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Research Paper

Targeting IL-17A signaling in suicidality, promise or the long arm of coincidence? Evidence in psychiatric populations revisited

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ABSTRACT

Interleukin 17 (IL-17) is a potent pro-inflammatory cytokine which plays a role in autoimmune disorders, such as psoriasis and multiple sclerosis, and is important for the defense against pathogens, particularly in the gut. However, IL-17 has recently also gained attention in association with suicidal behavior. In this review, we review the literature regarding IL-17 in psychiatric disorders and suicidality. We also take a closer look at the suicides which occurred in the clinical trial for psoriasis with *brodalumab,* a monoclonal antibody targeting the IL-17 receptor. Lastly, we discuss potential working mechanisms relevant to neuroinflammation and the possible involvement of IL-17.

1. Review article

Suicide is amongst the leading causes of death worldwide. Every year, close to 800.000 people (or one person every 40 seconds) die due to suicide (World Health Organization W, 2021). However, no single etiopathological cause for suicide can be identified. Rather, it is the consequence of an interplay between psychological, social, economic and biological determinants. Nevertheless, in the search for treatment targets, one particularly potential biological determinant of suicide/-suicidal behavior has caught our interest: the immune system, and in particular Interleukin (IL)-17 signaling. The interest in IL-17, and its role in suicidality, has been, coincidentally, stimulated by treatment studies for psoriasis, where an agent targeting the IL-17 pathway was unexpectedly linked to reports of increased suicide risk (Papp et al., 2020). This observation appears to be paradoxical at first glance, because higher levels of IL-17 have previously been linked to neuro-inflammation (Mills, 2022) and depression (Kim et al., 2021). Blocking IL-17 signaling should therefore attenuate, rather than aggravate, suicidal ideation. In this review, we take a closer look at the possible explanations for the suicides which occurred in the psoriasis treatment trial with *brodalumab,* and consider the current evidence of IL-17 and its relevance in the context of psychiatric disorders, in particular suicidal ideation and behavior. We also summarize possible mechanistic links of this relationship, and, finally, offer suggestions for future research.

1.1. Interleukin 17- a role for suicide?

One of the most widely investigated cytokines belonging to the IL-17 family, is IL-17A (hereafter referred to as IL-17), which binds to the IL-17 receptor (IL-17R) subunits A and C (Mills, 2022). It is produced by various T cells (the best known are T-helper, T-cytotoxic and γδ T cells) and other cell types (e.g., natural killer, innate lymphoid cells and mast cells, amongst others) (Mills, 2022). IL-17 is crucial for the mucosal immune system, for the defense against pathogens, but also for the role it plays in abnormal immune system functioning, as observed in (T cell-mediated) autoimmune diseases, such as multiple sclerosis (MS) (Tzartos et al., 2008) and psoriasis (Burkett and Kuchroo, 2016). It is generally considered a pro-inflammatory cytokine and is tightly regulated by anti-inflammatory control loops. However, when the regulation is insufficient or fails, this can contribute to inflammation and autoimmune disorder development. Psoriasis is of particular interest in the context of suicidality, since suicidal ideation, suicide attempts, and completed suicides are higher in patients with psoriasis compared to the general population. Indeed, it has been hypothesized that particularly those patients with psoriasis who have increased serum IL-17A, may also have a higher risk for depression (Zafiriou et al., 2021).

