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The CNS Innate Immune System and the Emerging Roles of the Neuroimmune Regulators (NIRegs) in Response to Infection, Neoplasia and Neurodegeneration

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1. Introduction

The mammalian CNS relies upon the ancient, innate immune system, to provide defence against attack by pathogens (virus, bacteria, fungi and parasites) and the clearance of both neurotoxic proteins and apoptotic cells. The main function(s) of the CNS innate immune system can be summarised as the detection of "non self"(pathogens) and " altered self " (neurotoxic proteins and apoptotic cells), with their subsequent clearance, designed to facilitate tissue repair and rapid return to normal function. The failure to express an effective protective response to detect and remove a pathogen (non –self) prolongs the innate immune response and this is associated with autoimmunity, chronic inflammatory diseases (Multiple sclerosis) and neuro degeneration (Alzheimer's and Prion disease) (Hauwel et al., 2005 Griffiths et al., 2009). The failure to detect and clear apoptotic cells results in their accumulation and subsequent release of neurotoxic proteins and enzymes, contributing to excessive tissue damage (Griffiths et al., 2009).

2. The blood brain barrier and immuno privilege

Insects, have a brain lymph barrier, whereas, the vertebrate blood brain barrier (BBB) evolved 50-100 million years before the appearance of the adaptive immune system (Abbot 1995; Lowenstein 2002). For this reason, the CNS immune response against pathogens relies upon the ancient and highly conserved innate immune system that first appeared in limited form in the Agnatha, 500 million years ago and almost 100 million years before the emergence of the systemic adaptive immune system in bony fish. (Lowenstein 2002). The vertebrate type BBB, was therefore present, long before the adaptive immune system and this barrier provide some immunoregulatory control of the CNS response to pathogens (Abbot 1995; Lowenstein 2002).

Other protective physical barriers, are the choroid plexus between the systemic circulation and ventricular CSF (cerebro spinal fluid) and the specialized, ciliated ependymal (glia) layer, that lines ventricles containing the CSF(Martino et al., 2001). Both these epithelial layers express highly conserved receptors that are able to detect pathogens in the CSF and regulate intra CSF inflammation (McMenamin., 1999; Laflamme and Rivest 2001; Canova et al., 2006; Rivest 2009).

The presence of a BBB composed of endothelial cells linked by tight junctions and surrounded by astrocyte foot processes (Pachter et al., 2003) contributed to the development of homeostatic systems to preserve CNS electrolyte and hydrostatic pressure gradients (Abott 1995). To some extent, this also prevented infiltration into the brain by systemic cells (lymphocytes, myeloid related cells) of the more recent adaptive immune system and provided some evidence of immuno regulatory function. Once the vertebrate BBB had developed, the brain relied upon the resident glia and neurons (also perivascular cells and choroid plexus) to deliver the CNS immune response against pathogen invasion (Lowenstein 2002).

To reflect this function, the resident glial cells have been termed" amateur "innate immune cells, in contrast with the" professional" innate immune system cells such as macrophages, dendritic cells and natural killer cells (Hauwel et al., 2005).

3. The CNS innate immune response involves detection of " non self" and clearance of dangerous pathogens, neurotoxic proteins and apoptotic cells

The cells responsible for delivering the CNS innate immune response are microglia, astrocytes, endothelial cells, ependymal cells and to a lesser extent neurons (Rivest 2009). Of great importance, is the capacity of these cells to discriminate between" non –self"defined by pathogens and "altered self " (apoptotic cells and dangerous proteins)from "self " (host cells) (Takeuchi et al., 2010; Elward and Gasque 2003). This discrimination relies upon the expression by microglia and the other glia of ancient, highly conserved, pattern recognition receptors PRR (TLR, RLR, NRL) that are localized upon the cell membrane, within endosomes and also released in soluble form (Jane way 1992; Kawai and Akira 2010).

PRR, are able to detect unique, pathogen associated molecular patterns or PAMPs as represented by bacterial cell wall constituents, such as lipopolysaccharide (LPS). (Medzithov and Janeway 200). This property of the PRR is important for the danger theory as proposed by Matzinger; that while the immune system distinguishes between "self "and "non –self", it also must discriminate dangerous from non -dangerous signals (Matzinger 1994). Endogenous molecules such as S-100 proteins (Foell et al., 2007) and high mobility box group I (HMBG1) (Bianchi 2007; Castiglioni et al., 2011) are released during non -apoptotic cell injury and initiate host tissue inflammation: they are regarded as either "alarmins" or "danger signals "and are identified by the PRR of the innate immune system, because they express, damage associated molecular patterns or DAMPs (Klune et al., 2008; Biannchi 2007).

Apoptotic cells express a range of "altered self "molecules on their surface, so called apoptotic cell associated molecular patterns or ACAMPs (Elward and Gasque 2003; Gregory and Devitt 2004; Griffiths et al., 2009). The detection of " altered self" by PRR as defined by DAMPS and ACAMPs, results in the activation of signalling pathways composed of intra cellular adaptor proteins regulating the expression of pro inflammatory cytokines such as the interferons (INFα/β), interleukins (IL) and tumour necrosis factor (TNFα) (Griffiths et al 2009).

Scavenger receptors (SR), Mannose macrophage receptor (MMR), CD14, CD36, CD91(α2 macroglobulin or LRP low density lipoprotein receptor) and phosphatidylserine recepotor (PRS) are present on the host cell membrane or intracellular endosomes. These receptors are multifunctional because they detect PAMPS, ACAMPs and DAMPs to initiate engulfment and phagocytosis of pathogens or apoptotic cells (Stahl and Ezekowitz., 1998. Fadok et al., 2000 and b, Hanayama et al., 2002; Gregory and Devitt 2004; Mukhopadhyay et al., 2004.)

The resident cells of the CNS express two of the three complement pathways(CP) the classical and alternative, but not the lectin activated pathway (Gasque P et al., 2000; Morgan and Gasque 1996). The first complement component, C1q, functions as a PRR, a property shared with a wide range of other C lectins including, mannan binding protein (MBL) and the pentraxins; all these molecules are able to function as both opsonins and PRR capable of detecting PAMPS and ACAMPs. (Tenner AJ 1999; Lu et al., 2002; Thielens et al 2002; Ogden et al., 2005).

After binding to either an apoptotic cell (by detecting ACAMPS) or bacteria (through PAMPS), the opsonins provide a signal on a phagocytic cell that enhances phagcoytosis, either through activation of the complement C pathway or facilitating binding to a PRR such as the β2 integrin, CR3/CR4, receptors (Ehlers et al., 2000; Gasque et al 2000; Gasque 2004). Phagocytosis of opsonized pathogens, neurotoxic proteins and apoptotic cells by microglia and macrophages will promote a reduction in local inflammation (non -phlogistic response) stimulating the recruitment of stem cells from a distance niche and assisting tissue repair (Griffiths et al., 2009).

4. Regulatory pathways prevent an uncontrolled innate immune response; the Neuro immuno-regulatory molecules (NIRegs)

The uncontrolled activation of the innate immune response results in the production of neurotoxic factors and unregulated inflammatory cytokine release. These two factors contribute to any indiscriminate bystander damage and the amplification of underlying disease state. For this reason, the innate immune response must be regulated in order to prevent bystander neuron loss and an uncontrolled inflammatory response. There is now evidence of a group of neuro immuno regulatory (NIRegs) molecules, that by analogy are similar to T reg lymphocytes (Griffiths al., 2007; Hoarau et al., 2011). These T cells are responsible for regulating /controlling the innate immune response and for shaping the resident cells towards a protective phenotype. Several NIRegs, CD47 and CD 200, are capable of acting as “don’t eat me “signals allowing host cells to evade detection and phagocytosis by microglia and macrophages (Elward and Gasque 2003; Barclay et al., 2002; Brown and Frazier., 2001; Hoek et al., 2000). The Siglecs, a family of lectins, also detect cells expressing “don’t eat me” signals in the form of sialic acid containing molecules (Crocker and Varki 2005). Pathogens do not generally express sialic acid residues and the absence of sialic acids provides a “ non -self “ signal, sometimes referred to as an “eat me signal “and this is detected by lectins, including Siglecs, and complement proteins.

The CP is also strictly regulated by a series of complement regulatory proteins CRP (FH, CD55, CD46) preventing inappropriate activation and host destruction (Elward et al., 2005; Griffiths et al., 2009; Zipfel et al., 2009). Furthermore, components of the CP including C3a, are also capable of recruiting stem cells into areas of tissue damage and increasing growth factor expression, both facilitating tissue repair (Griffiths et al., 2010).

5. Toll like receptors (TLRs) are PRR with multiple roles in infection including pathogen detection and inflammatory response

The TLR are an ancient, highly conserved family of PRR, which belong to the type-1 trans membrane receptors. They are characterized by a cytosolic C-terminal signalling domain – Toll/interleukin -1receptor (TIR) required for intracellular signal transduction and terminal LRR(leucine rich repeats) domain that mediates the recognition of PAMPs (Kawai and Akira 2010). This family of PRR are vital for the detection of PAMPs, including cell wall lipoproteins and nucleic acids, derived from bacteria, viruses, parasites and fungi (Iwaski and Medhitov 2010).

