POSSIBLE ROLE OF TGF-B PATHWAYS IN SCHIZOPHRENIA

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MOGUĆA ULOGA TGF-B SIGNALNIH PUTEVA U SHIZOFRENIJI

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ABSTRACT

The phenomenological uniqueness of each patient with schizophrenia is determined by complex symptomatology, particularly the overlapping of symptoms and their prominence in certain phases of this mental disorder. Establishing biological markers is an important step in the further objectivisation and quantification of schizophrenia. Identifying the cytokine profiles that precede a psychotic episode could direct the strategies for relapse prevention and be useful in predicting disease progression and treatment response. In the context of inflammation, TGF-β exerts potent anti-inflammatory and immunosuppressive functions by inhibiting pro-inflammatory cytokine synthesis, but it can also have pro-inflammatory functions through its stimulatory effects on inflammatory Th17 cells. It has been shown that the T helper cell type-1 and type-17 responses are reduced and type-2 response is increased in patients with schizophrenia. Both data from the literature and our results also indicate the presence of an anti-inflammatory response through production of the TGF-β regulatory cytokine. A meta-analysis of plasma cytokine alterations suggested that TGF-β is the state marker for acute exacerbation of schizophrenia, and we showed that TGF-β can also be a valuable marker for psychosis. Hyperactivity of TGF-β signalling pathways in schizophrenia may be both a neuroprotective mechanism and a possible therapeutic target.

Keywords: schizophrenia, biomarkers, TGF-β, neuroplasticity

SAŽETAK

Konstelacija simptoma opservirana kod svakog pacijenta sa shizofrenijom je jedinstvena i može se menjati progresijom bolesti. Aktuelni pokušaji objektivizacije i kvantifikacije u shizofreniji obuhvatili su i istraživanja bioloških markera ovog poremećaja. Određivanje specifičnih citokinskih profila u prodromalnoj fazi poremećaja može usmeriti nove strategije prevencije relapsa i biti od koristi u predviđanju toka bolesti i odgovora na terapiju. U kontekstu inflamacije, TGF-β ispoljava snažnu antiinflamatornu i imunosupresivnu aktivnost sprečavanjem sinteze proinflamatornih citokina, ali može imati i proinflamatornu ulogu stimulacijom inflamatornih Th17 ćelija. Pokazano je da su imunski odgovori tipa-1 i tipa-17 oslabljeni i tip-2 odgovor pojačan kod pacijenata sa shizofrenijom. Podaci iz literature i naši rezultati ukazuju i na antiinflamatorni odgovor u shizofreniji sekrecijom regulatornog citokina TGF-β. Meta-analiza studija, koje su određivale plazmatske nivoe citokina pacijenata sa shizofrenijom, ukazala je na TGF-β kao marker pogoršanja shizofrenije, a naši rezultati takođe pokazuju da TGF-β može biti koristan marker psihoze. Hiperaktivnost TGF-β signalnih puteva u shizofreniji može biti neuroprotektivni mehanizam i potencijalni terapijski cilj.

Ključne reči: Shizofrenija, biomarkeri, TGF-β, neuroplastičnost

INTRODUCTION

The phenomenological uniqueness of each patient with schizophrenia is determined by complex symptomatology, particularly the overlapping of symptoms and their prominence in certain phases of this mental disorder (1). Different approaches to evaluating and characterising schizophrenia can lead to misunderstandings among clinicians and researchers (2).