1.2. Biologics Treatment: A link to suicidality?

As indicated above, IL-17 has been mentioned in the context of

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suicidality in psoriasis. Targeting the IL-17 signaling pathway has yielded highly effective treatments for psoriasis, which often surpass traditional treatment options, and may also be useful to treat depressive symptoms (Griffiths et al., 2017). Most agents target IL-17 directly, e.g., the monoclonal antibodies *secukinumab*, and *ixekizumab*. However, *brodalumab* is a recombinant, fully human IgG2 monoclonal antibody targeting the human interleukin-17 receptor A (IL-17RA) (Puig, 2017) (and thus does not target its ligand, IL-17, directly). It is this latter drug that caused some concern regarding the link with suicide: The occurrence of 4 suicides in patients with psoriasis who were in the open-label treatment arm in the AMAGINE-1 and AMAGINE-2 studies, led to initial concern regarding *brodalumab*. This concern was later judged without foundation, since no causal link was established in a thorough investigation (Lebwohl et al., 2018). Nevertheless, clinicians may still lean towards prescribing alternative medications targeting the IL-17 pathway, because of these initial reports (Rieder, 2018), despite it being a safe medication (Facheris et al., 2020). Paradoxically, reports of IL-17 levels mostly show increased levels in psychiatric patient populations (see below), and in line with this, overall, treatment with *brodalumab* decreased levels of depression and anxiety in the trials (Lebwohl et al., 2018). How then, should the initial concerns be understood, and might there be a mechanistic link to increasing suicidal behavior rather than reducing it?

Since *brodalumab* effectively blocks the IL-17 receptor subunit A, it does lead to increased serum IL-17 levels in a dose-dependent manner. Patients with available data in the clinical trial, receiving 210mg of this agent showed a ~4-fold increase of IL-17 during treatment (Food and Drug Administration, 2015). In pharmacokinetic studies, it was previously shown that these levels do gradually return to baseline, but with a time lag of 30 days after a single dose. Interestingly, the data of the 4 psoriasis subjects who committed suicide in the trial shows that 3 of the 4 patients had received the last dose of *brodalumab* within this time frame, e.g., the last 30 days (precisely, 14, 19 and 27 days). One subject had the last dose 58 days prior to suicide (Food and Drug Administration, 2015). While interesting, IL-17 levels in the subjects at the time of suicide were not known, and no link could thus be established. Furthermore, other trial participants did show higher levels of IL-17 and did also show a higher serum concentration of *brodalumab*, placing the suicide victims somewhere in the middle (Food and Drug Administration, 2015). Additionally, psychologically stressful factors were also detected in the review of the patients' history. A thorough review of the literature and several expert opinions (e.g., (Lebwohl et al., 2018; Chiricozzi et al., 2016)) have thus concluded that *brodalumab* is safe to use, and no direct link could be established between blockade of the IL-17RA and suicidality in psoriasis patients.

The association between suicidality and biologics is, however, not a unique occurrence for *brodalumab*: a recent large-scale study investigated suicidal ideation/behaviors across treatment studies using monoclonal antibodies, and found that particularly patients with immunosuppressive drugs, including *natalizumab* (targeting α4β1 integrin on white blood cells) and *belimumab* (inhibiting B-cell activating factor (BAFF)) were at increased risk for suicide (Minnema et al., 2019). Since immune cells are in a steady crosstalk, it is likely that several biological targets are involved in suicidal behavior, rather than a single target of the IL-17 pathway. However, since suicidal ideation and behavior do occur more often in patients with autoimmune disorders, the study of treatment-emergent adverse events may be inherently biased. It is thus essential to explore the current literature regarding IL-17 and suicidality in psychiatric disorders, and whether or not a link to suicide has been established.