TLR 4, or heterodimers TLR2-TLR1, TLR2-TLR6 and TLR5 (but notTLR3) binds to a ligand such as a PAMP or DAMP, the complex is internailized within the endosome and this triggers intracellular transduction pathways by recruiting the TIR interaction domain that forms multimers with, a number of adaptor proteins such as myeloid differentiation primary response protein, My D88, My D88 adaptor like (Mal, also TIR domain containing adaptor protein, TIRAP), TIR domain containing adaptor inducing IFN–γ(TRIF) and TRIF –related adaptor molecule TRAM. Activation of TLR by PAMPS recruits one of the above adaptor molecules and activates the My D 88 dependent pathway with NF- kB activation. An alternative signalling pathway following TLR binding to a ligand involves the activation of the TRIF –dependent pathway, with the induction of the type I interferon (anti -virus) response, with the expression of IFNβ and inflammatory cytokines (Netea et al., 2004 Creagh and O Neill 2006).

Mice deficient in the individual TRL negative regulatory proteins, such as zinc finger proteins, autophagy related molecules and ubiquitin are unable to regulate the inflammatory response subsequent to TLR ligand binding. This uncontrolled inflammatory response results in multi organ inflammation such as, chronic inflammatory bowel disease and auto immune arthritis. Conversly, MyD 88 deficiency reduces inflammation (Kwai and Akira 2010 for detailed discussion).

A detailed review of the intra cellular signalling pathways linked to TLR activation by viral nucleic acids, bacterial lipo proteins and other ligands, with subsequent inflammatory cytokine synthesis is outside the scope of this review, but see Takeuchi and Akira 2007; Iwaski and Medhitov 2010; Kawai and Akira 2010)

5.1 TLR act in combination with other PRRs and not always alone

Interestingly, TLR2, forms hetero dimers with TLR-1 and this combination is able to detect Gram negative bacteria, whereas the heterodimer TLR-2-TLR-6 combination recognizes Gram positive organisms. Further cooperation between TLR -4 and the SR co -receptors, CD14 and CD36, together with the C lectin receptor, dendritic cell –specific intercellular molecule -3 grabbing non –integrin (DC –SIGN), detects glucuronoxylmannans found on the cell wall of fungi (Kumar et al 2010).

5.2 TLR distribution in the CNS

Ten functional TLRs have been identified in humans, of these, nine are conserved in both humans and mice. In the human and mouse CNS, TLR 3, , TLR 7 and TLR 8 are located on the cell surface of neurons (Bisibi et al., 2002; Prehaud et al., 2005; Jackson et al., 2006), microglia (Alexopoulou et al., 2001; Olson et al., 2004; Jack 2005), astrocytes (Bsibi et al., 2001; Bisibi et al 2006 Farina et al., 2005; Rivieccio et al., 2006; Carpentier et al., 2007) ependyma and oligodendrocytes (Bsibi 2002). TLR 7 and 8 on microglia (Olson et al., 2004), astrocytes (Buchiet al., 2008) neurons (Ma et al., 2006), TLR 9 on microglia (Mc Kimme et al., 2006). Cells of the meninges, choroid plexus and circum ventricular organs are all exposed to the systemic circulation and express TLR 2 and TLR 4 (Lafalamme and Rivest 2001; Bowman et al., 2003; Laflamme et al., 2003;) see table1

TLR, 3 TLR7, TLR8 and TLR 9 are distributed within intracellular organelles, endoplasmic reticulum, lysosomes and endolysosomes so they are strategically placed to detect intra cytoplasmic viral nucleic acids, both RNA and DNA (Griffin 2003; Kumar et al., 2011). Conversly, TLR2, TLR5 and TLR 6, are present on the cell surface and detect various bacterial components (Kumar et al., 2011; Iwasaki and Medzhitov 2010)

TLRs11-13 have been described in neurons, astrocytes, ependymal and endothelial cells(Mishra er al., 2008). see table 1

5.3 TLRs; Innate immune response to bacterial infection

TLRs are expressed by glial and choroid plexus cells following bacterial infection (Bowman et al., 2003 Carpentier et al., 2008). TLR- 4 forms a complex with MD2 on the host cell surface and they provide the main Lipopolysaccharide (LPS), binding site. Further interaction between LPS binding protein with CD14**,** a glycophosphatidylinositol protein (GPI) with leucine repeat protein, delivers LPS to the TLR4-MD2 complex, this is internalized into endosomes and through the My88 protein intracellular signalling pathway eventually results in cytokine expression. TLR4 also detects virus envelope proteins and *Streptococcus pneumoniae* pneumolysin (Kwai and Akira 2010. Akira and Uematas., 2006).

TLR2, is able to detect a wide range of bacterial wall PAMPS, including peptidoglycan, Mycobacteria (lipoarabinomannan mycobcateria), fungal (zymosan), haemagluttin on influenza virus, together with mucin molecules from *Trypanosoma cruzei.* The glucans are a main constituent of the fungal cell wall and in association with dectins -1(a C type – lectin)are detected by the TLR2 receptor and internalized to produce a protective inflammatory response (Netea et al., 2004). TLR2 is not able to detect viral nucleic acids.

TLR5 and TLR9 detect a different range of bacterial constituents; TLR5 recognizes the flagellin protein expressed by flagellated bacteria, whereas TLR9, detects bacterial and viral DNA, especially CpG DNA motifs, that are rarely found in mammalian cells (Kawai and Akira 2010). (see table 1). TRL 11, recognizes bacteria found in the genitourinary tract as well as a profilin, a molecule expressed by *Toxoplasmosis gondii* (Yarovinsky et al., 2005), and also neurocysticercosis (Mishra er al 2008).

5.4 TLR; virus detection and the anti virus response

TLR3 detects double stranded (ds) RNA formed during replication of RNAand DNA viruses (Alexopoulou et al., 2001; Wang T et al., 2004; Daffis et al., 2008) the viral nucleic acid binds to N and C terminal sites on the TLR3 ectodomain activating the TRIF and NF- kB dependent pathways to produce an interferon type 1 anti- virus (IFN type -1) response (Paul et al., 2007)

Conversly, TLR7 and TLR 9 detect single stranded viral (ss)RNA and DNA respectively, and signal through the adaptor protein (MyD88) to initiate intracellular signalling by activating transcription factors NF-kB and the interferon regulatory factors (IRFs).

IRFs are translocated to the host cell nucleus where they regulate inflammatory cytokine synthesis and stimulate IFN type I interferon synthesis(IFNα/β expression) resulting in a protective response in adjacent cells, uninfected with a virus (Katze et al., 2002; Paul et al 2007). IFNα/βbinds to the IFN surface receptor (IFNAR) on an uninfected host cell leading to the activation of Janus kinases (JAK) with phosphorylation of transcription factors Signal Transducer and Activation of Signal (STAT1 and STAT2). These two proteins enter the host nucleus to drive the expression of IFN stimulated genes (ISGs)to intiate the anti virus host response.

Many of the emerging RNA viruses responsible for encephalitis express viral proteins that inhibit the host's innate anti -virus response by inhibiting specific steps in the pathway for IFN α/β synthesis, namely the ISGs and several anti -virus proteins blocking the hosts anti virus response (Type 1 interferon) (Griffin 2003; Paul et al., 2007) Examples of viruses and their individual proteins that block the host's IFN expression include, West Nile Fever (Envelope protein E), Influenza (Non Structual protein -1), Ebola (VP 24, VP35) Rabies (Rabies virus phosphoprotein), Enterovirus (structural protein 3C).

5.5 TLR detection of DAMPs in the absence of infection promotes inflammation

Necrotic cells release a range of endogenous proteins such as, heat shock proteins (HSP), S - 100, High mobility group box 1 Interleukin (HMGB1), ATP and mitochondrial proteins that are all regarded as DAMPS, because they can initiate an inflammatory response. (Roth et al., 2003; Lotze et al 2005; Krysko et al., 2010).

Several PRR including TLR-3, TLR-7 and TLR-9 function as sensors of tissue necrosis (Cavassani et al., 2008; Marshak- Rothstein and Rifkin 2007). Chromatin –DNA and ribonucleoprotein complexes all of which contain "self"nucleotides that activate the intracellular PRRs, TLR 7and TLR 9, resulting in an autoimmune disease(Tian et al 2010). Self nucleic acids are usually unable to activate the innate immune system, but after degradation by serum nucleases they are detected by TLRs in endolysosomes resulting in a further inflammatory response (Cavassani et al., 2008) In Systemic lupus erythematosus SLE, (a chronic inflammatory multi-organ disease charachterized by antibody production against self antigens such as DNA). On this basis SLE is regarded as a typical autoimmune disease because serum auto antibodies bind to " self" nucleic acids and are internalized by FcγR IIIa receptors on DC. These complexes are detected by TLR7 and 9, leading to interferon type I response and persistent autoimmune inflammation (Marshak- Rothstein and Rifkin 2007).

HMBG1 is an important DAMP, because it can bind to self DNA and pathogens. The receptor for activated glycation endproducts (RAGE) is also a PRR, and binds with HMBG1 to form a complex. This is delivered to endosomes containing TLR9, activating both DC and

B lymphocytes, with an up regulation of inflammatory cytokines (Tian et al., 2007). The regulation of HMGBI is clearly an important factor contributing to reducing DAMP initiated inflammation. One regulator of this interaction is Thrombomodulin (CD141); it is expressed by microglia and has been shown to bind to HMBG before it can form a complex with RAGE, to prevent this complex being detected by TLR and promoting an inflammatory response. (Abeyama et al 2005).

Heat shock proteins (HSP) and S-100, are important DAMPs and also interact with TLR 2-4 /CD91 and the RAGE receptor. This complex also signals through the NF-kB pathway to activate proinflammatory cytokine expression (Foell et al., 2007; Yu et al., 2006). The regulation of DAMP initiated inflammation is not well understood; however two macrophage (and possibly microglial) related lectins, MINCL and Clec9A, both bind to ribonucleoproteins, SAP 130, released by necrotic cells preventing DAMPS binding to TLR, with a down regulation of cytokine expression (Sancho et al 2009).

