive)	Moretto et al. (1993)
TNFR?	Human	Fts	Astrocytes		Sheng et al. (2005)
TNFR1/TNFR2	Human	Fts 8-10 weeks	Neural progenitor cells	Hippocampus	Kajiwara et al. (2005)
TNFR1	Rat	Fts ED16	Neurons	Hippocampus	Harry et al. (2008)
TNFR1/TNFR2	Mouse	PD21	Neurons primarily	Cerebellum	Oldrieve et al. (2010)
TNFR1/TNFR2	Mouse	Ad (high)	Neurons	Hippocampus	Iosif et al. (2006)
TNFR1/TNFR2	Mouse	Ad	Neurons	Hippocampus	Dopp et al. (1997), Iosif et al. (2006)
TNFR1/TNFR2	Mouse	Ad (low)	Neural progenitor cells	Throughout, especially hippocampus	Balosso et al. (2005)
TNFR2	Mouse	Ad	Neurons	Cortex	Patel et al. (2008)
TNFR1/TNFR2	Rat	Ad (10 months - high)	Neurons	Cortex	Patel et al. (2008)
TNFR1/TNFR2	Rat	Ad (24 months - high)	Neurons		Dopp et al. (1997)
TNFR1	Rat	PD6-15	Glia		Dopp et al. (1997)
TNFR2	Rat		Astrocytes		Dopp et al. (1997)
TNFR2	Rat		Oligodendrocytes		
DR3	Mouse	ED12-13 then downregulated before birth		Mesencephalic ventricle, midbrain, roof of neopallial cortex	Harrison et al. (2000)
		PD6-7 into			
		Ad			
		Ad		Throughout	
DR3	Mouse	Ad		Throughout including hippocampus, cortex	Wang et al. (2001)
DR3	Mouse	Ad	Neurons	Throughout including cortex, striatum, hippocampus and cerebellum	Twohig et al. (2010)
DR3	Human	Ad		Throughout including hippocampus, cortex	Newman et al. (2000)
DR3	Rat				Harrison et al. (2000)
TL1A	Mouse		Astrocytes		Twohig et al. (2010)
$p75^{NTR}$	Mouse	ED	Radial glial cells		Mathius et al. (2010)
$p75^{NTR}$	Human	Fts 14-20 weeks (high)	Neurons	Throughout including cerebellum, neocortex and hippocampus. Positional changes with development	
		Fts 22 weeks - birth (low)			

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TNFRSF/TNFSF member	Species	Period of development[a]	Cell type	Region	Reference
p75^{NTR}	Human	Ad (high)	Neurons	Primarily forebrain but in other places	Kordower et al. (2002)
		Ad (high)		Primarily forebrain and cerebellum	
p75^{NTR}	Mouse		Neurons		Salama-Cohen et al. (2005)
p75^{NTR}	Rat	Ad (high)	Neurons	Forebrain	Pioro et al. (1990); Hartig et al. (1998)
		Ad (high)		Primarily forebrain and cerebellum but in other places	Hefti et al. (1986)
p75^{NTR}	Human		Neurons	Primarily forebrain but in other places	Kordower et al. (1988); Kordower et al. (1994)
p75^{NTR}	Monkey	Ad (low)	Neurons		Mufsan et al. (1989, 1992)
p75^{NTR}	Human		Neurons		
TROY	Mouse	ED11.5-13.5	Radial glial cells, Neuroepithelial cells	Forebrain, mid brain- ventricular/subventricular zone, olfactory bulb, telencephalic neuroepithelium, dorsal neural tube	Kojima et al. (2000); Hisaoka et al. (2003, 2006a,b);Morikawa et al. (2008)
TROY	Mouse			Forebrain, hippocampus-dentate SVZ dentate gyrus	Hisaoka et al. (2006a)
			Radial glial cells	Molecular Layer	Hisaoka et al. (2006a)
TROY	Mouse	ED15.5-17.5		Hippocampal hilus, DG subgranular zone	
			Radial Glial/astrocyte	Cerebral cortex-microvascular associated	
			progenitors		
TROY	Mouse	Post-natal	Radial glial cells	Throughout including forebrain, hippocampus, striatum and cortex	Park et al. (2005)
			Neurons	Cortex and hippocamus	
TROY	Mouse	PD7-14		Forebrain, hippocampus, striatum, cortex, amygdale, thalamus, midbrain, cerebellum, olfactory bulb particularly rostral migratory	Trifunofski et al. (1996)
				stream and SVZ	
TROY	Mouse	PD28		Scattered throughout	Hisaoka et al. (2006a,b)
			Neuronal progenitor cells		
TROY	Rat	Ad		Scattered throughout cortex, hippocampus and striatum	
TROY	Mouse	Ad			Sotah et al. (2007)
TROY	Human	Aged Ad (high)	Neurons and astrocytes, most microglia		
TROY	Mouse	Ad	Astrocytes and glia		Hisaoka et al. (2006a,b)
CD40L	Mouse	Newborn/Ad	Microglia, Astrocytes	Scattered throughout whole brain	Tan et al. (2002)
					Calingasan et al. (2002)

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TNFRSF/TNFSF member	Species	Period of development[a]	Cell type	Region	Reference
	Mouse	Very Aged Ad	Smooth muscle, Endothelial cells, Microvasculature	Hippocampus, cortex	Calingasan et al. (2002)
			Neurons		Calingasan et al. (2002)
CD40	Mouse	Ad		Hippocampus, DG and pyramidal cell layer	Tan et al. (2002)
					Hou et al. (2008)
GITRL/GITR	Mouse	ED15-18	Sympathetic Neurons	No expression in the brain,	O'Keeffe et al. (2008)
GITRL/GITR	Mouse	PD1-P5		Strong expression in the peripheral neurotissues	
	Mouse	Ad			
GITRL/GITR	Human	? (very low)			Gurney et al. (1999)
EDAR	Mouse	ED10-12		Thalamus, mid-brain, lateral ventricles	Pispa et al. (2003)
EDA	Mouse	ED10-12		Diencephalon, lateral ventricles, hindbrain	Pispa et al. (2003)

[a]ED, embryonic day; PD, post-natal day; Fts, fetus; Ad, adult.