1.3. Is there evidence that IL-17 is involved in psychiatric disorders?

Most studies measuring cytokines in psychiatric disorders use multiplex panels, which rarely contain IL-17. There are, however, some studies specifically assessing levels of IL-17, IL17 gene expression or Th17 cells in patients with psychiatric disorders (see Table 1), few of which have also explored the link to suicidality. The majority of studies in patients with depressive disorders did find significantly higher levels of IL-17 or IL17 mRNA expression (Gałecka et al., 2021; Chen et al., 2011; Syed et al., 2018; Mao et al., 2022; Bliźniewska-Kowalska et al., 2020; Davami et al., 2016; Alvarez-Mon et al., 2021; Schiweck et al., 2020; Becerril-Villanueva et al., 2019; Kiraly et al., 2017; Ghosh et al., 2020; Ling et al., 2022; Primo de Carvalho Alves and Sica da Rocha, 2020; Kim et al., 2021). This difference could even be observed in one small study with community-dwelling participants with depressive symptoms (Tsuboi et al., 2018). Although the observed higher levels of IL-17 in depression are quite homogeneous, the study designs cannot explain whether high IL-17 could lead to depression or vice versa, whether depression leads to high IL-17. Also, some investigators found no significant association of IL-17 with depression (Kiraly et al., 2017; Kim et al., 2013). The association with symptom severity is mixed, with some reporting no association (Gałecka et al., 2021; Mao et al., 2022; Bliźniewska-Kowalska et al., 2020; Jha et al., 2017). In psychotic disorders, results are mixed with some studies reporting lower (Borovcanin et al., 2012), some higher (Schwarz et al., 2012; Chen et al., 2021) and the majority no change of IL-17 (Şimşek et al., 2016; Ding et al., 2014; Noto et al., 2015). A recent meta-analysis in patients with first episode schizophrenia also did not find a meaningful association with IL-17 (Fang et al., 2018). Suicidality often occurs in patients with depression and psychotic disorders, however, despite the general interest in this relationship, few studies have formally explored the link between IL-17 and suicidality, nor did they report scores related to suicidality or percentages of patients with suicidal ideation. One exception is the study by Fatt et al. (2022) who found the IL-17 producing, γδ T cell subset, to be higher in 11 adolescents with suicidal ideation compared to 4 controls: Others, like Keshri et al. (2018), have found no difference in IL-17 between 7 patients with bipolar disorder and suicidality compared to 34 patients with bipolar disorder but without suicidality. Two studies (Primo de Carvalho Alves and Sica da Rocha, 2020; Kim et al., 2021) reported higher levels of IL-17 in the overall sample with moderate suicidality (moderate suicidal ideation scores/high prevalence of suicide attempts in the past) compared to controls, but did not explicitly explore this association; and our own study (Schiweck et al., 2020), showing higher percentages of Th17 cells in patients with high risk for suicide.

Recently, three studies explored the relationship between treatment response and IL-17A. One study found that the increased IL-17 baseline levels were associated with depression severity, and decreased after treatment with SSRIs (Mao et al., 2022). Another study showed that higher baseline IL-17 predicted a favorable response to bupropion-SSRI combination treatment in depression, but baseline IL-17 was not related to either depression severity, nor suicidal ideation (Jha et al., 2017). Finally, the last study did not show any association with treatment response (Kim et al., 2013). Although the data regarding suicidality was likely collected using semi-structured interviews, such as the MINI, only one of the identified studies had an openly available dataset, which prevents any further analyses on this relationship.

2. Potential mechanisms of action

While convincing data on the link between suicidality and IL-17 is still missing, it is interesting to explore potential mechanistic links between both. How could inflammation, and in particular IL-17 signaling influence suicidal behavior? It is known that depressive symptoms can be induced by immune activation, as seen during interferon-based therapy (Trask et al., 2000), and as discussed above, increased risk for suicide is associated with immune-modifying treatments (Minnema et al., 2019). Possibilities of how the peripheral inflammatory effects lead to suicidal behavior via the brain, includes, among others, microglial activation, blood-brain barrier disruption, and altered autonomic nervous system functioning which affects the gut-brain axis. In the following section, we will explore current research on each of these

Table 1
Studies investigating IL-17 and IL-17 producing cells in psychiatric disorders compared to controls. Dep: Depressive Disorders; BD: bipolar disorder, PSY: psychotic disorders; SB: Suicidal Behavior, CTRL: controls, n: number included.

