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Review Article

γδ T lymphocytes in the pathogenesis of multiple sclerosis and experimental autoimmune encephalomyelitis

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ABSTRACT

The aim of the current review is to summarize the results of studies on the role of γδ T cells in the pathogenesis of multiple sclerosis and its animal model – the experimental autoimmune encephalomyelitis. Despite the fact that numerous studies have been performed, the role of γδ T is still not fully understood. It seems that there are two distinct subpopulations – one exacerbating the disease (IL-17-producing) and the other playing a protective role (IFN-γ-secreting). Nevertheless, future studies are required for an understanding of γδ T cells role in multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) affects approximately 700,000 patients in Europe, but actual morbidity varies highly. According to the European Multiple Sclerosis Platform, it ranges from 227 per 100,000 inhabitants in Denmark to 30 per 100,000 inhabitants in Romania (Gitto, 2017). Unfortunately, a significant part of European MS epidemiological data is a pure estimation due to a lack of well organised MS registers in numerous European countries. Nevertheless, available data indicate that MS should be considered a major socio-medical problem in Europe. The currently available data on the immunopathogenesis of MS is, unfortunately, highly inconclusive and incomplete. The aim of the current review is to summarize the state of knowledge about the contribution of γδ T cells to the pathogenesis of multiple sclerosis and suggest possible new research areas. The current paper is based on the results of human studies as well as studies on animal model of MS – the Experimental Autoimmune Encephalomyelitis (EAE).

2. γδ T cells in peripheral blood and cerebrospinal fluid of MS patients

Data on the frequency of γδ T cells in peripheral blood of MS patients is considerably limited and inconclusive. A study by Stinissen et al., which utilised limited dilution analysis, revealed an increased frequency of γδ T cells in the peripheral blood of MS patients in comparison with both patients with other neurological diseases and healthy controls (Stinissen et al., 1995a). The same investigation found no significant differences in γδ T cell frequency between relapsing-remitting MS (RRMS) and primary progressive MS (Stinissen et al., 1995a). Nick et al. observed no significant difference in the percentage of γδ T cells in peripheral blood between MS patients and healthy donors (Nick et al., 1995). Similar result was obtained by Paź et al. (1999) and Singh et al. (2017). A recent Australian study by Ramos et al. revealed a decrease in peripheral blood γδ T cells (as a percentage of total lymphocytes) in MS patients compared to healthy control (Ramos et al., 2016). Ramos et al. reported also a decrease in Vδ2-subset of γδ T cells, measured as a proportion of total γδ T. Similarly, a significant increase in Vδ1-subset in peripheral blood of MS patients compared to healthy controls was noted (Singh et al., 2017). The percentage of γδ T cells among $CD3^+$ lymphocytes in peripheral blood was found to be elevated in relapsing MS patients compared to non-inflammatory control (Schirmer et al., 2013).

Stinissen et al. studied γδ T cells in cerebrospinal fluid and found an increase in their frequency among MS patients compared to patients with other neurological diseases (Stinissen et al., 1995a). Perrella et al. found no significant difference in the incidence of γδ T cells between MS patients and a group of patients with other neurological diseases (Perrella et al., 1993). No significant difference in γδ T percentage in CSF was observed by Nick et al. between MS patients and controls (mostly other neurological problems), either (Nick et al., 1995). However, in the same study a significantly higher percentage of Vδ1 γδ T cells was observed in CSF than in peripheral blood. Shimonkevitz et al. concluded that Vδ1 γδ T are the predominant γδ T subpopulation in the CSF of all MS patients except for one – in this case Vδ2 preponderated (Shimonkevitz et al., 1993). The expression of CD45RA was found to be higher on γδ T cells from CSF of MS patients than in paired samples of

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peripheral blood (Droogan et al., 1996). The Th17-like fraction of γδ T cells ($CD161^{high}$ $CCR6^{+}$) is significantly increased in the CSF of patients during relapse (Schirmer et al., 2013).

