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Research paper

An opinion on the debatable function of brain resident immune protein, T-cell receptor beta subunit in the central nervous system

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ABSTRACT

In recent years scientific research has established that the nervous and immune systems have shared molecular signaling components. Proteins native to immune cells, which are also found in the brain, have neuronal functions in the nervous system where they affect synaptic plasticity, axonal regeneration, neurogenesis, and neurotransmission. Certain native immune molecules like major histocompatibility complex I (MHC-I), paired immunoglobulin receptor B (PirB), toll-like receptor (TLR), cluster of differentiation-3 zeta (CD3ζ), CD4 co-receptor, and T-cell receptor beta (TCR-β) expression in neurons have been extensively documented. In this review, we provide our opinion and discussed the possible roles of T-cell receptor beta subunits in modulating the function of neurons in the central nervous system. Based on the previous findings of Syken and Shatz., 2003; Nishiyori et al., 2004; Rodriguez et., 1993 and Komal et., 2014; we discuss whether restrictive expression of TCR-β subunits in selected brain regions could be involved in the pathology of neurological disorders and whether their aberrant enhancement in expression may be considered as a suitable biomarker for aging or neurodegenerative diseases like Huntington's disease (HD).

1. Overview of T-cell receptors (TCRs)

The discovery of certain native immune molecules and their receptors like major histocompatibility complex (MHC) and T-cell receptor (TCR) subunits in brain tissue about two decades ago revolutionized the notion of the brain being an immune-privileged organ and opened up the possibility that these immune proteins may have a novel functional role in the central nervous system (Boulanger, 2004; Huh et al., 2000; Shatz, 2009; Syken and Shatz, 2003., Nishiyori et al., 2004). These immune proteins are well known for their contribution to regulating innate and adaptive immune responses (Marshall et al., 2018). In this section, we will discuss the pieces of evidence which suggest that immune receptors are not only expressed by neurons but also, play an important neuronal function in both normal and diseased brains (Bernaus et al., 2020; Bien et al., 2002; Boulanger, 2004; Boulanger and Shatz, 2004; Komal et al., 2014; Komal and Nashmi, 2015; Rodriguez et al., 1993; Shatz, 2009; Tian et al., 2012). Several molecules and receptors, like the major histocompatibility complex (MHC), which are traditionally well known to function in the immune system, have also been identified as mediators of synaptic refinement and plasticity in the visual system (Boulanger, 2004; Huh et al., 2000; Lee et al., 2014). In particular, the obligate partners of MHC-I molecules like CD3ζ (native light chain component for MHC-I) and TAP-1 (a component of the transporter that is required for the delivery of peptides to class I MHC and proceeds its cell surface expression in the immune system) are also expressed in the adult brain (Boulanger, 2004; Boulanger and Shatz, 2004; Corriveau et al., 1998; Huh et al., 2000). The work done by Corriveau and colleagues reported the neuronal expression of MHC-I, CD3ζ, and β2-microglobulin (β2M; an essential molecular component that is required for stable surface expression of MHC-I). They also documented that neurons were capable of expressing both the ligand (CD3ζ) and the signaling component for MHC-I (β2M) molecules in the adult brain (Corriveau et al., 1998). An enhancement in the MHC-I molecular expression was observed in the adult hippocampus when

Abbreviations: HD, Huntington's disease; PD, Parkinson's disease; AD, Alzheimer's disease; TAP-1, transporter associated with antigen processing 1; NMDA, N-methyl-D-aspartate; CP-AMPA, calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; α7 nAChRs, alpha7 nicotinic acetylcholine receptors; LTP, long-term potentiation.