6. Non-TLR PRRs in pathogen detection

6.1 RIG like receptor; RIG -1 and MDA5 receptors detect intracellular viral nucleic acids and initiate interferon synthesis

Retinoic acid inducible agent -1 and melanoma differentiation associated gene 5 (MDA5) are both RIG-1 –like receptors (RLRs) , are helicases and signal through the adaptor molecule IPS-1 (Yoneyama et al., 2004; Kato et al 2006; Kwaki and Akiar 2010). They are expressed by microglia and astrocytes, and are located in the cytosol (Miranada et al., 2009). RLRs detect mainly virus RNA, both short and long ds and ss RNA (. Fur et al., 2008; Yoshida et al., 2007) RIG-1 detects short double stranded RNA; negative sense single strand, Influenza A and Ebola viruses and positive sense single strand RNA, Japanese encephalitis and Hepatitis C (Yoneyama et al., 2004; Fuijita et al 2007., Mohamadzadeh et al., 2007) whereas, MDA-5 detects cytoplasmic positive sense RNA, for example Poliovirus. (Griffin 2003; Kato et al 2008)

6.2 RiG-1 and MDA-5 anti virus response

RIG-1 and MDA-5 contain caspase recruitment domains (CARDS) essential for down stream signalling and an intermediate DEeD/H-box RNA Helicase domain, essential for ligand binding and recognition. (Parisien et al., 2003) The interaction between the RIG-1 and MDA-5 with nucleic acid from a pathogen activates the CARD containing adaptor (IPS-1) known as Cardif, MAVS and VISA, resulting in the up regulation of interleukins and a range of anti -virus proteins (Kumar et al 2010: Kato 2006) promoting the IFN type I response, capable of inhibiting viral replication(Paul et al 2007). See table 1.

6.3 ND LR receptors; roles in the innate response against infection

The NDLR (nucleotide –binding domain leucine rich repeat) are a group of highly conserved proteins found in diverse species, including sea urchins and humans. They (twenty two have been identified in humans and thirty four in mice) are a family of intracellular cytoplasmic PRR that represent sensors for detecting Gram negative and Gram positive bacteria, mycobacteria and DAMPs (Karaparakis et al 2007: ; Ting et al., 2010; Kumar et al., 2011).

These receptors are characterized by an N -terminal effector domain caspase recruitment domain (CARD), a centrally located nucleoside binding domain NACHT (or NOD) domain for nucleotide binding and a C terminal of leucine rich (LRR) mediating PAMP ligand recognition, e. g peptioglycan and flagellin in the bacterial cell wall (Sterka and Marriott 2006: Kaparakis et al., 2007 Proell et al 2008).

The actual process wherby an NLR detects either a PAMP or DAMP, is not understood. However, the C terminal LRR region recognizes PAMPS, but the crucial step in NLR activation is the oligomerization of NACHT domain and this permits binding to a series of intracellular adaptor proteins and eventually the intiation of IFN synthesis as the inflammatory response. (Proel2008)Further information about potential homo and heterotypical interactions between NLR s is needed to determine whether or not different combinations of NLRS demonstrate functional differences. Mutations in the genes encoding individual NLR have been linked to several chronic inflammatory disorders (such as Crohn's disease and asthma) underlying the potential importance of NLR in human disease (Tinget al 2010).

The expression of the NLR in the CNS is not clearly defined, although NOD 2 is expressed by monocytes, microglia and astrocytes (Chauhan et al; 2009)

NOD1 and 2 are cytosol proteins, they are able to detect major components of bacteria cell walls, g –D glutamyl –meso –diaminopimelic acid (iE- DAP) present in numerous organisms including Listeria Bacillus subtilis, Shigella Flexneri, Campylobacter jejuni and, Helicobacter pylori; NOD-2 detects murmayl dipepetide from Salmonella Typhimurium, Mycobacteria tuberculosis, Listeria monocytogenes, Saphylococcus aureus and Neiseeria menigitidis (Sterka et al., 2006) Kumar et al 2011). Uncontrolled NOD-2 activation can, however, result in demyelinization, representing the detrimental effects of unregulated activation of the innate immune system against pathogen invasion. (Proell et al., 2008).

NLR3, is a key component of NLR- 3 inflammosome (NLR 3, ASC and procaspase -1) because it is able to detect a wide range of PAMPs including viruses (adeno and influenzaviruses), bacteria (Staphylococcus aureus) and fungi (Candida albicans) (Osawa et al., 2010) and various DAMPs (HSP and BCL-2)(Schroder 2010). Of interest, is the association between a mutation in the nucleotide –binding oligomerization domain gene 2(NOD2) and Crohn's disease, an inflammatory bowel disease (Rehaume et al; ., 2010; Ting et al., 2010).

The explanation for the role of NOD2 in some forms of bowel inflammation (Crohn's disease) provides several insights into the more general immuno regulatory roles for NOD -2. Firstly, as an activator of the transcription factor NF-kB, to increase cytokine synthesis, or as a negative regulator of the host TLR response to pathogens, thirdly, a capacity to increase host defence by up regulating the expression of small molecular weight (18-45 amino acids) molecules called the α defensins in Paneth cells. The defensins assist with the intracellular lysis of phagocytosed bacteria, therfore regulating the severity of inflammation in the intestine wall (Rehaume et al., 2010).

The precise mechanism by which intra cellular sensing of PAMPs, such as bacterial peptidoglycan derived molecules, meso –diaminopimelic acid and muramyl dipeptide is carried out is as yet, not known (Ting et al 2010). Once a PAMP or DAMP is detected by the NLR this activates the inflammasome pathway (a complex composed of NLR, the adaptor

ASC (apoptotic speck-containing protein) with a CARD and procaspase -1 increasing the expression of proinflammatory cytokines IL-β and IL-18. (Royet et al., 2007; Hoarau et al., 2011).

The involvement of NLR in virus infection requires the mitochondrial located anti virus signalling protein, MAVS (also Cardif, IPS-1, VISA), that is responsible for type I interferon response. An NLR protein family member, NLRX1, regulates the interferon type 1 response by inhibiting the interaction between RIG-1 and MAVS, whereas NOD 2, also inhibits RNA virus production through its interaction with the anti- viral protein, 2-5 oligodenylate synthase type 2 (OAS2) (Ting et al 2010). see table 1.

7. Scavenger Receptors (SR) detect pathogens, apoptotic cells and endogenous proteins; vital components of the innate immune response

7.1 CD14, CD36 and SCARB

CD14 is expressed by microglia and is both a membrane anchored glycophosphatidylinositol protein (GPI) and soluble PRR. It has a co-operative interaction with TLR- 4 to facilitate bacterial LPS detection and it interacts with apoptotic lymphocytes, via the intercellular adhesion molecule(ICAM-3) to facilitate their phagocytosis (Gregory 2000). Clearance of apoptotic cells by CD14, depends upon detection of ACAMPS and this is also an anti -inflammatory response, reducing tissue damage, because the soluble form CD14 switches off activated T cells (Pender 2001).

7.2 Scavenger receptors class A (SRAI, SRABI/II) and class B, CD36

The best characterised SR is CD36, a multifunctional receptor, expressed by microglia and astrocytes (Husemann etal., 2002). It is able to bind to phosphatidyl (PS) and oxidized low density lipoprotein, both present on apoptotic cells (as ACAMPs) as well as neurotoxic proteins such as Aβ4 (Ren et al., 1995; Coraci et al., 2002). Macrophage, CD36, co-operates with the vitronectin receptor $\alpha v \beta_3$ (CD51/CD61) to increase phagocytosis, because this complex recognizes the protein thrombospondin (TSP) located on the surface of apoptotic cells. (Lamy et al 2007: Fadok et al., 1998).

A further receptor, Scavenger receptor B, SCARB (Lysosomal integral membrane protein II or CD36b like-2) is expressed by many different tissues and has also been identified as a receptor for the enterovirus EV71and coxsackie virus A16, although only EV71 is responsible for encephalitis. SCARB is expressed in most tissues, so it not possible to explain the neurotophic effect of EV71 as the result of this virus binding this new receptor. (Yamayoshi et al, 2009).