3. TCR types and subsets of γδ T cells in MS

The initial studies on γδ T cells in MS, performed in 1990s, focused mostly on the TCR rearrangements and aimed to answer the question, whether γδ T cells in MS patients are oligoclonal. The results of studies by Bieganowski et al. (1996), Nowak et al. (2001, 1997), Liedtke et al. (1997), Battistini et al. (1995b, 1995a), Hvas et al. (1993) and Shimonkevitz et al. (1993) altogether suggest possible oligoclonal expansion of γδ T cells within CNS of MS patients which may be a sign of response to a common antigen. The more recent studies divided γδ T cells into subpopulations by the types of TCR γ and δ chains. A significantly increased Vδ1/Vδ2 ratio was noted in MS patients along with decreased percentage of Vδ2 IFN-γ^{+} γδ T cells (Maimaitijiang et al., 2018). Moreover, the percentage of Vδ2Vγ9 γδ T cells negatively correlated with disease severity, suggesting important roles of both whole γδ T cell populations as well as the balance between various subsets of those lymphocytes. On the other hand the percentage of IFN-γ^{+} Vδ1 γδ T lymphocytes is significantly increased in freshly diagnosed MS patients and correlate positively with disease activity (Singh et al., 2017). The treatment with natalizumab normalized the IFN-γ^{+} Vδ1 γδ T cell percentage.

The γδ T lymphocytes can be divided into naïve ($CD45RA^{+}$ $CD27^{+}$), central memory ($CD45RA^{-}$ $CD27^{+}$), effector memory ($CD45RA^{-}$ $CD27^{-}$) and terminally differentiated effector memory ($CD45RA^{+}$ $CD27^{-}$) cells (Pang et al., 2012). That classification was tested in MS patients by Monteiro et al. (2018). They observed increased percentage of naïve cells in both relapse and remission and decreased percentage of central memory cells in remission compared to healthy controls. Moreover, a significant decrease in terminally differentiated effector memory γδ T lymphocytes was noted in relapse compared to remission. Together with no significant difference in the percentage of total γδ T cells in the peripheral blood, this suggests the importance of the imbalance between γδ T cell subsets in the pathogenesis of MS. No significant differences between freshly diagnosed MS patients and healthy controls was, however, noted in any of those subsets among Vδ1 cells (Singh et al., 2017).

The γδ T cells can be also divided into Th_1-, Th_2-, Th_{17}-, T_{FH}, T_{reg}, T_{APC}-like subsets, similarly to αβ T cells (Pang et al., 2012). This division has, however, not been utilised in any study on MS.

4. Transmigration through vascular endothelium

An increase in CSF cellularity may be attributed to a disturbed blood-brain barrier and, therefore, an increased transmigration of cells to the CSF and CNS during MS. Most of the γδ T lymphocytes express TCR Vγ9Vδ2. Two major sub-populations of γδ T cells, namely Vδ1 and Vδ2 derived from peripheral blood of both healthy controls and MS patients, utilise different pathways in the process of transmigration. $V\delta1^{+}$ uses PECAM1 and PI-3K, Vδ2 utilises NKRP1a (CD161), which activates Akt/PKBα and CAMKII afterwards (Poggi et al., 2002). $V\delta2^{+}$ subpopulation expressing NKRP1A has a significantly heightened ability to transmigrate from blood vessels and IL-12 in the micro-environment promotes expression of NKRP1A even further (Poggi et al., 1999). Poggi et al. have concluded that about 70% of γδ T cells in peripheral blood of MS patients and only 20% among healthy donors are $NKRP1A^{+}$ (Poggi et al., 1999).

5. Chemokines and their receptors

The γδ T lymphocytes of MS patients have higher CXCR3 and significantly lower CCR5 and CXCR1 expression (Murzenok et al., 2002). They also produce higher amounts of RANTES (Murzenok et al., 2002). The percentage of $CCR5^{+}$ γδ T cells is decreased both in the peripheral blood and CSF of RRMS patients (Monteiro et al., 2018; Murzenok et al., 2002). The expression of CXCR3 is viable for T lymphocyte recruitment to the site of inflammation (Groom and Luster, 2011), and may possibly be related to the capability of T cell migration to MS plaques, as CXCR3 expression on lymphocytes was detected in perivascular cuffs of a vast majority of active MS lesions (Sørensen et al., 1999). CXCR3 responses to two ligands: IP-10 and CCL21 (Poggi et al., 2007). The former is elevated in serum of relapsing-remitting and primary progressive multiple sclerosis patients (Scarpini et al., 2002). The latter is significantly reduced in CSF during remission, no significant differences have been observed in serum level of CCL21 (Edwards et al., 2013).