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prone to high neuronal activity like those observed during seizures. Thus, they found that increased MHC-I gene expression happened both during normal neuronal development and also under abnormal conditions like seizures. Another study undertaken by Huh and colleagues specifically showed synaptic localization of MHC-I molecules in the adult hippocampus. The same group observed that the genetic ablation of accessory molecules for MHC-I molecules like CD3ζ, β2M, and TAP1 in mice showed, N-methyl-D-aspartate (NMDA) receptor-dependent enhancement in the long-term potentiation (LTP). The same authors suggested that MHC-I/CD3ζ dependent signaling regulated synaptic plasticity in hippocampus neurons. Later, Fourgeaud and his colleagues documented the functional effect of MHC-I on the NMDA receptor, which is an excitatory ligand-gated ion channel in the central nervous system (CNS) activated by glutamate. In their study, MHC-I deficient mice showed an enhancement in NMDA whole-cell current response with no change in total surface receptor expression. The authors argued on the possibility of migration of NMDA receptors from peri-synaptic to synaptic sites by MHC-I or whether it mediated post-translational modification of NMDA receptors located already in the dendritic spines (Fourgeaud et al., 2010). The above studies provided convincing details on not only the postsynaptic localization and expression of MHC-I in the CNS but also its functional consequences i.e. its regulatory effect on NMDA receptors in a cell-autonomous manner. The genetic ablation of MHC-I molecules and its binding partner CD3ζ also caused significant impairment in synaptic connections in the visual system and its target regions of the CNS (Corriveau et al., 1998; Huh et al., 2000; Lee et al., 2014). Lee and colleagues demonstrated that MHC-I knockout (KO) mice, even with intact retinal waves and normal basal synaptic transmission in the retinogeniculate synapses, showed significant impairment in LTD. The restoration of MHC-I expression in the neurons of KO mice rescued deficits in LTD via downregulating the function of calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (CP-AMPA) only at retinogeniculate synapses. Altogether, all the above evidence provided enough sufficient data which demonstrated the neuronal function of MHC-I molecules in synaptic transmission and plasticity. Thus, the discovery of two molecules essential to TCR immune signaling, the major histocompatibility complex class-I (MHC-I) and the T-cell surface glycoprotein cluster of differentiation-zeta (CD3ζ) in the mammalian brain raised the question of whether other components of T-cell receptor molecules like TCR-β subunit might be expressed on neuronal cell surfaces. This question was answered by Syken and Shatz (2003), who found that the T-cell receptor β locus was expressed in distinct brain regions and dynamically regulated over development. Together with MHC-I and TCR-β, the CD4 coreceptor was also documented to be neuronally expressed (Boulanger, 2004; Cebrián et al., 2014; Huh et al., 2000; Omri et al., 1994; Syken and Shatz, 2003). RAG-1 and RAG-2 are also expressed by vertebrate neurons (Chun et al., 1991; Jessen et al., 2001). The neuronally expressed TCR-β was proposed not to undergo gene recombination and the neuronal TCR-β transcripts were discovered to be transcribed from unrearranged genomic loci (Syken and Shatz, 2003). Thus, the TCR-β gene was shown to be aberrantly transcribed without DNA rearrangement in the murine neocortex and thalamus to produce an unusual transcript in the brain.

These facts raised the possibility of TCR-β subunit expression in neurons. Though the functional role of these molecules in neuronal function has not yet been fully uncovered, Komal and colleagues showed that exogenous activation of the entire T-cell receptor (TCR; Fig. 1) machinery with its entire accessory molecules like TCR-β, CD3-ζ, and CD4 coreceptors negatively impacted cholinergic neurotransmission via downregulation in the function and expression of α7 nicotinic acetylcholine receptors (α7 nAChRs) in the healthy brain (Komal et al. 2014). Whether an abnormal increase in the expression of the TCR-β subunit causes impairments in synaptic transmission and plasticity as shown for MHC-I molecules however, remains unexplored. In this review, we propose that an aberrant elevation in the expression of TCR-β subunits

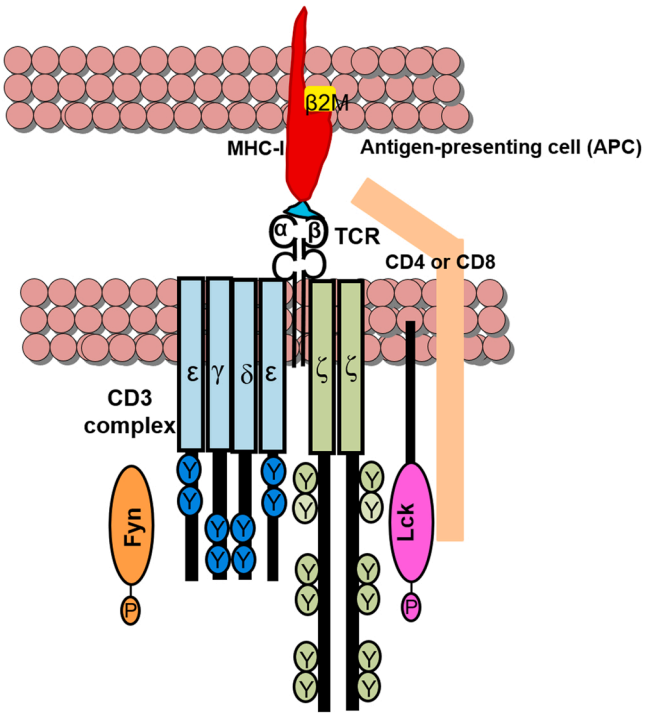

Fig. 1. Diagrammatic representation of the MHCI-TCR complex. In the immune system a functional TCR complex comprises a group of closely associated proteins required for signal transduction and signal propagation into the cell. The T-cell receptor (TCR) is a cell surface receptor endogenously expressed on the surface of T- lymphocytes or T-cells and initiates cell-cell communication via its interaction with the major histocompatibility complex class-I (MHC-I) or MHC-II in the immune system (Gascoigne, 2008). TCR alpha and beta subunit receptor (TCR α/β) interacts with the peptide presented by an antigen presenting cell (either by MHC-I or MHC-II) which mediates downstream signaling processes controlled by the ten immunoreceptor tyrosine-based activation motifs (ITAMs). These ITAMS are present in the invariant chains of the TCR complex namely TCR CD3-zeta (cluster of differentiation-3, CD3-ζ), CD3-gamma (CD3-γ), CD3-delta (CD3-δ) and CD3-epsilon (CD3-ε); Mørch et al., 2020; Komal and Nashmi, 2015; Pitcher and Oers, 2003). Each ITAM of a CD3 chain is represented by a pair of tyrosine residues i.e "Y''s. These tyrosine residues can be phosphorylated by Src family of tyrosine kinases, Fyn and Lck kinases, and can act as a docking site and activator of SH2 containing Src kinase family. CD8 or CD-4 is a co-receptor of the TCR and assists with the binding of the TCR to the antigen presenting cell through the interaction between CD8 or CD-4 and MHC-I.