Reference	Diagnosis	n	Finding in depressed group	Link to suicidality
(Tsuboi et al., 2018)	depressive symptoms	10↑depressive symptoms; 10↓depressive symptoms	↑IL-17 in high symptom s group	Not explored
(Gałecka et al., 2021)	depression	190DEP, 100CTRL	↑IL17 mRNA; ↑IL-17	Not explored
(Kim et al., 2013)	depression	26DEP, 28 CTRL	= IL-17	Not explored
(Chen et al., 2011)	depression	40DEP, 30CTRL	↑Th17, ↑RORγt mRNA, ↑IL-17	Not explored
(Alvarez-Mon et al., 2021)	depression	30DEP, 30 CTRL	↑IL-17+ Th cells, ↑IL-17	Not explored
(Bliźniewska-Kowalska et al., 2020)	depression	95DEP, 30CTRL	↑IL17 mRNA; ↑IL-17	Not explored
(Kim et al., 2021)	depression (young adults)	50DEP, 50CTRL	↑IL-17	Not explored; moderate suicidal ideation reported
(Ling et al., 2022)	depression (children)	92 DEP, 48 CTRL	↑IL-17	Not explored
(Becerril-Villanueva et al., 2019)	depression (adolescent)	22DEP, 18 CTRL	↑IL-17	Not explored
(Syed et al., 2018)	depression	171DEP, 64CTRL,	↑IL-17	Significant current suicidality excluded
(Kiraly et al., 2017)	depression	33DEP, 26CTRL	=IL-17	23% history of suicide attempt
(Davami et al., 2016)	depression	41DEP, 40CTRL	↑IL-17	Not explored
(Schiweck et al., 2020)	depression	153 DEP, 153 CTRL	↑% of Th17 cells	↑%Th17 cells in high risk for suicide patients
(Ghosh et al., 2020)	depression	53DEP, 53CTRL	↑% of Th17	Not explored
(Primo de Carvalho Alves and Sica da Rocha, 2020)	depression	139DEP, 100CTRL	↑IL-17	90 patients (65%) reported at least one previous suicide attempt
(Mao et al., 2022)	depression	40DEP, 40CTRL	↑IL-17	Not explored
(Keshri et al., 2018)	bipolar disorder	41BD, 41CTRL	↑IL-17	=No link found, only 7 of 41 cases showed SB
(Ding et al., 2014)	psychotic disorders	69PSY, 60CTRL	↑%of Th17, = IL-17	Not explored
(Schwarz et al., 2012)	psychotic disorders	71PSY, 59CTRL	↑IL-17 in	Not explored
(Şimşek et al., 2016)	psychotic disorders	30PSY, 30 CTRL	=IL-17	Not explored
(Noto et al., 2015)	psychotic disorders	55PSY, 57CTRL	=IL-17	Not explored
(Borovcanin et al., 2012)	psychotic disorders	36 PSY, 113 CTRL	↓IL-17	Not explored
(Chen et al., 2021)	psychotic disorders	113PSY, 58CTRL	↑IL-17	Not explored
(Chin Fatt et al., 2022)	suicidality	11SB, 4CTRL	↑γδ T cells	Higher γδ T cell count compared to controls

mechanisms. See Fig. 1 for an overview of the potential contributors along the IL-17 axis.

3. Peripheral and central inflammation

Immunological, post-mortem, and brain imaging studies suggest that patients who experience suicidal ideation do have relevant (neuro-) inflammatory alterations. In their metanalysis of 18 studies, on 583 psychiatric patients with suicidality, 315 psychiatric patients without suicidality, and 845 controls, Black and Miller found robustly elevated levels of inflammatory cytokines, IL-1β and IL-6, in peripheral blood of patients with suicidality.

Interestingly, these elevated levels of IL-1β and IL-6 were also detected in post-mortem brain samples of individuals who died by suicide compared to healthy controls (Black and Miller, 2015), suggesting that in suicide victims, inflammation in the CNS may be involved. Since only few studies assessed IL-17, this cytokine was not included in the meta-analysis.