7.3 CD91; a multi functional PRR

The α2 macroglobulin LRP receptor-related or the lipoprotein low density lipoprotein receptor (CD91) is expressed by microglia and neurons (Marzolo et al., 2000), and functions as an entry receptor for both bacteria and viruses. HIV-1 utilizes CD91 as a docking receptor to enter the CNS via endocytosis; the toxin of the bacterium Pseudomonas is taken up by CD91 (Herz et al., 2001). Despite this evidence, the contribution made by this SR in defending against neuro infection is not yet clarified; CD91 is also able to bind toAβ4 amyloid and apoptotic cells (Marzolo et al., 2000). As the result of apoptosis, calreticulin, a soluble protein located on the endoplasmic reticulum migrates to the cell surface and becomes a potentially important ligand for phagocyte receptors, including mannan binding lectin (MBL), the first complement proteinC1q and the CD91 complex. (Ogden et al., 2001; Gardai et al., 2005)

7.4 TREM -2; a new scavenger receptor

Triggering receptor expressed by myeloid cells (TREM-2) and is an SR expressed on monocyte derived dendritic cells, osteoclasts and microglia (Takahashiet al., 2007). The TREM-2 receptor is expressed by microglia in conjunction with the receptor DAP-12 that shares many features with Draper, an ancient phagocytic receptor found in *Drosphila*. The microglial, DAP-12 receptor and Draper, both contain ITAM (immuno receptor tyrosine based activation motifs) and stimulation of this signalling pathway increases microglial phagocytosis and pro inflammatory cytokine expression. (Linnaetz et al., 2010). In vitro, microglia expressing TREM -2 demonstrated increased phagocytosis of membrane fragments from apoptotic neurons. This effect was also reproduced in experimental autoimmune encephalomyelitis(EAE)following the intravenous administration of TREM-2 in bone marrow precursor cells and was accompanied by a down regulation of tumour necrosis factor (TNFα). A loss of function mutation in both TREM-2 and Draper proteins are associated with a chronic neurodegenerative disease, Nasu-Hakola, characterized by the failure to clear neurotoxic proteins, representing a contributory factor in this form of early onset dementia (Colonna M et al., 2003)**.** The TREM -2 mediated apoptotic response was inhibited by inflammatory signals activating the ITIM (immuno receptor tyrosine based inhibitory motifs) leading to the recruitment src homology 2 (SH) domains of syk protein kinases, preventing phagocytosis and down regulating both the microglial inflammatory and anti -pathogen responses.

7.5 Lectins as PRR in the innate immune response to infection and injury

The lectins are a range of carbohydrate binding proteins and glycoproteins, either homo or hetero oligomers of non -covalently bound, polypeptide units and carbohydrate recognition domains (CRD) that bind to a sugar molecule in a Ca 2+ dependent manner (Cambi et al., 2005). One important role for the lectins is to establish tolerance between bacteria living inside the host through molecular mimicry. Bacteria display surface lectin molecules similar to those present on host cells so bacterial lectins are detected as ” self “ by the host immune system, allowing them to remain in the gut with mutual benefit to both host and bacteria.

The innate immune response also includes the C- type lectins (acting as PRRs) to detect PAMPS (Endo et al., 2006; Geijten beek et al., 2009). The most important families of lectins are the Pentraxins (extracellular), the Macrophage mannose receptor (MMR) located on the endoplasmic reticulum)(Stahl and Ezowitz 1998), the non classical C-type lectins, dectins 1and 2, expressed by microglia (Brown G et al., 2006) Siglecs (cell membrane)(Crocker and Varki, 2001) and the newly identified C –type lectin member 4E (Clec4) (Sancho et al., 2009). The galectins, expressed by cerebral blood vessels, are an increasingly important family of lectins, functioning as a PRR to detect both intracranial l PAMPs and DAMPs (Sato et al., 2009; Vasa, 2009).

7.6 MMR and DC-SIGN are PRR for "non self", complex carbohydrates

Glia, express trans membrane C- type lectins (Burundi et al., 1999) namely MMR (microglia, astrocytes and peri vascular cells) (Linehan et al., 1999) and DC- SIGN receptor that recognizes "self "intercellular adhesion glycoproteins ICAM. (van Kooyk et al., 2003). The DC-SIGN receptor is expressed by peri vascular cells and a population of dendritic cells, both associated with cerebral blood vessels (Mukhtar et al., 2002; Schwartz et al., 2002; Greter., 2005). MMR and DC- SIGN function as PRRs binding to and internalising viruses by endocytosis, promoting their degradation and antigen presentation to T cells in association with MHC (Stahl et al 1998; van Kooyk et al., 2003).

Both, MMR and DC-SIGN, also recognize "non self" molecules containing a high mannose content (functioning as PAMPs), as found on enveloped viruses. Both MMR and DC-SIGN receptors provide a pathway for a virus to enter the CNS (le Cabec et al., 2005) and this is the case for Dengue (Miller et al 2008), HIV, Ebola and Marburg (both ss RNA Filo viruses), West Nile Fever virus (WNFV), Influenza A, all target MMR (Upham et al 2010*.).* Whereas, WNV and Ebola virus target the DC- SIGN receptor (Alvarez et al., 2002; Schwartz et al., 2002; Mohameazah et al., 2007)

7.7 Pentraxins

The pentraxins are highly conserved proteins with a cyclic multimeric structure and include the acute phase reactant C protein (CRP) and serum amyloid protein (SAP). Microglia and neurons express CRP and SAP, both of which are capable of opsonising apoptotic cells with subsequent binding to the collectin, C1q, the first C pathway protein to stimulate phagocytosis. (Elward and Gasque 2003; Nauta et al 2003). CRP recognizes apoptotic cells through binding to phosphorylcholine found in oxidized lipids which are regarded as ACAMPs (Chang et al., 2002). Pentraxins, as opsonins, also initiate phagocytosis of apoptotic cells as they are capable of binding directly to microglial Ig (FcγR) receptors and C1q (Chang et al 2002: Nauta et al., 2003) Despite this evidence, the contribution of the pentraxins to the removal of apoptotic cells from the CNS in neurodegenerative and inflammatory disease is yet to be defined.

7.8 Galectins are lectins and PRR with multiple roles

Most galectins are non – glycosylated, soluble proteins, distributed in most mammalian tissues, including the innate and adaptive immune systems (Sato et al., 2010: Vasta 2010)**.** Glactins(previously known as S- type lectins) are expressed by cerebral vessel wall endothelium (Joubert et al., 1998). They are also examples of PRR capable of binding to viruses, bacteria (*Streptococcus pneumonia*, *Neisseria meningitides, Haemophilus influenza* and fungi *Candida albicans,* the protozoan *Trypanosoma cruzi* and parasite *Toxoplasmosis gondii*. Glactins are able to prevent Nipah virus entry in to endothelial cells by preventing virus fusion with ephrin B2 and B3 receptors on endothelial cell surface (Lo et al., 2010; Garner et al., 2010) However, this protective function of glactein is exploited by the HIV -1 virus, because it binds to glactin -1 and enters host cells. Organs that represent reservoirs for HIV-1 infection express abundant glactin –1 on their cell surface, confirming glactins are " non self" detecting PRR. (Sato 2009).

7.9 Defense collagens or collectins (MBL and SPA)

These are soluble molecules expressed by the liver, lungs and astrocytes (Kuraya et al., 2003; Wagner et al 2003)and include mannose binding lectin (MBL) and Lung surfactant protein A (SPA). Both these collectins are capable of recognizing carbohydrate patterns containing large numbers of mannose and fucose molecules characterized as PAMPs, and found in the cell wall of bacteria and viruses (non self), but not expressed by mammalian cells (Tenner AJ 1999; Elward Gasque 2003). The globular carboxyl C terminal of the defence collagen acts as PRR recognizes PAMPs and potentially ACAMPs, whereas the N -terminal domain links defence collagen to a receptor on phagocytic cells e. g microglia. MBL binds to Ebola and Marburg envelope gylco proteins, preventing these viruses gaining “subversive “entry to the host cell through the DC –SIGN receptor (Ji et al 2005). SPA and MBL are capable of binding to apoptotic cells and neutrophils, functioning as a bridging molecules, between the apoptotic cell and the phagocyte receptor CD91 (Vandivier et al., 2002).

7.10 Siglecs detect sialic residues as markers of “self”

Siglecs (sialic acid –binding immunoglobulin like lectins) are a subgroup of the Ig super family, type 1 membrane proteins with an amino terminal V –set immunoglobulin domain; they represent a family of receptors that detect sialylated glycoproteins and glycolipids (Crocker and Varki 2001 Crocker etal., 2007). Two group of Siglecs can be identified; Siglecs common to mammals Siglec -1(sialoahesin, CD169) (Delputte et al., 2011), Siglec 2 (CD22), myelin associated siglec 4 and those Siglecs related to the CD33 family including siglec -10, 11 and 16 (Lock et al., 2009 Mott et al., 2004). Most siglecs, are present on haemopoietic tissue however, sialoadhesin is expressed only on macrophages as a specific adhesion molecule, whereas siglec -11 is expressed by microglia (Angata et al., 2002). The CD33 family of siglecs are expressed on most mammalian cells, with each siglec having a unique specificity for a sialylated ligands (sialic acid), so there is room for overlapping functions within the family of Siglec receptors (Cao and Crocker 2010). Their main function is the detection of “self ” indicated by sialic acid residues and the suppression of inappropriate microglial directed host cell phagocytosis.

7.11 Complement system provides first line defence against pathogens PAMPS, DAMPs and ACAMPs

The C system is an extremely ancient component of the innate immune system. It is thought to have evolved 300 million years ago, as part of the coagulation protein pathway. The complement system comprises of three pathways, the classical, alternative and lectin activated pathways. (Sjoberg et al., 2008; Gasque 2004; Gasque et al., 2000)

The first component of the classical C pathway, C1q, has a multimeric structure, that represents a PRR and is expressed by astrocytes and neurons (Gasque et al., 2000). C1q is able to detect a variety of pathogens, apoptotic cells and neurotoxic misfolded proteins (mutant Prions, fibrillary amyloid), antigen –antibody complexes and DNA (Nauata et al 2002; Korb et al., 1997). The identity of the C1q receptor is not well defined, but candidates include, CD93, expressed by microglia or C1qRp (Dean et al 2000 Webster et al., 2002. ; Elward and Gasque 2003).