may be indicative of neuronal atrophy and synaptic impairments. It must be emphasized here that a substantial experimental evidence is still needed to determine whether under normal basal conditions TCR-β solely participates in synaptic transmission or does aging or a neuropathological insult aberrantly enhances TCR-β expression to facilitate neuronal loss as observed across a spectrum of neurodegenerative diseases including Huntington's disease (HD; Cherubini et al., 2020; Costa and Scorrano, 2012; Islam, 2017; Maity et al., 2022; Paul and Snyder, 2019).

T-cell receptors are natively expressed by T-lymphocytes (or T-cells) which constitute a vital component of the adaptive immune system (Marshall et al., 2018). The principal function of T-cells is to provide a highly specific line of immunological defense against foreign pathogen invasion and distinguish between self- and non-self-antigens (Gascoigne, 2008; Marshall et al., 2018). This role of T-cells heavily relies on recombination-acting genes (*Rag 1* and *Rag 2*) which produce a vast diversity of antigen receptors on T-cells and immunoglobulin receptors on B-cells, to defend against foreign pathogenic insult (Dong et al., 2021; Kumari et al., 2021; Miyazaki et al., 2020). There are four well-defined antigen receptor polypeptides (α, β, γ, δ) on T-cells which occur either in

α/β or in γ/δ heterodimeric combinations (Davis and Bjorkman, 1988). These receptor polypeptides resemble immunoglobulins (Ig) in primary sequence, gene organization, and modes of rearrangement (Davis and Bjorkman, 1988). TCRs comprise either an alpha and a beta chain (TCR α/β) in the majority of T cells, or less frequently, gamma and delta chains (TCR γ/δ). Each α and β polypeptide contains one constant (C) and one variable (V) domain which occurs through genetic recombination of variable (V), diversity (D), and joining (J) gene segments (Thomas et al., 2019; Wu and Bassing, 2020). A functional TCR is formed when each V (D) J connects with a downstream constant (C) region, to produce a diverse repertoire of antigen-receptor specificities required by the vertebrate immune system (Janeway et al., 2001; Thomas et al., 2019). In the process of V(D) J recombination the two site-specific endonucleases (RAG 1 and RAG2) create a double-stranded break which constitutes the diverse pool of T-cell receptors (Miyazaki et al., 2020). TCR-gene rearrangements can generate ~10^{15} different TCRs (Davis and Bjorkman, 1988). The TCR is a cell surface receptor that initiates cell-cell communication via its interaction with major histocompatibility complex class-I (MHC-I) or MHC-II in the immune system (Gascoigne, 2008). TCR-mediated downstream signaling processes are controlled by the ten immunoreceptor tyrosine-based activation motifs (ITAMs) present in the invariant chains of the TCR complex namely TCR CD3-zeta (cluster of differentiation −3, CD3-ζ), CD3-gamma (CD-γ), CD3-delta (CD3-δ) and CD3-epsilon (CD3-ε); (Fig. 1; Mørch et al., 2020; Komal and Nashmi, 2015; Pitcher and Oers, 2003). The adaptor protein CD3 and co-stimulatory molecule, CD4 and CD8 coreceptors are vital for TCR-mediated downstream molecular activation (Davis and Bjorkman, 1988; Komal and Nashmi, 2015; Love and Hayes, 2010). Thus, a functional TCR complex comprises a group of closely associated proteins required for signal transduction and signal propagation into the cell.

It is known that the mammalian brain undergoes extensive immune surveillance both under normal and pathological conditions (Alam et al., 2020; Kettenmann et al., 2011; Nayak et al., 2012; Ousman and Kubes, 2012). CNS patrolling and invasion of peripheral immune cells like T-lymphocytes following an injury, infection, ischemia, and neurodegeneration in the CNS is also well documented (Bachiller et al., 2018; Brochard et al., 2009; Evans et al., 2019; Nazmi et al., 2018; Zhang et al., 2018). While the migration of peripheral T lymphocytes (T-cell) into the central nervous system has been well documented (Brochard et al., 2009; Marshall et al., 2018; Tian et al., 2012), for the purpose of this review, we will restrict our attention on neuronally expressed immune molecules including MHC-I, paired immunoglobulin-like receptor B (PirB), toll-like receptors (TLRs) and T-cell receptor components such as CD3ζ with a primary focus on T-cell receptor beta (TCR-β) subunits.