4. Evidence for glial activation and impaired neurogenesis

Evidence shows microglial activation in the brains of patients with suicidal thoughts and suicide victims. Holmes et al. (2018), using positron emission tomography (PET) with the ligand for translocator protein (TSPO), which is upregulated in activated glia, showed increased microglial activation in patients with MDD with suicidal thoughts, but not in those without (Holmes et al., 2018). Several reports on increased microglial density and/or activation patterns in suicide victims, affected brain regions include the dorsolateral prefrontal cortex, anterior cingulate cortex (ACC) and mediodorsal thalamus (Steiner et al., 2006; Steiner et al., 2011; Schnieder et al., 2014). It has been suggested that changes in the ventral prefrontal cortex and dorsal prefrontal cortex, which are involved in emotion and impulse regulation, are linked to suicidal ideation (Schmaal et al., 2020); the areas of microglial activation may thus partly overlap. Furthermore, IL-17 has been reported to decrease neurogenesis in the adult dentate gyrus (DG) of hippocampus (Liu et al., 2014) and, recently, Di Filippo et al. (2021) showed a role for IL-17 in synaptic plasticity. This is because IL-17 exposure disrupted hippocampal long-term potentiation in a dose dependent manner, and partially improved LTP during acute blockade of IL-17 in an experimental autoimmune encephalitis (EAE) model. Interestingly, cognitive performance was also better in (both control and EAE) mice lacking IL-17. However, the IL-17 receptor is ubiquitously expressed in the brain, and therefore a role for suicide-associated neuro-inflammation and/or neurodegeneration specifically involving the IL17 signaling cascade, as opposed to general inflammatory activity, cannot be definitively established.

Remarkably, some researchers have found that the association between suicide and inflammation cuts across diagnostic categories. Rather than going on the basis of the diagnosis of schizophrenia or depression as such, it was suicide that was associated specifically with microgliosis in several post-mortem brain regions of suicide victims when compared to patients who died of other causes (Schnieder et al., 2014). While IL-17 has not been assessed in these studies, it is conceivable that IL-17 influences microglial activation: In vitro studies have shown that IL-17 treatment upregulated the microglial production of IL-6, macrophage inflammatory protein-2, nitric oxide, adhesion molecules, and neurotrophic factors; and, microglia can produce IL-17 in response to IL-23 or IL1β (Kawanokuchi et al., 2008). It was also shown that in mice, chronic mild stress exposure as a proxy model of depression, led to an increase in microglial activation in the hippocampus, amygdala, and prefrontal cortex, which was particularly associated with increased IL-17, alongside a more than 2-fold increased Th17 cell population in the brain (Kim et al., 2021). Interestingly, anti-IL-17