The activation of the classical C pathway generates two anaphylotoxins (C3a, C5a) responsible for recruiting inflammatory cells into areas of tissue injury, as welll as opsonins (iC3b and C3) and the cytolytic membrane activation complex (MAC). With regards to pathogens such as bacteria and fungi, the opsonins (C3b and iC3b) coat the pathogen making it a more attractive target for microglia expressing the β2 integrin (CR3 /CR4)receptors (Akiyma and Mc Geer 1990: Ehlers 2000; Reichart et al., 2003). Apoptotic cells contain activated DNA and this enables C1q to directly bind to apoptotic cells, activating the classical C pathway with the generation of opsonins C3b and iC3b, again providing targets for phagocytosis by CR3 and CR4 to reduce host cell damage (Mevorach et al., 1998; Korb et al., 1997). There is also evidence that the Ficolins (lectins) bind to ACAMPs expressed by apoptotic cells, activate complement and generate the opsonin C3, facilitating phagocytosis (Matsushita., 2010)

8. Neurodegeneration; The detection and clearance of Pathogen protein associated molecular patterns (PPAMPS) and innate immune system activation

Neurodegeneration produces neuronal loss and is characterized by intra and extra neuronal accumulation of dangerous(neurotoxic) intrinsic proteins (fibrillary amyloid, mutant prions, α–synuclein, mutant tau) classified as PPAMPs(pathogen protein associated molecular patterns) regarded as a sub type of DAMPS. PPAMPs are detected by a range of PRRs with resulting proinflammatory cytokine expression (Wyss-Coray and Mucke 2002). During chronic CNS inflammation, the accumulation of endogenous protein aggregates is perceived by the innate immune system as “stranger” or “danger” signals (DAMPs). In AD, it has been suggested that a variety of glial related PRR (CD14, TLR, CD36, CD91) with opsonins(C 1q, iC3b, C3) derived from C activation contribute to the removal of Aβ4amyloid fibrils (Coraci et al., 2002: Elkhoury et al., 2003; Fassbender et al., 2004; Alarcon et al 2005: Tahara et al., 2006; Landreth et al., 2009)The SR, CD36, facilitates the assembly of a heteromeric complex composed of CD36, TLR4 and TLR6 following binding to Aβ 4 (Stewart et al., 2010).

Aβ fibrils can activate microglia and astrocytes through TLR4 (together with CD14 and MD2 in microglia), leading to the activation of downstream inflammatory response genes (Reed - Geaghan et al., 2009; Walter et al., 2007; Chen et al., 2006: Lehnardt et al., 2003, Bamberger et al., 2003). This explanation is consistent with mice carrying a nonfunctional TLR4 crossed with a mouse model of AD (APP/PS1 double transgenic mice) having a lower level of inflammatory cytokines than wild type animals (Walter et al., 2007; Jin et al., 2008). A TLR4 polymorphism was shown to be associated with protection against late-onset AD in an Italian population, suggesting that theTLR4–mediated innate immune inflammation could influence AD pathology (Minorettiet al., 2006). TLR2 also may be a sensor for fibrillar Aβ (Chen K et al., 2006; Jana et al 2008). Blocking TLR2 signaling with antibody or by knockdown of the receptor gene *in vitro* suggested that TLR2 stimulation by Aβ promotes neurotoxic inflammation. However, mice lacking TLR2 crossed with APP/PS1 transgenic AD mice were reported to show a delay in Aβ deposition and improved behavior on memory tests (Richard et al., 2008) These apparently contradictory functions of TLR could be due to differences in the cell types as well as signaling pathways that are engaged by the amyloid peptides and/or fibrils. (Tahara et al., 2006)

NOD-like receptors (NLRs) are also involved in Aβ-induced inflammatory response. In AD, Aβ oligomers and fibrils induce lysosomal damage and trigger NALP3, a member of the NLR family that is expressed in microglia (Halle et al., 2008) NALPs activate downstream signaling proteins, such as ASC and this will lead to caspase 1 activation and increased processing of proinflammatory mediators like IL-1β and IL-18.

Fibrillary amyloid and aggregated forms of mutant prion protein are opsonized by complement components (C1q, C3) to promote clearance by macrophages and microglia CR3/CR4(Tenner 2001: Kovacs et al., 2004). In AD as the result of C1q binding to fibrillary Aβ4, the C pathway is activated increasing C3 and C5 as part of the protective response promoting clearance of the amyloid plaque (Mc Geer et al., 1989; Jian et al., 1994; Eikelenboom et al., 2002); inhibition of the complement cascade increased amyloid plaque burden (Wyss Coray and Mucke., 2002). However, in the context of acute inflammation, microglia and astrocytes express complement and it is plausible C activation on myelin/ neuronal debris contributes to secondary brain injury. The formation of the MAC and non-specific binding to host cells would cause bystander damage.

In Huntington's disease the expression of C1q, C3, iC3b and C4 is increased on microglia and astrocytes, C activation is also present in experimental models of ischaemia (van Beek et al., 2000; van Beek et al., 2001: Singhrao et al., 1999). Interestingly, administration of a C1q inhibitor C1-INH, resulted in neuron protection after experimental ischaemia, but its protective effect was interpreted as independent of C1q activation of the complement pathway (De Simoni et al., 2004).

A further sensing system for Aβ, is provided by RAGE (receptor for advanced glycation endproducts) a PRR and trans membrane receptor of the immunoglobulin super family RAGE is expressed on the surface of microglia, astrocytes, vascular endothelial cells, and particularly on neurons (Fang F et al 2010). Several reports suggest that Aβ peptide as well as Aβ oligomers bind to RAGE and contributing to the activation of microglia and the production of proinflammatory mediator (Yan et al., 2006). RAGE is also suggested to play an important role in the clearance of Aβ4 and to be involved in cellular processing and signaling (Origlia et al, 2008; Takuma et al 2009). The role of the SRs, CD36, CD14 and particularly CD91, in AD is ambiguous; studies indicate that CD91 has the capacity to influence both the production and the clearance of Aβ. CD91 is a receptor for APP, apoE, and α2M, which all have been genetically linked to AD (. Bu, 2006). Clearance of Aβ complexed to these ligands could contribute to a reduction in amyloid plaque burden (Herz et al., 2001).

8.1 Phagocytosis of apoptotic cells (altered self) reduces local inflammation (the non phlogistic response)

Apoptotic cells result from the consquences of infection, ischaemic infarction and neurodegeneration; they express a range of apoptotic cell associated molecular patterns or ACAMPs on their surface. In general phagocytosis of apoptotic cells reduces local tissue inflammation, as the so called "non pholgistic response", providing some degree of local immunoregulation. (Chan et al., 2001: Chang et al., 2001; Magus et al., 2002; Griffith set al., 2009. The result of clearing apoptotic cells reduces local inflammation (non phlogistic response) and this is in contrast to the increase inflammatory response, following attempted clearance of pathogens (phlogistic response). The clearance of apoptotic cells by CD14 is anti-inflammatory (non phlogistic) as it binds to and switches off T cells (Gold1991), releases the anti-inflammatory cytokines TGFβ and prostaglandin E2, together with growth factors such as Vascular endothelial growth factor (VEGF), all reducing local inflammation and promoting tissue repair (Griffiths., 2009 et al, Golpon HA et al., 2004, Huynh et al., 2002, Voll R et al., 1997)

ACAMPs include nucleic acids and sugars, the best characterized ACAMPs are, phosphatidyl serine (PS) and calreticulin (Fadok et al., 2000: Hoffman et al 2001; Gardai et al., 2005; Gardai et al., 2006).

Glia and macrophages express PRRs that recognize ACAMPS, including the PS receptor (PSR), CD14 (in conjunction with ICAM), LRP, CD36, the soluble bridging molecules milk - fat gobulin (MFG -EGF 8), growth arrest –specific gene 6, and TREM-2 (Prieto et al., 1999, Gregory 2000; Hanayama et al., 2002; Leonardi –Essman et al., 2005 Gardaiet al., 2006). Thrombospondin, a protein expressed by glia, acts as a bridging molecule between an as yet undefined ligand on the apoptotic cell and CD36, to promote phagocytic clearance (Lamy et al., 2007). PS on apoptotic cells and IgM both bind to C1q to activate C pathway and opsonin (C3b iC3b) synthesis, to provide targets for CR3 and CR4 (Kim et al., 2002).

Animals deficient in C1q accumulate apoptotic cells, resulting in glomerulonephritis and an (SLE**)-** like disease, because the accumulated DNA and RNA both function as DAMPs and trigger autoimmune inflammation (Botto et al 1998). Activated microglial and Kolmer cells in the choroid plexus (Singhrao et al., 1999) express C3R /CR4 and both detect C1q, C3b, C3b as well as MBL, underlining the importance of glia for removing apoptotic cells opsonised with C from the CSF (Mevorach et al., 1998; Reichart et al., 2003). The lectins, Ficolins and MBL, are capable of interacting with ACAMPs such as calcireticulin, to initiate clearance of apoptotic cells (Ogden et al., 2001).

Phagocytes involved in apoptotic cell clearance also express, the T cell immunoglobulin domain mucin domain protein 4 receptor (TIM4) and the TAM receptors (Tyro2, Axland Mer) which bind to Gas 6 both are expressed by neurons (Lemke and Rothlin 2008). These receptors regulate the effects of TLR mediated response by inducing the expression of Suppressor of Cytokine Signalling proteins (SOCS 1 and 3), a family of intracellular inducible proteins, that inhibit cytokine synthesis. (Baker et al., 2009).

8.2 Neuroimmunoregulatory molecules (NIRegs) regulate the innate immune response and prevents inappropriate activation

One basic property of the NIRegs is their expression by host cells, but neither by pathogens nor by apoptotic cells. NIRegs interact with either macrophages or microglia to provide immuno regulation, promoting a reduction in the severity of inflammation and facilitating tissue repair (Hoarau et al., 2011).