2. Probable neuronal functions of immune protein, TCR-β subunit in the central nervous system

Previously, the possibility of neuronal expression of immune proteins such as the T-cell receptor was not contemplated since the brain was considered an immune-privileged organ. The discovery of the TCR subunit complex, CD4 and tyrosine protein kinases (c-Src and Fyn) in the brain raised the possibility of an alternative neuronal function of TCR-β mediated signal transduction cascade in the brain like those which occur in the adaptive immune system (Grant et al., 1992; Omri et al., 1994; Ross et al., 1988; Syken and Shatz, 2003). A decade later after TCR-β expression was elucidated in the CNS, Komal et al. (2014) deciphered a direct effect of TCR activation on neuronal function through modulation of α7 nicotinic acetylcholine receptors. The findings of the study reflected a possible role of TCR-β on basal neuronal information processing capacity as TCR-β knockout mice showed enhanced spiking in layer 1 cortical neurons. TCR activation through the application of exogenous ligand, *concanavalin A* (ConA) was demonstrated to affect α7 nicotinic acetylcholine receptor trafficking, expression, and function. TCR stimulation mediated a decrease in α7 single-channel conductance, whole-cell current, and surface expression of the channel due to the downstream activation of Src kinases, namely Fyn and Lck kinases. Elevated activity of Fyn kinases under neuropathological conditions like those seen in Huntington's disease is reported and possibly suggests that elevated TCR signaling may function as an active partner facilitating neurodegeneration (Guglietti et al., 2021; Tang et al., 2020). This statement is validated by a recent finding where inhibition of Fyn activity rescued memory function and synaptic loss (Tang et al., 2020). In other words, it is plausible to hypothesize that upregulation of TCR and Fyn activity as shown by Komal et al. (2014) in parallel with inhibition of α7 receptor activity, supports the idea that TCR might have a broader functional neuronal role in both healthy and diseased brain. Fyn-mediated effect on α7 nicotinic acetylcholine receptor responses was abrogated when cells were cotransfected with an inactive form of Fyn (kinase-dead form, FKD). Fyn-mediated direct phosphorylation of a tyrosine residue located in the cytoplasmic loop of the α7 channel was found to downregulate the surface expression and single-channel conductance of α7 receptors. *In vitro* results also confirmed the requirement of Lck kinase and its active participation in TCR-mediated decrease in α7 nicotinic receptor (α7 nAChRs) whole-cell current responses. Genetic ablation of Lck kinase in Jurkat T-cells did not result in TCR activation, even upon Con A stimulation. Thus, these results supported the involvement of Lck kinase in mediating downstream activation of TCR. Similarly, in absence of the TCR-β subunit, no TCR activation occurred and no change in α7 receptor-mediated whole-cell response occurred in both in vivo in layer 1 cortical neurons and in vitro model of Jurkat T-cells (Komal et al., 2014). In the same study, TCR-β KO mice displayed increased excitability in layer 1 interneurons, supporting the idea that increased synaptic signaling is mediated by cholinergic α7 receptors. Also, increased excitability observed in these TCR-β KO mice also begs the question of what effect elevated neuronal TCR-β expression might have on memory and synaptogenesis. The functions of native partners for TCR are MHC-I molecules and it is known that MHC-I molecules at neuronal synapses contribute toward synaptic plasticity, synaptic transmission, and glutamate receptor trafficking (Boulanger, 2004; Boulanger and Shatz, 2004; Huh et al., 2000). This is already well documented in another review (Komal and Nashmi, 2015). Hence, it is very likely that TCR-β, like MHC-I, does have an impact on the neuronal activity as genetic ablation of TCR-β enhanced the cholinergic neurotransmission.

An increased MHC-I expression on dopaminergic neurons was recently demonstrated in Parkinson's disease (PD) where the authors argued that this enhancement in MHC-I expression also augmented neurodegeneration characterized by increased oxidative stress and dysfunctional mitochondria (Wang et al., 2021). In PD, Src kinase inhibition is also documented to be a potential therapeutic target to combat neuroinflammation (Yang et al., 2020). Presently, we don't know whether similar neurotoxic conditions associated with increased neuroinflammation also induce a high expression of T-cell receptor β subunit facilitating neuronal loss in neurological disorders. Therefore, it is observed that immune molecules like MHC-I played a vital function in both healthy and diseased brain conditions. In summary, it is known that a variety of immune proteins such as the major histocompatibility complex type I (MHCI) (Boulanger and Shatz, 2004), T-cell receptor β subunit (Syken and Shatz, 2003), the T-cell receptor CD3ζ subunit (Baudouin et al., 2008) and the activatedT-cell receptor complex (Komal et al.; 2014) are implicated in having important neuronal functions, where they modulate ion channel receptor function in the central nervous system. In particular, work done by Komal et al. (2014) demonstrated the downregulation of α7 nicotinic acetylcholine receptor function via T-cell receptor activation in a Jurkat T-cell line as well as in a murine model.