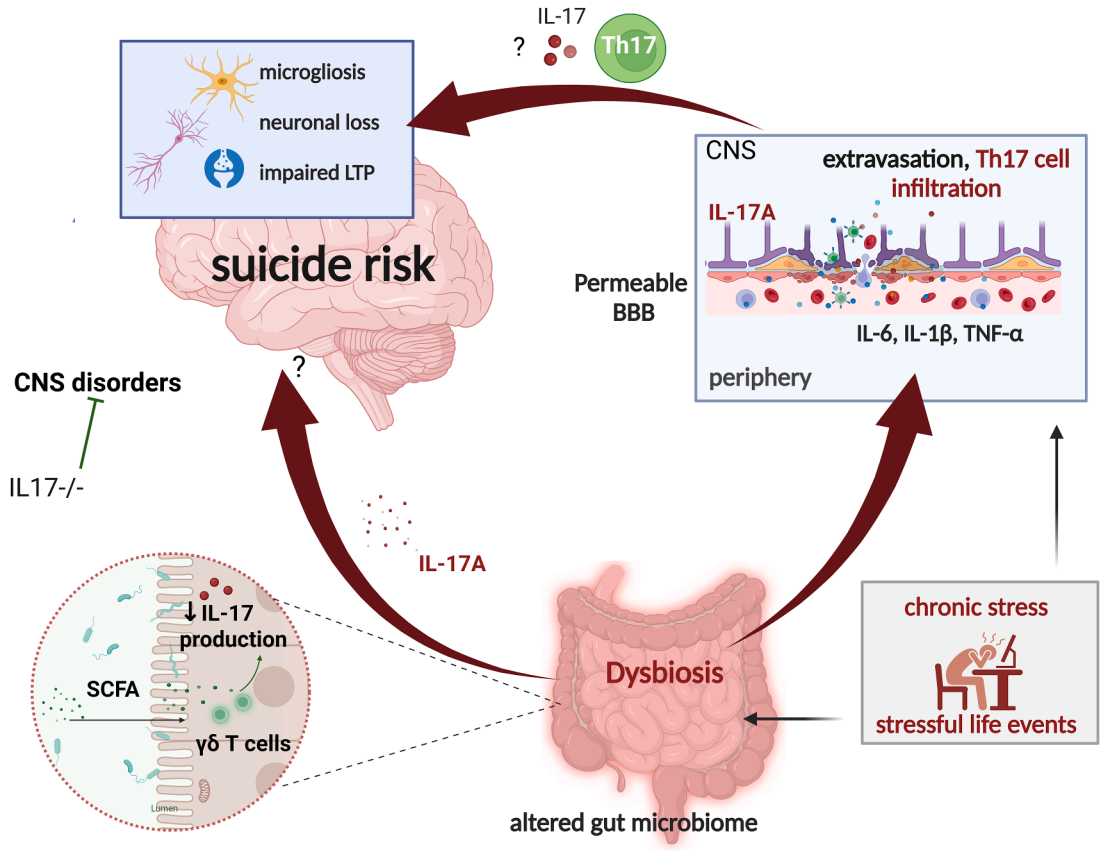

Fig. 1. Potential IL-17-related mechanisms linked to suicidal behavior. Chronic stress has been shown to increase blood brain barrier permeability in mice and stressful life events often precede suicide. IL-17 producing Th17 cells (among others) can enter the CNS in inflammatory conditions and IL-17 has been associated with impaired long-term potentiation and microglial activation. In suicide, microgliosis and neuronal loss may occur, but the possible link to IL-17 is so far unexplored. Dysbiosis in the gut can impair communication along the gut brain axis, and studies in rodents have shown that the gut microbiome and IL-17 in the intestinal tract are important mediators for experimental autoimmune encephalitis (EAE) models of MS. Knock-out of IL-17, or reduction of IL-17 production by exposure of γδ T cells to short chain fatty acids (SCFA) can lead to attenuated EAE development. The direct effect of IL-17/anti-IL17 treatment on suicidal behavior remains to be explored.

treatment was able to relieve anxiety and depression-like behavior in these mice (Kim et al., 2021). In addition, disease animal models give some clues as to the effect of IL-17 on microglia. Evidence from rodent intracerebral hemorrhage models showed that IL-17 contributed to microglial activation, while the use of an IL17A-neutralizing antibody reduced microglial activation (Yu et al., 2016). Experimental autoimmune encephalomyelitis (EAE) models have also identified IL-17 as an important mediator for the disease (Komiyama et al., 2006), that induces the production of IL-1β and IL-6 in astrocytes (Shan et al., 2017), thereby possibly contributing to an inflammatory milieu.