Examples of NIRegs, include CD200 and CD47; these two molecules both represent “don’t eat me” signals cells, to prevent un warranted phagocytosis, whereas the Siglecs detect sialic acid (a “don’t eat me” signal) on host cells resulting in immuno regulation and inhibition of microglial activation. CRProteins modulate complement activation whereas, the the CD24/siglec 10 pathway inhibits DAMPs initiated inflammatory response (Chen et al., 2009). see table 2, for a summary of the current NIreg s.

8.3 Complement regulatory proteins (CRP) as NIRegs

To avoid self-destruction, host cells employ a range of regulatory molecules, including the CRP, which inhibit assembly of either the C3-cleaving enzymes or the formation of the membrane attack complex (MAC) on host cell surface. As pathogens lack these inhibitors, activation of the complement cascade can proceed and results in lysis or phagocytosis of microbial intruders. (Zipfle and Skerka 2009). However, animals deficient in CRP are also likely to experience severe inflammation, because unregulated activation of the C system will generate C3a and C5a, both anaphylatoxins(chemotaxis of macrophages and neutrophils) with uncontrolled activation of MAC.

Similarly, as “self” cells progress to “altered self” (apoptotic cells), there is a down-regulation of complement inhibitors (including CRP) at the cell surface including a low sialic acid content and the loss of the CRP, FH(Crocker and Verki 2001). The loss of CRP based membrane inhibitors, such as CD46, can lead to moderate and limited opsinonisation of apoptotic cells with the complement proteins (C3b, iC3b) with the promotion of phagocytosis by CR3/CR4. (Elward et al., 2005)

The soluble C1 inhibitor (C1-INH), C4b-binding protein (C4bp), factor H (fH), factor I (fI), S protein (Sp) and clusterin are all CRP, expressed by glia and neurons (Gasque 2004). C4bp is an important NIReg, because it is able to inhibit the DAMP effect of DNA released from necrotic cells and has been detected upon amyloid plaques in AD, potentially limiting C activation (Torouw et al., 2007; Torouw et al., 2005).

The other CRP are expressed on the cell membrane and include two trans membrane proteins CR1, membrane cofactor protein (MCP, CD46) and two GPI-anchored proteins, Decay Accelerating Factor (DAF, CD55) and CD59 (see comprehensive review Zipel and Skerka., 2009). Moreover, since CD55 is a ligand for CD97 on macrophages it is tantalizing to speculate that CD55-CD97 interactions could play an important role regulating phagocytosis (Hamann et al., 1996).

FH, CD55 and CD59, fulfill the criteria for an NIReg given that they are broadly expressed and extremely important in the control of complement activation on self-cells. Neurons also express NIRegs in the form of the CRP, Factor H. This CRP is able to reduce axonal degeneration (self injury) in a MOG induced EAE model, as the result of inhibiting C pathway activation. (Griffiths et al., 2009)

8.4 Siglecs are an emerging NIReg

The Siglecs, are expressed by monocytes, microglia and macrophages; they have a potentially important immuno regulatory function in the CNS (Linnartz et al., 2010) The absence of sialic acid expression on micro-organsims or apoptotic cells is detected by siglecs as a signal of “missing self “and this promotes phagocytosis (Crocker and Virki 2001). To emphasize the importance of sialic acid residues as a signal of “self”, over twenty, pathogens have evolved the capacity to synthesize or capture sialic acids, providing molecular mimics of host (“self “) and thus avoiding detection by their host (Jones et al., 2003). This possibility is supported by evidence showing Group B Streptocci with siaylated surface molecules bind to neutrophils expressing siglec 9, with reduction in their killing response aiding the survival of bacteria (CaoCrocker 2010).

The CD33 related sub-family of Siglecs (includes human Siglec 10, Siglec 11, Siglec 16) and the CD22 related Siglecs, both signal through cytosolic ITIM (immuno receptor tyrosine based inhibitory motifs) that provide inhibitory regulation of receptor pathways (Crocker and Varki 2003; Lemke and Rothlin 2008). This association strengths the potential NIReg regulatory role for both CD33 and CD22 siglecs on the basis of their capacity to detect sialylated glycans (α-2, 6 α–2, 3 and α–2, 8 linked sialic acids) representing markers of" self "on host cells.

The interaction between CD22 and B cells results in a phosphorylation of ITIMS with the recruitment of the Src homology 2 domain –containing protein tyrosine phophatases(SHP-1 and SHP-2 proteins) with a down regulation of inflammatory signalling. (Crocker 2007).

Cortical neurons express high levels of CD 22 and on ligation with microglial CD45 it reduced LPS induced microglial expression of TNF–α acting as a negative regulator of microglial cytokine release (Mott et al., 2004). Siglec 11, expressing microglia have a reduced neurotoxic capacity and fail to phagocytose apoptotic material in micro glial- neuron co culture experiments. (Wang et al., 2010: Toguchi et al 2009).

CD33 related Siglecs inhibit cell proliferation, negatively regulate TLR, increase apoptosis and reduce IFN production, again through ITIM signalling pathways (Cao and Crocker 2010). The absence of sialic acid in the cell wall of a pathogen will prevent the interaction with CD22, CD33, resulting in the failure to promote an ITIM related inhibitory response with an increased host " protective " inflammatory response (Crocker 2010). The presence of sialic acid residues defines host cell as "self" and initiates an inhibitory signal to down regulate any inflammatory response and prevent inappropriate phagocytosis of host cells. A further immunoregulatory role for Siglecs is their inhibitory response to TLR signalling activated by DAMPs.

8.5 CD24/siglec 10; an NIReg pathway that regulates DAMPS and reduces tissue injury

The successful resolution of pathogen invasion of the CNS requires the detection of PAMPs and also DAMPs released by tissue injury. HMBG, S100 and HSP are all examples of a DAMPand released from cells after injury. The innate immune system can be activated by DAMPs as a consequence of being detected by a RAGE and TLRs and triggering the TLR – MyD88 –NFkB pathway (Liu et al., 2009). Of interest, is the relatively low level inflammatory response elicted by DAMPs, raising the possibility that DAMPS are capable of regulating the inflammatory response.

One pathway, capable of imunoregulating DAMPS involves, CD24, a heat stable antigen and GPI anchored protein, that binds to HMBG, reducing the pro inflammatory properties of this DAMP. Two lines of evidence support the regulatory role of CD24; individuals with polymorphisms of CD24 appear to at risk of developing so called autoimune disease involving inflammation and when T cells are introduced into CD24 deficient mice, they undergo rapid proliferation. Furthermore CD24, is expressed in the developing CNS and by stem cells; although not fully characterized, it is known to regulate cell proliferation and neuritic outgrowth (Kleene et al., 2001: Shewan et al., 1996).

CD24 detect s DAMPs, but not PAMPS and the CD24- DAMP complex binds to the Siglec 10, which has an ITIM motif and recruits SHP-1 SHP-2 and SHIP complexes. The presence of

Siglec 10- SHIP-1 compex inhibits the DAMP-TLR /NLR based activation of the NF-kB pathway, reducing DAMP activated inflammatory cytokine expression. PAMP activation of the TLR –MyD88 –Nf-kB pathway remains intact and inflammatory cytokines are synthesised. This proposed pathway, based upon CD24 binding to DAMPS, but not PAMPS, allows the host to regulate endogenous protein activation of inflammation following infection and neuro degeneration, adding a further protective pathway to reduce the severity of tissue injury.

Mice deficient in the human homologue of siglec 10 have an increased proinflammatory response to pathogens (Chen et al., 2009). Further evidence, that the CD24/siglec 10 interaction presents an NIReg pathway is the inhibition of the inflammatory response initiated by the DAMPS, HSP 70 and HSP90 (Liu et al., 2009). The CD24 /Siglec 10 pathway represent an NIReg pathway capable of regulating endogenous DAMPs released during injury, neurodegeneration and infection. (Liu et al 2009; Hoarau et al., 20011)

8.6 CD200-200R an NIReg pathway for evasion of phagocytosis

CD200, is a well defined member of the NIRegs family it is expressed by reactive astrocytes; its counter receptor, C200R is expressed by microglia and perivascular macrophages (Barclay et al., 2002; Broderick et al., 2002 Lyons et al., 2007). The interaction between CD200 and CD200R results in down regulation of microglial phagcocytosis, preventing "self" attack (Barclay et al., 2002: Hoek et al., 2000). CD200 is a 41-47kD surface molecule and a member of the immunoglobulin Ig supergene family, characterized by two IgSF domains (Barclay et al., 2002; Wright et al., 2001). It is a highly conserved and found in invertebrates and vertebrates; like many of the glycoproteins containing this molecular arrangement they are involved with regulation of the immune system.

In the brain CD200, is expressed by microglia, cerebellar and retinal neurons, together with vascular endothelium. (Broderick et al., 2002). The counter receptor to CD200, CD200R, also contains two IgSF domains and is expressed by myeloid cells and brain microglia (Koning et al., 2009; Koning et al., 2007). In CD200 deficient mice, the number of activated microglia and macrophages were more numerous after an experimental lesion, as compared to wild type animals, providing evidence that the CD200/CD200R interaction is related to regulation of microglial activation and regulation of local inflammation (Hoek et al., 2000). This interpretation is supported by experiments in CD200 -/-mice inoculated with myelin oligodendrocyte glycoprotein MOG peptide to induce EAE. In these experiments the severity of the EAE was increased owing to the loss of CD200 regulation of microglial activity (Hoeket al., 2000). The contribution made by the CD200 (astrocytes)-CD200R (microglia) interaction on microglia in MS and AD remains to be established, although evidence for a dysregulation of CD200-CD200R pathway as a contributory factor to increase the severity of inflammation in MS has been proposed (Koning et al., 2009).