6. γδ T cytotoxicity

γδ T lymphocytes exhibit significant cytotoxicity against oligodendrocytes (28 ± 5%), comparable with cytotoxicity against U937[1] (30 ± 3%), a well known γδ T target, but no significant difference between γδ T cells from healthy donors and MS patients was noted. Moreover, the cytotoxicity has been found to be unconnected with the expression of heat-shock protein 72 (HSP72) (Freedman et al., 1991). The $\delta1^{+}$ γδ T lymphocytes co-localize with $hsp65^{+}$ oligodendrocytes in chronic lesions, which may suggest some kind of functional connection (Selmaj et al., 1991). Similarly, immature $hsp\text{-}65^{+}$ oligodendrocytes co-localize with γδ T lymphocytes within the sites of remyelination (Selmaj et al., 1992). Moreover, γδ T cells exhibit cytotoxic activity against cells pulsed with either Staphylococcus enterotoxin A or B – both toxins structurally resemble hsp-65 (Stinissen et al., 1995b).

Their cytotoxic activity is not limited to physical contact with target-cells, but to a lesser extent can also be exerted *via* soluble factor – perforin (Zeine et al., 1998). Granzyme B tends to influence the total cytotoxic potential, but only as a minor component (Zeine et al., 1998). In fact, the γδ T cytotoxicity against oligodendrocytes is predominantly related to the perforin-dependent way (Zeine et al., 1998). A $CD16^{+}$ subset of γδ T express high cytotoxic potential in the mechanism of antibody-dependent cellular cytotoxicity (Chen and Freedman, 2008a). That subpopulation is indeed elevated in MS patients (Chen and Freedman, 2008b). Concluding, γδ T cells may play an important role as a demyelinating factor in the course of MS.

7. γδ T cells in MS lesions

The $\delta1^{+}$ γδ T lymphocytes were identified in three out of 10 acute lesions (mostly on the edges of the plaque), eight out of 12 chronic active lesions (mostly in their centres) and 17 out of 21 chronic silent lesions. In the last type of plaques the $\delta1^{+}$ γδ T lymphocytes have been observed both at the margins and in the centre of the lesions and constituted most of the $CD3^{+}$ cells (Selmaj et al., 1991). Up to one fourth of total T cells accumulated in active MS plaques may be γδ T, while they are usually just a minor population within chronic plaques (Wucherpfennig et al., 1992). The location of γδ T cells within plaques is summarised in Table 1.

Repeated sequences in δ chains of γδ T cells in active plaques indicate a possible clonal expansion on the site of inflammation (Wucherpfennig et al., 1992). Oligodendrocytes express hsp-60 and are probably capable of γδ T cell growth stimulation, as observed *in vitro* (Freedman et al., 1997). This reveals an image of a complicated net of both dependencies and influences between γδ T cells and oligodendrocytes within plaques – it seems that oligodendrocytes may possibly be both a target of γδ T cell cytotoxicity and a cause of γδ T cell expansion at the site of CNS inflammation.

[1] Human lymphoblast cell line

Table 1
γδ T location in MS plaques.

Plaque type	γδ T occurrence	Location in plaques	Amount	References
Acute	In some plaques	Edges	Up to ¼ of T cells	(Wucherpfennig et al., 1992)
Chronic active	In most of the plaques	Centre	Minor T cell subpopulation	(Selmaj et al., 1991)
Chronic silent	In nearly all of the plaques	Centre and edges	Major T cell subpopulation	(Selmaj et al., 1991)

8. γδ T cells in the course of experimental autoimmune encephalomyelitis

A study by Raverdeau et al. on the murine model of MS and mouse-derived γδ T cells has revealed a significant suppressive potential of retinoic acid on IL-17 production by those lymphocytes (Raverdeau et al., 2016). The IL-17-producing γδ T cells have been found to have a 34-fold higher expression of retinoic acid receptor RORα than IFN-γ-producing subpopulation (Raverdeau et al., 2016). An exposure to retinoic acid provokes a decrease in RORγT expression (Raverdeau et al., 2016). Raverdeau et al. have also studied *in-vivo* effects of retinoic acid on IL-17A production by γδ T in both naïve and EAE-induced mice, and found it to be significantly decreased (Raverdeau et al., 2016). Adoptive transfer of MOG-specific T cells containing retinoic-acid-pretreated γδ T cells leads to significantly delayed onset and decreased symptoms of EAE (Raverdeau et al., 2016). This suggests an important role of γδ T lymphocytes in both EAE, and presumably also MS pathogenesis, which is highly related to their capacity of IL-17-production early in the disease.