5. Evidence for blood-brain barrier disruption by IL-17

IL-17 is highly relevant in the neuro-inflammation hypothesis because it can cross and disrupt the blood-brain barrier in experimental autoimmune encephalitis models of MS. Indeed, one of the first reports assessing IL-17 in EAE, found that IL-17 disrupted BBB tight junctions in vitro and in vivo and once disrupted, Th17 cells infiltrate the brain and produce cytokines and cytolytic enzymes (Kebir et al., 2007). Since then, others have found that this disruption is caused by impaired endothelium tight junctions and monolayer integrity (e.g., (Setiadi et al., 2019)). However, EAE is a particular immunological condition with strong immune activation, different from the low-grade peripheral inflammation observed in suicidality. The mechanisms that could lead to microglial activation in the context of suicide and the role of modestly increased IL-17 serum levels in this activation, is still unknown, and no animal model exists to assess this relationship. A peripheral proxy that is often used for blood brain barrier integrity is S100B. Several studies have reported higher levels of S100B in individuals with higher suicidal ideation (e.g., (Falcone et al., 2010; Falcone et al., 2015)) and one study found that victims of suicide had higher levels of S100B in the cerebrospinal fluid compared to individuals who did not die by suicide (Dogan et al., 2016). While these studies may suggest the possibility of disrupted BBB integrity in suicidality, it should be noted that the validity of S100B as an accurate marker for BBB integrity has been questioned (Kleindienst et al., 2010).

6. Evidence for a disturbed gut-brain axis signaling

Another interesting possibility for IL-17 influencing suicidal behavior, is the gut-brain axis. It is now recognized that the gut microbiota (and its metabolites), the immune system and the brain are in a constant bi-directional exchange of information, and can influence each other via several routes. The most prominent communication route is via the vagus nerve (e.g., inflammation can be regulated via the cholinergic anti-inflammatory pathway (CAIP) (Martelli et al., 2014)). In a dysbiotic environment, this communication can become dysregulated, inducing an altered permeability of the BBB and neuro-inflammatory processes (Rutsch et al., 2020).

Dysbiosis of the gut is indeed strongly linked to inflammatory reactions in various CNS disorders (Benakis et al., 2020). Which role does IL-17 play in in this relationship? In the gut, IL-17 is a highly important cytokine for healthy functioning, but it is also involved in intestinal inflammation. The role of the microbiota/microbial metabolites in the

gut and immune cells is crucial for healthy functioning as it can repress IL-17 production. This has recently been shown for cecal γδ T cells (Dupraz et al., 2021), which take on an important role in the communication with the gut microbiota (Papotto et al., 2021). It has also been shown that mice who are deficient in IL-17A and F have an altered composition of their gut microbiota (most alterations in the family of *barnesiellaceae*) and do not develop EAE. Reestablishing the microbiota or IL-17A administration in the gut epithelium of these mice, led to vulnerability for EAE, suggesting a highly important role for the gut microbiota in EAE-related central inflammatory processes (Regen et al., 2021). Additionally, it has been shown that bacterial metabolites, such as short chain fatty acids, can reduce the pathogenicity of Th17 cells (Luu et al., 2021). This suggests a CNS-relevant role of IL-17specifically mediated by the gut-brain axis. As mentioned above, γδ T cells were also found to be higher in adolescents with high suicidal ideation, but further research needs to determine the exact role of microbiota, metabolites, and the immune-brain crosstalk in suicidal behavior.

6.1. *Quo vadis?*

Current evidence suggests that in animal models, particularly in the context of immunological insult, IL-17 does play a role in neuroinflammation and depression-like behaviors. Data on humans is inconsistent, but evidence suggests that IL-17 is linked to depressive symptoms. However, the literature exploring the role of IL-17 in suicide is insufficient. Currently, a phase 2 clinical trial using the anti-IL-17 monoclonal antibody, *ixekizumab,* is on the way for treatment resistant depression (NCT04979910). Innovative approaches which modify the microbiome and consequent IL-17 production should be undertaken alongside novel neuroimaging techniques to help clarify the role of the IL-17 axis, as opposed to other biologics targeting neuroinflammation and suicidality.

7. Limitations

No systematic approach was used for this review, therefore, it is possible that other articles exist which explore the link between IL-17 signaling and suicidal behaviors, that the authors are unaware of.

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Carmen Schiweck: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Mareike Aichholzer:** Writing – original draft, Writing – review & editing. **Andreas Reif:** Writing – original draft, Writing – review & editing. **Sharmili Edwin Thanarajah:** Writing – original draft, Writing – review & editing.

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