3. Can TCR-β be considered a neuropathological biomarker?

Evidence suggests that ''immune receptors'' like major histocompatibility complexes type I (MHC-I), CD-3 zeta and Pir-B receptors play a

role in neurodegenerative -diseases and could be a potential therapeutic target for neurological disorders like Alzheimer's disease (AD) (Kim et al., 2013; Welberg, 2013). Immune proteins native to the immune system but expressed in the nervous system are known to have neuronal functions, where they affect vital brain functions like neuronal physiology, neuronal excitability and synaptic plasticity (Boulanger, 2004; Boulanger and Shatz, 2004; Huh et al., 2000; Komal et al., 2014). An enhancement in MHC-I expression has been documented in autoimmune diseases, neurological disorders like epilepsy, schizophrenia, ischemia, stroke, autism spectrum disorder, amyloid lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD) (Alves et al., 2007; Cebrián et al., 2014; Guzman-Martinez et al., 2019; Naito et al., 2021; Sellgren et al., 2019; Wang et al., 2021). Another innate immune system receptor molecule i.e paired immunoglobulin-like receptor B (PirB) is recognized as an important contributor of spine density and spine turnover in the visual cortex (Djurisic et al., 2013; Kim et al., 2013). Djurisic and his co-workers showed that PirB receptors were negative regulators of synaptic structure and plasticity. In the deeper layers of both juvenile and adult mouse visual cortex, the authors found that in absence of PirB receptors, there was a substantial reduction in dendritic spine motility which was accompanied with increase in spine density. Their studies proved that PirB receptors were a critical regulatory component capable of initiating molecular signaling and capable of transducing experience-dependent plasticity into stable synapses. Another study showed that deletion of PirB receptors could combat amyloid-β (Aβ) plaque aggregation in murine models of Alzheimer's disease (Kim et al., 2013). The human orthologue for PirB receptors is known as leukocyte immunoglobulin-like receptor B2 or LilrB2. Kim and colleagues observed an equal protein expression of LilrB2 in non-AD as well as in AD patients. However, they found subtle differences in the downstream signaling cascade initiated, when LilrB2 or PirB receptors were attached to soluble synthetic Aβ oligomer (Aβ42) used in their experiments. The same group proved that LilrB2 acted as a high affinity endogenous receptor for Aβ oligomers in AD and this interaction was possible with just the presence of extracellular, N-terminal immunoglobulin (Ig) domains (D1D2) of PirB and LilrB2 receptors. Other evidence on the role of PirB or LilrB2 in AD comes from the same group showing deficits in long-term potentiation (LTP) and memory dysfunction in PirB wild type mice and not in its genetic deleted counterparts (PirB-/- knockout mice), reflecting the binding of Aβ oligomer to PirB receptors occurring only during AD neuropathology. It is known that Aβ generation and accumulation result in the dysfunction of synaptic transmission by weakening synaptic plasticity (Djurisic et al., 2013; Kim et al., 2013; William et al., 2012). Altogether, the above findings emphasized the functional importance of innate immune protein receptor in both healthy and neuropathological conditions, where engagement of PirB or LilrB2 receptors with Aβ oligomer initiated a detrimental downstream signaling cascade which ultimately resulted in alteration in synaptic function and potentiated cognitive and memory impairments. The immune molecules mediated signaling cascades led to a loss of actin polymerization, a reduction in post-synaptic density protein, PSD-95, and elevated phosphatase activity of PP2A and PP2B (or calcineurin), which ultimately resulted in synapse elimination (Djurisic et al., 2013; Kim et al., 2013). Thus, an increased expression of native immune molecules like PirB receptors or CD3ζ significantly impaired neuronal activity and potentiated neurotoxic conditions as observed in AD or PD.

The contribution towards synaptic dysfunction was also observed for other immune proteins in the brain such as MHC-I molecules, complement system proteins and cytokines in neuropsychiatric disorders like Schizophrenia, Alzheimer's, Parkinson's and Huntington's disease (Sakai, 2020; Schartz and Tenner, 2020; Sellgren et al., 2019; Tenner et al., 2018; William et al., 2012; Ziabska et al., 2021). However, it remains to be seen whether a substantial increase in TCR-β is also observed under such neuropathological conditions like those observed in HD. Although Boulanger and Shatz in their review argued that the products of MHC-I gene can be linked with neurological disorders including HD, it remains unexplored whether a substantial enhancement in the TCR-β subunit expression ultimately causes synaptotoxicity in HD, as documented previously by Kim and his collegues for PirB/LilrB2 receptors (Boulanger and Shatz., 2004; Kim et al., 2013). A very recent study by Kim and co-workers showed that activation of toll-like receptor (TLRs) may impair autophagy and interfere with the degradation of α-synuclein (α-syn) fibrils in Parkinson's disease (PD) and dementia (Kim et al., 2021). The same study specifically explored the interaction of different α-syn aggregates with an innate immune receptor i.e TLR. The authors demonstrated that merely the activation of TLR2 on brain resident cells like neurons, microglia and astrocytes, in absence of any direct interaction, showed increased uptake of α-syn fibrils. This increased expression of TLR2 accelerated microglial activation and potentiated the neuronal pathology associated with PD. In Huntington's disease, Pérez-Rodríguez and his colleagues showed that mutant huntingtin protein (mHtt) caused an aberrant wave of neuroinflammation triggered by toll-like receptor- 4 (TLR-4) outside the CNS. mHtt abrogated the innate immune function of mast cells and abolished the signals induced by TLR-4 in a transgenic mouse model of HD (Pérez-Rodríguez et al., 2020). Thus, neurodegeneration, neuroinflammation and neurotoxic conditions not only enhanced the surface expression of native immune molecules like MHC-I, PirB or TLRs receptors in the CNS but they also impeded the neuronal or immune cell functions.