8.1. γδ T and the severity of EAE

A number of studies were performed to evaluate the effect of γδ T manipulation on EAE course and therefore their general role in the disease (Clark and Lingenheld, 1998; Odyniec et al., 2004; Ponomarev et al., 2004; Ponomarev and Dittel, 2005; Rajan et al., 2000; Spahn et al., 1999; Wohler et al., 2009). The results of those studies remain inconclusive – some reported milder while the other more sever course of EAE. As proposed by Blink et al., those discrepancies may be the results of different mouse strains and different methodology used eg. antigen used to induce EAE or type of γδ T manipulation (Blink et al., 2014). This may also be the result of the heterogeneity of γδ T lymphocytes, which should be treated as a complex group of different subsets, similarly to the T helpers, rather than a single homogenous population.

On the other hand, it seems that γδ T-deficient mice have problems with recovering from EAE (Ponomarev et al., 2004; Ponomarev and Dittel, 2005). The γδ T cells, although producing limited amount of IFN-γ themselves, are important for the regulation of IFN-γ production by $CD4^+$ and $CD8^+$ T cells in CNS (Ponomarev et al., 2004). The number of CNS infiltrating cells in TCRδ-knockout animals is similar to control ones at the peak of the disease, but unlike in control, the number remains high throughout its course (Ponomarev and Dittel, 2005). The results of γδ T manipulation on the course of EAE is summarised in Table 2.

The γδ T depletion causes a significant decrease in the CNS concentration of RANTES, eotaxin, MIP-1α, MIP-1β, MIP-2, IP-10 and MCP-1 at the onset of the disease, with no difference at the later stages (Rajan et al., 2000). Similarly, a 2.5-fold decrease in IL-12 concentration within culture supernatant was observed after γδ T depletion (Odyniec et al., 2004). The *in vivo* depletion of γδ T cells leads to severe decrease in the expression of IL-1, IL-6, TNF, IFN-γ and lymphotoxin at the onset of the disease, at the peak of the symptoms only IFN-γ is still significantly lowered (Rajan et al., 1998). This seems especially important as lymphotoxin along with IL-17 and IL-22 are necessary for the formation of tertiary lymphoid tissue within meninges and, thus, promotion of neuroinflammation (Pikor et al., 2015).

8.2. Neuropathology in EAE

CD69 and CD25 expression is highly elevated in the acute phase of EAE and slightly elevated in the chronic phase (Gao et al., 2001). Expression of CD62L is significantly lower in the CNS when compared to spleen during all the stages of the disease, with the biggest difference at the peak of the acute phase and during first remission. Fas and FasL are expressed on most of CNS-inflitrating γδ T lymphocytes with slightly lower values at the onset and peak of the disease (Gao et al., 2001). Concluding, most of CNS-infiltrating γδ T lymphocytes are activated ($CD69^+$, $CD25^+$, $CD62L^-$).

The γδ T lymphocytes comprise > 10% of the T cells in the CNS during the peak of the disease and the chronic phase of EAE (Rajan et al., 1996). They can be found predominantly within lesion margins (Gao et al., 2001) and in the perivascular cuffs both in the brain and the spinal cord (Blink et al., 2014; Rajan et al., 1996). Moreover, they co-localize with auto-reactive $CD4^+$ T cells and the number of CNS-infiltrating γδ T cells correlates with EAE severity (Blink et al., 2014). This may be connected with the fact that 50% to 80% of γδ T cells infiltrating brain secrete IL-17 (Sutton et al., 2009). On the other hand, Smith and Barnum reported that almost all of γδ T cells in CNS during EAE express either one or both of the following: IFN-γ and TNF (Smith and Barnum, 2008). IFN-γ^+ cells were noticeable in the spinal cord long after the peak of the symptoms (Smith and Barnum, 2008). Moreover, γδ T cells tend to co-localize with CC-1 and MBP-expressing oligodendrocytes and may be partially responsible for oligodendrocytes killing (Blink et al., 2014) – a direct cell-cell interaction may be needed for γδ T cells to perform their actions in response to MBP (Odyniec et al., 2004). On the other hand, nearly no γδ T lymphocytes were found in the CNS during EAE in Lewis rats, suggesting that there may be important differences between various experimental settings used (Matsumoto et al., 1998).