To address this problem, reliable diagnostic criteria have been defined (3, 4). Additionally, clinical assessment scales are used to evaluate the severity of illness and the degree of treatment response. New diagnostic criteria should account for the knowledge gained over the past 20 years, especially in the field of neurobiology of mental disorders (5). Establishing biological markers is an important step in
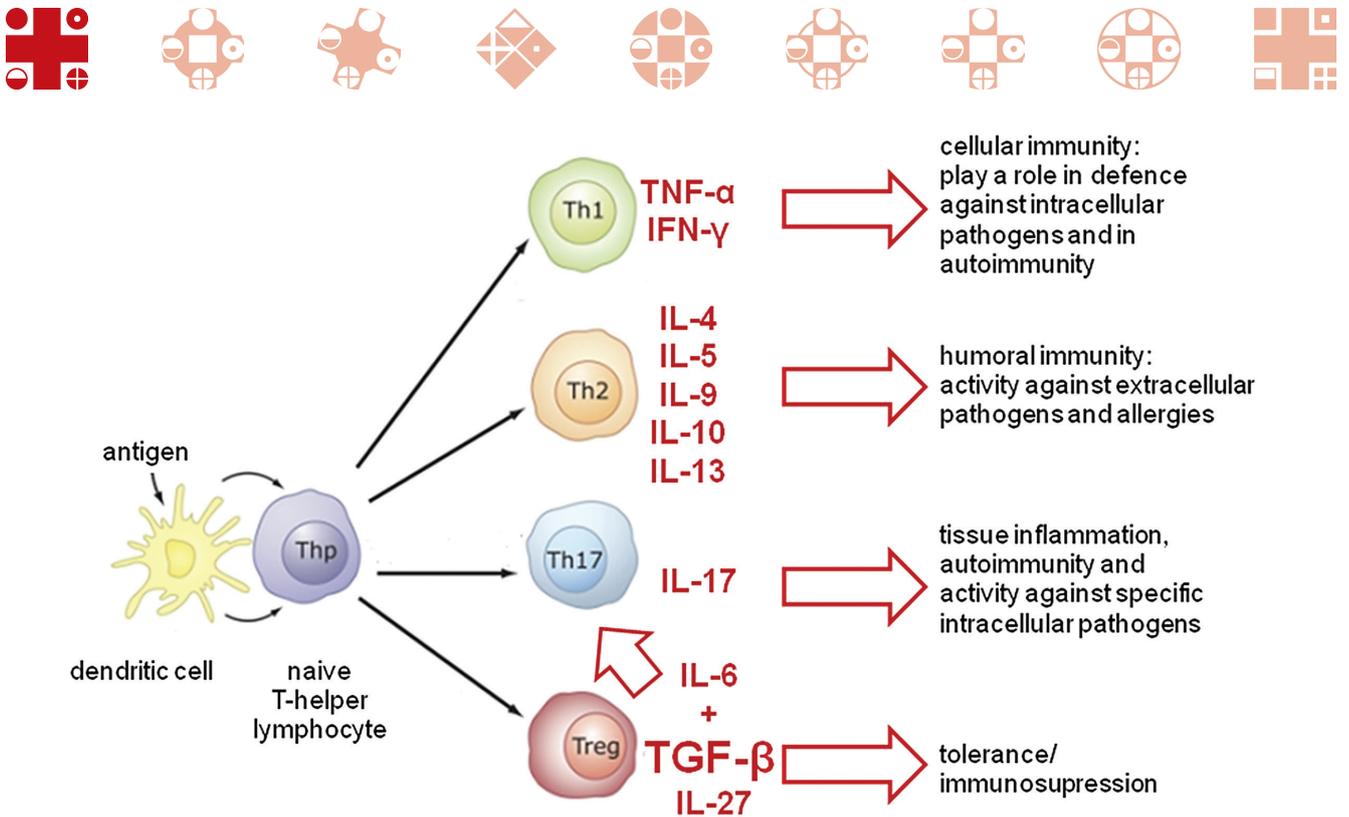
Figure 1. Types of immune responses and role of TGF-β

the further objectivisation and quantification of symptoms of schizophrenia.

Studies have shown that the molecular basis of schizophrenia changes from early stage of the disease to the chronic form, thus providing proof of the progressive nature of the schizophrenic disease process (6). Short-term schizophrenia is linked to transcription, metal binding, expression of ribonucleic acid and vesicular transport, whereas the long-term, chronic form of the illness has been linked to inflammation, response to stimuli and immune functions (7).