The accumulation and aggregation of misfolded proteins are known to be a common feature of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) (Lim and Yue, 2015). Neurotoxicity is also commonly observed in most neurodegenerative disorders characterized by chronic stress and chronic neuroinflammation (Bernaus et al., 2020; Guzman-Martinez et al., 2019; Owens, 2017; Tian et al., 2012). In such a scenario, it may be argued that the neuronal TCR-β expression may be robustly upregulated like another innate immune receptor, the Toll-like receptors (TLRs) or PirB receptors (Djurisic et al., 2013; Kim et al., 2013; Kim et al., 2018; Kwon et al., 2019). Based on these evidences, a comparable link between modulation of TCR-β subunit expression with protein aggregates observed in HD (mHtt) can be made which presently remains a mystery in the area of neuroimmunology (Fig. 2). Interestingly, our lab has found that the gene expression of TCR-β subunit receptor was significantly enhanced in two vital brain regions, namely the cortex and the striatum, in an experimental mouse model of HD (unpublished data). These two brain areas are known to be most vulnerable in undergoing neurodegeneration in HD (Blumenstock and Dudanova, 2020; Lewitus et al., 2014; Manjari et al.; 2022). It may be hypothesized that high neuronal expression of TCR-β expression on medium spiny neurons (MSNs) and cortical neurons might increase the likelihood to undergo neuronal atrophy in HD. Thus, one purely speculative cause for the high susceptibility of MSNs to undergo neurodegeneration and followed by cortical neurons could be due to an abnormal increase in the surface expression of TCR-β subunit.

A long-standing question in the field of neuroscience is what makes neurons the most vulnerable cell types in the face of disease-related aggregate formation? One potential answer could be the upregulation of adaptive immune receptor proteins such as the TCR-β subunit expression on neurons. It may be argued that under normal physiological conditions TCR-β may serve as a neuron-specific recognition molecule at certain synapses to form highly ordered neuronal networks. The Shatz paper raised an open question about the possibility of TCR-β in synapse remodeling (Syken and Shatz, 2003). However, presently it is unknown if under these conditions there is a concomitant increase in TCR-β expression. It is known that the loss of synapses is one of the hallmarks of several neurodegenerative diseases including HD (Blumenstock and Dudanova, 2020; Gil and Rego, 2008). Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder which results in massive death of neurons in the striatum (Gil and Rego, 2008). We speculate that there are a number of diverse contributors towards selective loss of striatal neurons as observed in HD (Manjari