8.3. Expression of surface antigens

A slight increase in the expression of CD8 in predominantly heterodimeric form occurs during acute and chronic EAE (Gao et al., 2001). IL-18R is constitutively expressed on naïve γδ T cells in mice, during the course of EAE – it is further up-regulated (Lalor et al., 2011). Similarly, IL-23R and CD122 (IL-2Rβ) are constitutively expressed (Gao et al., 2001; Martin et al., 2009; Sutton et al., 2009). Two distinctive and opposing γδ T subpopulations can be found in EAE – the Vγ4 cells exacerbate the disease, while Vγ1 play protective role during EAE (Blink et al., 2014). Among the former, approximately three fourths secrete IL-17 in CNS during EAE, and single cell output is almost 2-times higher than an IL-17-secreting $CD4^+$ αβ T cell (Blink et al., 2014). The Vγ4 sub-population constitutes approximately 70% of brain-infiltrating γδ T cells during the acute phase of EAE (Sutton et al., 2009). The Vγ1, similarly to Tregs, expresses high levels of CCR5. Moreover, it also secretes CCL4, a Treg attractant (Blink et al., 2014). Different sub-populations within the brain were identified - Vγ1, Vγ2, Vγ3 and Vγ6 during the initial phase of EAE, with an increase in TCR heterogenicity as disease developed. Similarly, Vδ restriction was observed during early EAE (Vδ1, Vδ4, Vδ5), while not in clinically evident disease (Olive, 1995). γδ T can also be divided by CCR6 expression. The $CCR6^+$ γδ T cells express both TLR1 and TLR2 while $CCR6^-$ do not express any TLRs (Martin et al., 2009). The summarised data about the

Table 2
γδ T manipulation and its impact on the course of EAE.

EAE induction	Animals	γδ T treatment	Course	Ref.
MOG p35–55	C57BL/6 mice	TCRδ knockout	Milder, chronic	(Spahn et al., 1999)
Adoptive transfer post MBP-immunization	SJL/J, B10.PL	anti-pan TCRγδ depletion in cell culture or MACS negative sorting	Milder, chronic	(Odyniec et al., 2004)
Adoptive transfer post MBP Ac_{1-11}-immunization	B10.PL	TCRδ knockout	More severe, chronic	(Ponomarev et al., 2004)
Adoptive transfer post MBP Ac_{1-11}-immunization	B10.PL	TCRδ knockout	More severe, chronic	(Ponomarev and Dittel, 2005)
Adoptive transfer post MBP-immunization	SJL/J	anti-pan TCR γδ (GL3) depletion *in-vivo*	Milder, not-chronic	(Rajan et al., 2000, 1996)
Adoptive transfer post MBP-immunization	C57BL/6	TCRδ knockout	Slightly[a] more severe, not-chronic	(Clark and Lingenheld, 1998)
MOG p35–55	C57BL/6	TCRδ knockout	Significantly delayed, milder	(Wohler et al., 2009)

[a] Statistically insignificant.

most important γδ T subsets in EAE are shown in Table 3.

Prior to the induction of EAE γδ T express CD11a, CD11b and CD11d, during the disease the expression of those three β2-integrins is further increased, moreover, the fourth one (CD11c) is at that point also being expressed (Smith and Barnum, 2008). β2-integrins are important for the development of EAE (Bullard et al., 2007; Gordon et al., 1995), but this seems to be related to the function of αβT cells, as the β2-integrins-knockout in γδ T cells seems to not affect the course of EAE (Wohler et al., 2009).

8.4. The opposite subsets of γδ T cells

The number of IFN-γ^+ γδ T cells is the highest at the disease onset and decreases with the progression of EAE while IL-4 shows the opposite tendency (Gao et al., 2001). IFN-γ and IL-17 are secreted by two distinct subpopulations of γδ T – IL-23R^+ CCR6$^+$ and IL-23R^- NK1.1$^+$, respectively, the former depending to some extent on IL-6 (Petermann et al., 2010). IL-6 deficiency does not weaken the generation or survival of IL-17 secreting γδ T cells, while the lack of IL-23 causes severe impairment of both generation and maintenance thereof (Martin et al., 2009). Both subsets in mice become predestined to their cytokine profile within thymus, while in human they need activation in periphery (Haas et al., 2009; Papotto et al., 2017). These two subsets are not only spatially separated within thymus (Papotto et al., 2017), but also similarly in the periphery – in skin and intestine (Vantourout and Hayday, 2013).