8.7 CD47-C172 an NIReg pathway as a marker of " self" or "don't eat me".

CD47, is expressed by astrocytes, neurons, macrophages and endothelium. The interaction between CD47 with the counter receptor CD172a, down regulates microglial activity, complement activation and cytokine expression, overall reducing the severity of the inflammatory response (deVries et al., 2002 Reinholdet al., 1995)

CD47 has five trans membrane regions with alternatively spliced isoforms of CD47 having a tissue specific expression, form 2 is present in bone marrow, whereas form 4 is highly expressed in brain (Reinhold et al., 1995). CD47, has two counter receptors; CD172a is expressed by myeloid cells, microglia and neurons a plasma membrane protein with three Ig domains in its extracellular component (Brown et al., 2001) and thrombospondin TSP (Lamy et al., 2007).

The interaction between CD47 with CD172a, recruits tyrosine phosphotases SHP-1 and SHP-2, with down regulation of macrophage phagocytosis, complement activation and cytokine synthesis including (Vernon –Wilson et al 2001: Brown et al., 2001: Oldenborg et al., 2001: Seiffertet al., 2001. The protective activity of CD47 could also be extended to its beneficial role in supporting neural development and promoting clearance of amyloid fibrils, albeit by mechanisms that remain ill-characterized (Bamberger et al., 2003).

The interaction between CD47 and CD172a has been shown to reduce neutrophil migration across endothelium and blocking CD47 induced expression of inflammatory cytokines by dendritic cells. CD47 is capable of inducing apoptosis in both T cells and cells deficient in CD47 i. e. loss of “self” identity, these cells are subsequently cleared rapidly from the systemic circulation by the spleen. (Oldenborg et al., 2001). The interaction between CD47 and thrombospondin promotes apoptosis of activated T cells, therefore, reducing inflammation by terminating T cell activation (Lamy et al., 2007: Sarati et al., 2008).

Hence, CD47, represents an important “don’t eat me signal”, preventing inappropriate phagocytosis of host cells (Elward and Gasque 2003). Apoptotic cells rapidly loose CD47, reducing its ability to bind and phosphorylate CD172a to recruit inhibitory signals and increasing their clearance through phagocytosis. The presence of CD47 on neurons and T cells is capable of promoting apoptosis through the CD95/Fas and caspase independent pathways (Manna et al., 2005). In MS, CD47, but not CD172a expression, is reduced at the edge of a chronic plaque, contributing to the loss of immuno regulation of microglia in this chronic inflammatory disease(Koning et al 2009).

The finding that viable cells are readily ingested if ‘don’t eat me signals’ are disrupted raises the intriguing possibility that recognition and removal by phagocytosis is a default process that is actively prevented by inhibitory ligands on viable cells. Whether or not the CD47-CD172a pathway is capable of regulating microglial activity in disease remains to be determined. (Hoarau et al., 2011)

9. Emerging NIRegs; semaphorins and suppressor of cytokine signalling proteins (SOCS)

9.1 Semaphorins and microglia represent a potential pathway to regulate the host inflammatory response

The semaphorins are a diverse group of highly conserved trans membrane and extra cellular proteins with an extra cellular, 500 amino acid cysteine rich, semaphorine domains. Semaphorins bind to a diverse range of receptors; in the brain, plexins and neuropilins whereas in the immune system, the C -type lectin, CD72 is expressed mainly by T cells, but also on DC and macrophages. The functional importance of the semaphorins was initially directed towards control of axon growth, but it is now apparent these molecules are important immuno regulators in the CNS (Takegahara et al., 2005).

The interaction between Sema 4D (originally CD100), a trans membrane semaphorine, and the immune system CD72 results in an increased expression of cytokines by B cells, because Sema 4D turns off the inhibitory ITIM associated pathway (Suzuki et al., 2008). In the CNS microglia are activated by Sema 4D binding to plexin B1, rather than the CD72 molecule that is also expressed by microglia (Okuno et al; 2009)

Interestingly, plexin B1 and Sema 4D deficient mice are resistant to EAE induced by MOG derived peptide, because of the failure to generate MOG –specific T cells, emphasising the importance of functional Sema 4D for T cell activation and differentiation within the CNS (Takegahara et al., 2005). Antibodies raised against Sema 4D reduced inflammation during EAE, this was explained as the result of blocking T cells expressing Sema 4D interacting with microglial plexin to promote expression of pro inflammatory cytokines (Okuno et al., 2009).

In contrast to the other NIReg pathways, Sema 4D, increases the host inflammatory response by upregulating the level of cytokine expression and microglial activation. The regulation provided by Sema4D ensures the host inflammatory response is approporiate to counter the effects of pathogens and neurtoxic proteins. Conversly inhibition of the SEMA 4D-plexin pathway represents a potential new target to suppress and regulate neuro inflammation.

9.2 Suppressor of cytokine signalling proteins (SOCS)

SOCS, are a family of eight intracellular, cytokine inducible proteins, expressed by CNS cells (microglia, astrocytes and neurons) that inhibit IFN signalling in CNS cells (Baker etal., 2010). Through activation of STAT transcription factors the C terminal of the SOCS binds to and inhibits phosphorylated tyrosine residues on Janus kinases (JAK), in addition the of the N terminus contains a kinase inhibitory region, and this also inhibits INF synthesis and blocks the NF-kB pathway. In the brain, SOCS1 and 3 are induced by a variety of inflammatory cytokines including INFγand LPS. Overall, SOCS 1and 3 are examples of NIRegs because they block the JAK/STAT pathway regulating glial and neuron inflammatory cytokine synthesis.

SOCS1 and SOCS3 have potentially important clinical applications. Administration of SOCS-1 to experimental animals prevents EAE by inhibiting JAK-2 mediated phosphorylation reducing the expression of inflammatory cytokines IL-2, IL -5 and TNFα raising the possibility that SOCS-1 is a potential therapeutic agent to treat inflammatory mediated demyelination (Baker et al 2010)Furthermore, the level of SOCS 3 exppressed by T cells in relapsed MS was less than in remission and this correlated with STAT levels, such that reduced SOCS allowed STAT to rise increasing inflammatory cytokine levels and increasing the likelihood of relapse. (Baker et al 2009 for review of clinical studies involving SOCS)

9.3 Loss of immuno surveillance, NIRegs and CNS neoplasia

Glioblastoma (GBM), is the most common primary brain tumour in adults, it is highly aggressive and infiltrates throughout the brain. These tumours have developed the capacity to escape immune surveillance by suppressing the host anti -glioma response. Failure to promote an anti glioma response is associated with an accumulation of immunosuppressive, CD4-Fox P3+ regulatory T cells, both within and surrounding the tumour (Sonabend et al., 2008). Glioma stem cells and macrophages are also capable of inducing immuno supression in host microglia, because they express the anti -inflammatory cytokines TGF-1β MIC-1macrophage inhibitory factor and also inhibit microglial phagocytosis (Wu et al., 2010; Hussain et al., 2006). A pivotal role in this apparent loss of anti- glioma response is the inhibition of the JAK/STAT signalling pathway in glioma cells with resulting cell proliferation, inhibition of both host cell inflammatory response and tumour immuno surveillance (Brantley et al., 2008). The inhibition of STAT signalling pathway in GBM is thought to result from an over expression of the NIReg, SOCS -1that inhibits STAT and function as an immuno-modulatory molecule by blocking IFNβ and CD40, with the down regulation of both MHC I and II expression in GBM. However, the function role of the other SOCS proteins (SCOCS- 3) in GBM remains to be clarified; in vitro SOCS -3 increases the IL-10 mediated anti-inflammatory response and radio resistance, but therapeutic inhibition of STATalso promotes microglial recognition of glioma cells (Baker et al., 2009).

Glioma cells express a limited range of TLR and application of various ligands including LPS and Poly I; C did not have any therapeutic effect, probably due to the failure to stimulate intra tumour Antigen Presenting Cells. (Grauner et al., 2008. However, the injection of the TLR9 ligand, CpG, an oligonucleotide, resulted in effective anti glioma response with inhibition of local Tregs, together with an T effector cell mediated anti - glioma respons. TLR9 is not present in host cells surrounding the glioma, providing an explanation for the apparent failure of host cell to produce an effective T cell response (Grauner et al., 2008). The intra tumour injection of ligands such as CpG to selectively stimulate host expression of TLR is of potential therapeutic importance.

One further protective strategy employed by gliomas to evade imuno surveillance is the expression of C regulator proteins. Activation of C pathway is potentially able to lyse tumour cells, but several glioma cells lines have been shown to express complement regulators CD59, CD55, CD46 and FH on their cell surface, preventing C attack and generation of lytic MAC(Maenpaa A et al., 1996, Junnikkala S et al., 2000). One possible therapeutic route is infact, the use of surface CD46, this Creg is very similar to the adenovirus receptors (adenovirus serotype 3) and provides a target to deliver an adenovirus containing anti- glioma therapy. (Ulasov et al 2006)

Outside the CNS, squamous cell carcinoma of the skin, leukaemias and myeloma cells up regulate surface expression of the NIReg, CD200, and this inhibits local immune detection promoting metastatic potential. After spreading to local lymph nodes, metastatic tumour cells that are CD200+ interact with local CD200R+ myeloid drived cells such as macrophages and potentially microglia, enhancing their survival, conversely loss of CD200 reduces metastatic tumour survival. The expression of CD200 is a property of the primary tumour and this expression did not vary according the type of tissue infiltrated by metastatic tumour (Stumpova et al., 2010).