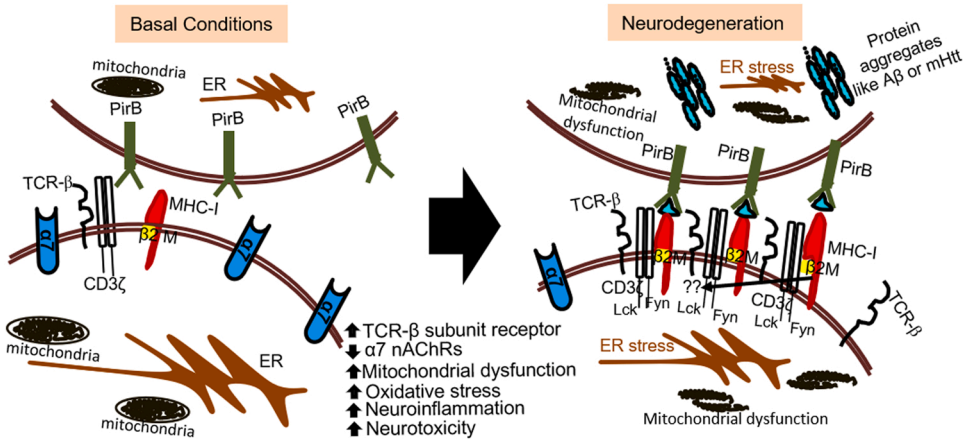

Fig. 2. A hypothetical model representing an elevated expression of TCR-β subunit occurrence under a neuropathological condition like those observed in Huntington's disease (HD). Under basal conditions, PirB receptors do not present protein oligomers formed in neurological disorders like Alzheimer's, disease (AD; Djurisic et al., 2013; Kim et al., 2013). However, increased mitochondrial dysfunction, oxidative stress, neuroinflammation, excitotoxicity and endoplasmic reticulum stress (ER-stress) as observed under a myriad of neuropathological conditions including HD may increase the surface expression of TCR-β subunits (Brouillet, 2014; Cherubini et al., 2020; Costa and Scorrano, 2012; Islam, 2017; Maity et al., 2022; Paul and Snyder, 2019). In HD, mutant huntingtin protein aggregates (mHtt) lead to an increase in ER stress and enhance Fyn kinase activity (Maity et al., 2022; Guglietti et al., 2021; Tang et al., 2020). Also, any of the neurotoxic conditions may increase the gene expression of TCR-β and decrease the function and expression of α7 nicotinic acetylcholine receptors. Also, it is very likely that under such a neurotoxic condition, PirB receptors which are known MHC-I binding partners in the brain and present protein aggregate oligomers (like β-amyloid [Aβ; Kim et al., 2013] to MHC-I molecules, enhance the downstream activation of Src family kinases like Fyn and Lck through an unknown mechanism in a cell-autonomous manner. It is known that MHC-I molecules interact with protein receptors located on the same cell or other cells (Boulanger and Shatz., 2004). Hence, it may be hypothesized here that a possible mechanism of interaction between TCR-β and CD3ζ subunit may be enough without the entire TCR octameric complex (Fig. 1) to activate Lck/Fyn kinase in a specific set of neurons (like MSNs) in the CNS which guide selective neurodegeneration like those seen in HD.

et al. 2022). The wild type huntingtin protein (wHTT) at synapses gets replaced by the mutant huntingtin protein (mHTT) which causes major synaptic dysfunction (Barron et al., 2021). Thereby, a concomitant enhancement in expression of TCR-β may result due to increased oxidative stress, ATP depletion and mitochondrial dysfunction, further leading to depletion of neurotrophins (Fig. 2). An abnormal TCR-β mediated signaling could impair cholinergic signaling as observed across several neurodegenerative diseases including HD (D'Souza and Waldvogel, 2016; Iarkov et al., 2021; Lin et al., 2014; Roberts et al., 2021; Schliebs and Arendt, 2011; Tropea et al., 2021). Nicotinic acetylcholine receptors are a family of ionotropic ligand-gated ion channels which play a pivotal role in neurotransmitter release, and synaptic plasticity (Komal et al., 2014; Komal et al., 2015; Nashmi et al., 2007; Nashmi and Lester, 2006). Altogether, based on the published reports of the involvement of immune proteins in neuronal function including PirB receptors, toll-like receptors (TLRs) and MHC-I molecules, we speculate that under neuropathological conditions an extremely high expression of TCR-β in CNS neurons may cause a hyperactivated molecular signalling cascade that downregulates the expression of nicotinic acetylcholine receptors, which in turn may cause extreme synaptic weakening and synaptic loss (Fig. 2). In such toxic condition, PirB receptors which are known MHC-I binding partners in the brain and presents protein aggregate oligomers to it (like β-amyloid [Aβ; Kim et al., 2013]) can be hypothesized to present mutant huntingtin protein (mHtt) also to MHC-I molecules causing downstream activation of Src family kinases like Fyn and Lck via CD3ζ molecules through unknown mechanism in a cell-autonomous manner (Fig. 2). MHC-I molecules are known to interact with known and unknown protein receptors located on the same cell or other cells (Boulanger and Shatz, 2004). Thus, this unknown protein receptor may be argued to be a TCR-β subunit which on its interaction with CD3ζ subunit may be sufficient without the entire TCR octameric complex (Fig. 1) to activate Lck/Fyn kinasein a specific set of neurons in the CNS such as medium spiny neurons (MSNs) which are prone to neurodegeneration in HD (Fig. 2). It has also recently been highlighted by Barron et al. (2021) that striatal dysfunction precedes behavioral impairments and striatal neurodegeneration. This synaptic dysfunction is undertaken by different brain resident immune proteins like the complement system, cytokinesMHC-I and PirB receptors preceding advanced stages of neurodegeneration (Debnath et al., 2018; Djurisic et al., 2013; Kim et al., 2013; Wang et al., 2021; Ziabska et al., 2021). It may be argued that TCR-β like PirB (paired immunoglobulin-like receptor B) and its human ortholog LilrB2 (leukocyte immunoglobulin-like receptor B2) may possibly modulate synaptic transmission and plasticity too. We also know that in the immune system, peptide presented by MHC-I molecules to T-cell receptor (TCR) causes functional elimination of inappropriate self-reactive T-cell populations (Gascoigne, 2008). Since the immunological synaptic components of both MHC-I and T-cell receptors are expressed by mammalian neurons, it is very likely that synaptic expression of TCR-β subunit like MHC-I also causes loss in the establishment of inappropriate synapses during neuronal development. However, under neuropathological conditions like those observed in neurological disorders, it remains to be determined if increased TCR-β subunits in given subsets of neurons could make them vulnerable to immune attack or undergo neurodegeneration. A high expression of TCR-β in the mammalian brain may act as an indicator of an aging brain or as a biomarker for the onset of several age-related neuropsychiatric disorders.