IL-17-secreting γδ T cells express similar markers as Th17 cells – IL-17A, IL-22, IL-23R, CCR6, AhR and RORγT (Martin et al., 2009). A very high percentage of IL-17-secreting γδ T cells at symptoms onset have been noted by Lalor et al. (Lalor et al., 2011). Lees et al. have reported that up to 40% of γδ T found in the CNS during EAE course in mice produced IL-17 (Lees et al., 2008). The expression of IL-17 can be promoted by IL-18 alone or, to a higher extent, by a combination of IL-18 and IL-1β (Lalor et al., 2011). IL-17 and IL-22 (to a limited extent also IFN-γ) are secreted by γδ T cells in response to either IL-23 and IL-1β or IL-23 and IL-18, in both cases no TCR engagement is required (Lalor et al., 2011; Sutton et al., 2009). Among γδ T lymphocytes, the IFN-γ-producing cells express CD122 (IL2Rβ) while the IL-17-secreting cells are CD25$^+$ (IL2Rα) (Shibata et al., 2008). They can be also distinguished by the expression of CD27 – the former subpopulation is CD27$^+$ while the latter CD27$^-$ (Michel et al., 2012). It seems that there are two main cytokines regulating the function of the IL-17-secreting γδ T cells – IL-7 and IL-2 (Michel et al., 2012; Shibata et al., 2008). The former seems to promote expansion thereof and therefore acts in long term while the latter although promotes massive production of IL-17, does also cause the IL-7R down-regulation leading to increased apoptosis (Michel et al., 2012; Shibata et al., 2008). The IL-17-secreting γδ T lymphocytes deprived of IL-2-stimulation are more prone to shift towards double positive cells, resembling the Th17.1, namely IL-17$^+$, IFN-γ^+ (Shibata et al., 2008). This may potentially decrease their encephalitogenic potential in EAE and maybe MS and may be partially responsible for the favourable results of clinical trials involving anti-IL-2Rα monoclonal antibody (daclizumab) in multiple sclerosis (Papadopoulou et al., 2017).

γδ T cells produce significantly higher amounts of IL-17 in response to IL-23 stimulation and IFN-γ in response to IL-12 than CD44+ αβ T cells (Petermann et al., 2010). γδ T cells are capable of rapid IL-17 production without need for prior antigen exposure and further differentiation as is in case of Th17 cells (Corpuz et al., 2017). γδ T17 lymphocytes, leaving the thymus, are already programmed for IL-17 production (Corpuz et al., 2017). It is probable that IL-17 secreted by γδ T cells early during the course of EAE is important stimulator of IL-17 expression by Th17 cells (Sutton et al., 2009). While only 7% of γδ T cells in lymph nodes of naive mice are IL-23R^+, this percentage rises to approximately one fourth after EAE is induced by MOG_{35-55} sensitization (Petermann et al., 2010). Percentages of both IL-17- and IFN-γ-

Table 3
γδ T subpopulations in EAE.

Immunophenotype	Function	Location	
IL-17+ IL-23R+ CCR6+ CD25+ CD27-	Secrete IL-17	Dominate in the CNS during EAE	(Michel et al., 2012; Petermann et al., 2010; Shibata et al., 2008)
IFN-γ + IL-23R- NK1.1+ CD122+ CD27+	Secrete IFN-γ	Dominate in the periphery during EAE	(Michel et al., 2012; Petermann et al., 2010; Shibata et al., 2008)
Vγ4 TCR	Exacerbate EAE, secrete mostly IL-17, but also GM-CSF, TNF-α, IL-21	Dominate in the CNS during EAE	(Blink et al., 2014)
Vγ1 TCR	Protect in EAE, secrete IL-22, IFN-γ, IL-1β, CCL4	Dominate in the spleen during EAE	(Blink et al., 2014)