10. Conclusion

The host inflammatory reaction is required to counter the detrimental effects of pathogen invasion (encephalitis and meningitis) and the accumulation of amyloid, mutant prions (neurodegenerative disease). One consequence of the host's protective inflammatory reaction is an inevitable amount of associated tissue injury. The detrimental effects of tissue injury have to be to be balanced against the, consequences of not removing a pathogen (or clearing neurotoxic proteins), usually this leads to peristent inflammation preventing any tissue repair. This balance between protective and destructive consquences is the so called "double edged sword"effect, that accompanies brain inflammation (Wyss- Coray and Mucke 2002). The role of the NIRegs is to modulate the level of the protective inflammatory response, in order to provide the "appropriate amount " of inflammation to allow the efficent clearance of pathogens and neurotoxic proteins from the brain.

The immune response against "non self" (pathogens, neurotoxic protiens) must be critically regulated in order to provide conditions of tissue repair without excessive destruction of "self "or host cells. Self (host) must be distinguish from " non –self "as defined by, pathogens PAMPs, apoptotic cells ACAMPs and "danger proteins" (HMGB1, HSP and S100) classified as (DAMPs). Non self (PAMPS, DAMPS), is detected by a range of intracellular and trans membrane PRR (TLR, RIG, NDLR,) whereas the scavenger receptors CD14, CD36, C lectins and TREM-2 provide a clerance pathway for apoptotic cells and neurotoxic proteins. Activation of the complement pathway by pathogens and neurotoxic proteins (Fibrillary Amyloid and mutant prion protein) results in MAC formation and anaphylotoxins C3a and C5a, all promoting inflammation and tissue destruction. The C pathway also assists the SR clear apoptotic cells through opsonins C3 and C4 localization on the surface of apoptotic cells.

To prevent excessive host tissue destruction, (NIRegs) must control the proinflammatory response and efficiently clear apoptotic cells (non-phlogistic response), before they are able to release neurotoxic enzymes to increase host tissue destruction. NIRegs, provide cell surface signals (CD200, CD47, sialic acid, CD46,) to identify "self " and through interaction with counter receptors (CD200R, CD172a, FH, Siglecs, CD24 –Siglec,) utilizing ITAM /ITIM pathways, inhibit microglial activation and phagocytosis of host cells. The C pathway is regulated by a series of CRP also regarded as NIRegs, because they reduce C activation and excessive host tissue destruction. The inhibiton of CRPs on tumour cells could provide a mechanism to increase host anti -tumour cell lysis as well as providing receptors for the delivery of viruses carrying anti glioma reagents. One emerging pathway controls, microglial activation as the result of T cells expressing Sema 4D; inhibiton of this pathway resulted in a down regulation of the severity of inflammation in MOG induced EAE. Similarly, the contribution made by the SOCS family of intracellular proteins to regulating the innate immune response in a diverse range of neuroinflammatory conditions requires clarification.

The therapeutic benefit of NIRegs is apparent, but to date, there is only limited evidence for their influence in clinical examples of neuro-degeneration and neuro-inflammation. CD200-CD200R, CD47 and SOCS have been detected in MS tissue providing evidence for dys regulation of the host inflammatory response. There is some experimental evidence to show PAMPS and DAMPs can be distinguished by the host and DAMP initiated inflammation is regulated by the emerging NIReg, CD24/Siglec, pathway. The cellular localization and functional importance for each of the NIRegs is summarised in table 2.

It is highly likely the NIRegs provide a range of potentially important therapeutic reagents that selectively regulate the host immune response and promote tissue repair in a variety of brain infections (viral and bacterial), neurodegerative diseases and neoplasia. The opportunity presented by the NIRegs as the means to selectively regulate the CNS immune response to a wide range of pathogens and neurotoxic proteins should be exploited as a matter of some importance.

Pattern Recognition Receptor PRR	Ligand detected	PRR and CNS cell expression	Function	Host Innate immune response
TLR2	Bacterial cell wall peptidoglycan Zymosan (Fungi) Haemagluttin (Measles virus)	Microglia Astrocytes Choroid plexus	Form hetero dimres with TLR-1 to detect Gram neg ative bacteria Co operates with Dectin -1to detect fungi	Microglia increased pro inflammatory cytokines Phagocytosis
TLR3	ds RNA	Neurons microglia astrocytes oligodendroglia	West Nile Virus Detect necrosis and danger signals (HMGB, HSP)	Microglial IFNβ TNFα IL-6 Systemic cytokines and BBB receptor
TLR4	Bacteria Lipopolysacahride LPS	Microglia, astrocytes ependyma Choroid plexus	Cooperates with CD36, CD14 and DC-SIGN to detect fungi and *Streptococcus pneumonia*	Microglia and astrocyte inflammatory cytokines phagocytosis of apoptotic cells
TLR 5	Flagellin, bacterial protein	Macrophage		
TLR7	ssRNA	Microglia, astrocytes ependyma, neurons	Influenza A Detect necrosis and "danger signal "HMGB, HSP	Astrocytes increased TNFα IFNβ MCP-1
TLR8	ssRNA	Neurons	RNA viruses	Astrocytes increased TNF α, IFNβ, MCP-1
TLR9	CpG DNA	Microglia, astrocytes	Detect necrosis and "danger signals" HMBG-1	Microglia express TNFα, IL-12, NO HMBG-1 /RAGE detected by TLR-9
TLR11	Profilin, bacterial protein	Genitourinary Neurons	Detects Toxoplasmosis Neurocysticerosis	Inflammatory cytokines
RIG-1	Short dsRNA	Microglia, astrocytes	Japanese encephalitis virus Influenza A, Ebola virus	Astrocytes express IFNβ, IL-6, IL-8 RANTES
MDA-5	Long dsRNA	Microglia astrocytes	?Nipah virus, polio virus,	Microglia express IFNβ
NOD like	Bacterial cell wall		*Listeria bacillius Shigella*	

Receptors NOD-1 and NOD-2		?Microglia, astrocytes	*Flexneri* *Helicobacter pylori* *Mycobacterium tuberculosis*	
NLR -3 (NLP-3)	Bacterial cell wall peptidglycan peptidoglycan and virus proteins	? in CNS	Bacteria Viruses Crohn's disease	Inflammasome(NLR ASC, procaspase -1) is engaged to produce inflammatory cytokines

Table 1. Shows the individual ligands detected by TLR and Non- TLR (R LR MDA and NLR), Pattern Recognition Receptors PRR in the CNS. The cellular distribution of each of these receptors in the CNS is provided together with their contribution to host CNS innate immune system in response to pathogens(PAMPS and danger signals (DAMPS).

Neuroimmuoregulatory (NIReg)	**NIReg- receptor/ligand**	**Cell –cell interaction**	**Mechanism of immune regulation**	**Human disease**
CD200 Astrocyte	CD200R microglia	Astrocyte – microglia	Reduce phagocytosis	Alzheimer's (AD) Multiple sclerosis (MS)
CD47 Astrocyte Endothelium neuron	CD172a myeloid cells microglia	Astrocyte – microglia	Reduce phagocytosis and cytokine expression	Multiple sclerosis
Complement regulators FH, CD46, CD55, CD59 C4bp CD46 (MCP) CD55(DAF)	Sialic acid Complement proteins	Astrocytes Microglia Neurons	Reduce C activation	Neurodegenerative disease AD Huntington's disease Inhibits complement regulation of glioma lysis
Siglecs CD33 family Siglec 10 Siglec 11	Sialic acid Detect absence of sialic acids " non self"	NK cells Microglia	Reduces inflammation ITIM pathway	Bacterial infection; bacteria mimic sialic acids to become " self "
CD24 -Siglec 10 pathway	DAMPs HMGB-1	microglia stem cells	Binds with SHP - 1, this complex inhibits DAMPS activation of NF-kB	Reduces DAMP associated inflammation Polymorphisms in CD24 associated with autoimmune disease
Suppressor of cytokine synthesis SOCS1 SOCS3	Inhibits IFN and IL cytokine stimulation of cytokine expression	Microglia astrocytes neurons	Blocks JAK/STAT cytokine pathway	Glioblastoma SOCS increased SOCS reduced in relapsed MS

Thrombomodulin CD141	HMBG1/ DAMPS	Microglia	Blocks HMBG binding to RAGE and TLR activation	
Semaphorin SEMA4	CD72 on T cells Plexin B1 on microglia	T cell with microglia	Blocks ITIM increases cytokine expression	Sema4D deficiency reduced EAE severity

Table 2. The potential of NIRegs and their cellular localization, ligands and mechanism whereby they produce immuno regulation. In the final column there is information relating to their contribution to infection, neurodegeneration and neuro inflammation as well as neoplasia, in the human CNS.

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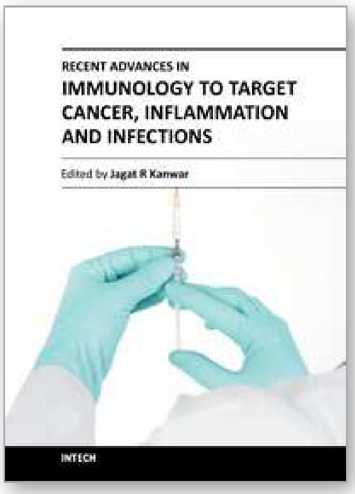

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.