A purely provocative but novel function proposed for TCR- β in HD is whether upregulation of TCR-β subunit mRNA by the striatal and cortical neurons could possibly potentiate synaptic elimination via downregulating nicotinic acetylcholine receptors, further accelerating disease progression. Upregulation of TCR-β subunit may reflect an abnormal ongoing plasticity accelerating motor dysfunction in HD. This notion further suggests that a simultaneous robust stimulation by cytokine such as interleukin-2 (IL-2) or other proinflammatory cytokines like tumor necrosis factor (TNF-α) and chemokines as observed in most neuropathological conditions may initiate an autocrine stimulation of neuronal TCR-β leading to a loss of neuronal survival. However, the relationship between enhanced TCR-β expression potentiating striatal neuronal loss in HD remains to be elucidated, and whether the downstream Src family kinase activation like Fyn/Lck kinase causes neuronal atrophy remains unexplored.

4. Can dysregulation of the TCR gene locus pose a high genetic risk for neurological disorders like HD?

An extensive effort has been made towards exploring genetic markers of neurological disorders like AD, PD and HD (Alves et al., 2007). Recently, the role of the MHC specific antigen, human leukocyte antigen (HLA), in genetic predisposition of neurodegenerative diseases

have been explored (Alves et al., 2007; Cifuentes and Murillo-Rojas, 2014; Muñiz-Castrillo et al., 2020; Naito et al., 2021; Ollila et al., 2018). The three types of classical human MHC class I proteins are HLA-A, HLA-B and HLA-C (Alves et al., 2007; Debnath et al., 2018; Naito et al., 2021). Mouse MHC antigen is called H-2 antigen, and there are three classical mouse class I proteins: H2-K, H2-D, and H2-L (Debnath et al., 2018). An increased evidence of genetic risk and genome-wide association studies undertaken in the field of neuropathology suggests polymorphisms within the TCR-β gene locus can also contribute to neuropathogenesis (Berliner et al., 1985; Dilliott et al., 2021; Gorgette et al., 2002; Gras et al., 2010; Ollila et al., 2018; Seboun et al., 1989). One study specifically demonstrated disturbances in the genetic factors within the gene loci encoding nicotinic acetylcholine receptor subunits contribute to the pathogenesis of myasthenia gravis (Chia et al., 2022). In the same study, HLA locus was found as a susceptibility locus for this autoimmune disease. A genetic link with other autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and ulcerative colitis was also explored (Ollila et al., 2018). Recently a study by Tropea and colleagues (2021) showed that deletion of α7 nicotinic acetylcholine receptors induced an AD-like pathology in rodent model characterized by synaptic plasticity and memory impairment, Aβ and tau neuropathology, and neuronal death. In 1985, Berliner et al. documented the possibility of detecting genetic disorders via identifying polymorphisms in the T-cell receptor-β chain locus. Another research showed that the inheritance of some loci of the TCR-β gene increased the individual's susceptibility to multiple sclerosis (Rodriguez et al., 1993; Seboun et al., 1989). A single nucleotide polymorphism (SNP) in the MHC-I gene has already been linked with cognitive impairment performance in patients with schizophrenia (Walters et al., 2013). Also, a very recent finding suggests that SNP and variability in the TCR germline can dramatically affect the composition of the TCR repertoire (Omer et al., 2022). Hence, it is very likely that genetic variability in the form of SNPs contribute towards neurodegeneration or aging (Corces et al., 2020; Dilliott et al., 2021; Femminella et al., 2021). Thus, there is compelling evidence emphasizing the possibility of aberrant gene rearrangement in TCR-β loci in the central nervous system which may drive brain atrophy as observed in aging or under a myriad of neuropsychiatric disorders including HD.

5. Conclusion and perspectives

We previously reported that TCR activation affects neuronal function in a healthy brain (Komal et al., 2014). However, whether TCR-β upregulation and its stimulation by other immune proteins in CNS contributes to the pathophysiology of age-related disorders like HD presently remains unknown. Future experiments emphasizing this area will provide vital information to close our knowledge gaps in the role of aberrant TCR-β signaling in neurodegenerative disorders and their possibility as an early biomarker for neurodegeneration such as HD. Further work is still required to elucidate whether TCRs are expressed as fully functional receptors along with their subunits as seen in the immune system or whether TCR-β appears as incomplete truncated cell surface receptors that may have a non-immune role to play in the central nervous system. Also, during neurological insult how does the function of these immune receptors get regulated? Furthermore, can neuronally expressed TCR-β subunits function in the nervous system without the entire TCR complex or do TCR-β subunits require any endogenous peptides for their activation?

Conflict of interest

The authors declare no conflict of interest.

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