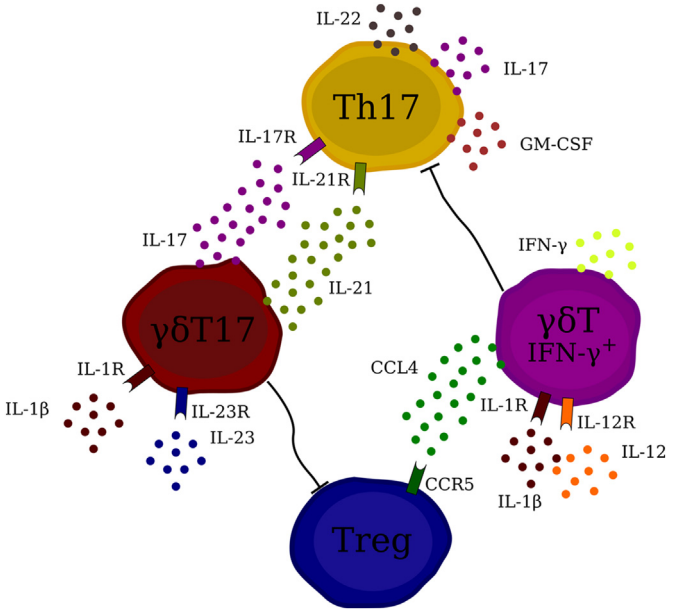

Fig. 1. The interaction between the IL-17- and IFN-γ-producing subsets of γδ T cells in the periphery. Blunt ended lines indicate negative interaction. IL-1β along with IL-23 promote IL-17 and IL-21 production by γδ T cells. IL-21 with IL-17 amplify the inflammation by promoting IL-17, IL-22 and GM-CSF production by Th17. On the other hand IL-1β and IL-12 promote secretion of IFN-γ by γδ T lymphocytes.

secreting γδ T cells rise in the course of EAE until the peak of the disease. Still, the latter outnumber the former subpopulation in the periphery. The opposite relation is observed in CNS (Petermann et al., 2010). During the recovery phase the percentages decrease to the pre-EAE state and, therefore, as Petermann et al. have concluded, IL-23R$^+$ γδ T percentage well reflects the observed intensity of EAE symptoms (Petermann et al., 2010). Moreover, IL-23-activated γδ T lymphocytes inhibit the conversion of naive αβ T cells into Foxp3+ Tregs in a yet unknown mechanism as well as revoke a Treg-mediated supression of effector T cells (Petermann et al., 2010).

Apart from the already mentioned cytokines, CCL3, CCL4 and CCL5 are also secreted by γδ T lymphocytes during EAE with significantly higher amounts produced by Vγ1 than Vγ4 (Blink et al., 2014). A small subset of γδ T cells is also capable of secreting IL-15, thus is termed γδ T15 (Wang et al., 2015). Through IL-15 they induce CD44^{hi} memory T cells, that can further differentiate into Th17.

8.5. The interplay between both opposite subsets

As previously described, the γδ T in CNS during the course of EAE express IL-17, but also IFN-γ. The IFN-γ$^+$ γδ T cells in the CNS opposing to those in the periphery are necessary for the neuroinflammation during EAE and are exacerbating symptoms (Blink et al., 2014; Wohler et al., 2009). The γδ T17 cells are especially important during early phases of EAE as kick-starters of inflammation – they rapidly secrete IL-17 and IL-21, which potently activates the function of Th17 cells (McGinley et al., 2018). The latter are capable of producing huge amounts of IL-17, leading to the disruption of blood-brain barrier and the consequent neuroinflammation. IFN-γ$^+$ γδ T play the opposite role – they are suppressing the Th17 activity (Ponomarev et al., 2004). IFN-γ$^+$ γδ T cells attracts Tregs by secreting CCL4 while IL-17$^+$ γδ T cells suppress the activity of Tregs (Blink et al., 2014). The interplay between both subsets of γδ T cells in EAE is shown in Fig. 1.

9. Conclusions

The contribution of γδ T cells to the pathogenesis of multiple sclerosis seems complicated and requires further studies. Those should include concepts from studies on the animal model eg. the opposite subsets of γδ T. In EAE, two distinct subpopulations can be noted – one IL-17- and the other IFN-γ-secreting. While the former seems to exacerbate the disease, the latter may play a protective role. Although γδ T cells are probably not required for the disease to begin or progress, they seem to be related to the severity of disease course.

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