Cytokines as biomarkers in schizophrenia

Studies of the role of the immune system in the emergence and development of schizophrenia have shown its important role in the wide range of possible factors affecting schizophrenia (8- 10). Th lymphocytes direct the function of other immune cells by secretion of cytokines. Activated Th cells can be divided into Th1, Th2, Th17 and regulatory T cells (Tregs), based on the cytokines secreted (11) (Figure 1). Macrophages, natural killer, natural killer T cells and dendritic cells may also secrete the same cytokines. Thus, it is more appropriate to categorise immune responses based on their specific cytokine profile, i.e., as type-1, type-2 or type -17.

The type-1 cytokines, such as IFN-γ and TNF-α, activate macrophages and play a role in both the defence against intracellular pathogens and autoimmunity (12). IL-4, IL-5, IL-9, IL-10 and IL-13 are mainly secreted in the type-2 immune response (13). Type-2 cytokines have a role in humoral immunity via activity against extracellular pathogens and in allergies (14). The representative cytokine of the type-17 immune response is IL-17, which is a potent mediator of inflammatory response in autoimmune disorders (15, 16). Regulatory T-cells also have an important role in controlling immune response, as a decrease in regulatory T-cell activation leads to autoimmunity (17). IL-23 was required during the restimulation of TGF-β in addition to IL-6-stimulated cells to maintain their IL-17 production (18).

Identifying the cytokine profiles that precede a psychotic episode could direct strategies for relapse prevention and be useful in prediction of disease progression and treatment response (19, 20). It has been shown that the type-1 response is blunted and that the type-2 response is heightened in schizophrenia (14, 21), and our results indicate reduced type-17 and anti-inflammatory response through production of the TGF-β regulatory cytokine (22- 24).

TGF-β is a pleiotropic cytokine that is secreted by immune and non-immune cells. TGF-β plays a role in immune regulation, but it is also important for embryonic development, cellular differentiation and wound healing (25, 26). The over-expression of TGF-β has been linked to impaired effector T cell responses to viral infections (27).

In the context of inflammation, TGF-β exerts potent anti-inflammatory and immunosuppressive effects by inhibiting pro-inflammatory cytokine synthesis and by dampening natural killer cell activity and growth of T- and

B-cells. However, TGF-β also has pro-inflammatory functions through its stimulatory effects on inflammatory Th17 cells (28) (Table 1). Stimulation of inflammatory Th17 cell genesis by TGF-β occurs primarily in the presence of IL-6 (18, 29- 30) (Figure 1).

TGF-β in schizophrenia

TGF-β family members bind to and activate transmembrane serine/threonine receptors (31). During canonical signalling, type I receptors phosphorylate receptor-activated Smads, which then associate with Smad4, which in turn accumulates in the nucleus and modulates transcription of target genes (32). Signalling through the canonical pathway is involved in multiple aspects of neurodevelopment, adult neurogenesis and neuroprotection (reviewed in 33). There is evidence that TGF signalling contributes to neurodegeneration in Alzheimer's disease (34, 35) and influences cognitive abilities and the level of cognitive decline between male and female schizophrenia patients (36, 37); further, it is altered in the hippocampus in schizophrenia and bipolar disorder (38) and in anxiety and depression (39- 41).

Elevated total TGF-β has been reported in the cerebrospinal fluid of patients with malignancies in the central nervous system, AIDS dementia complex, and neuropathologic disorders, including communicating hydrocephalus, Alzheimer's disease and glioblastoma (42- 44), and in patients with schizophrenia (45).

It has been observed that patients with schizophrenia have a higher percentage of anti-inflammatory regulatory T cells and IL-4-producing lymphocytes in peripheral blood (46). Schizophrenia has been associated with the enhanced peripheral release of TGF-β (47) and increased lymphocytic expression of TGF-β receptors (48, 49). Data from the literature also indicate that the serum levels of TGF-β are significantly increased in patients with schizophrenia in relapse and first-episode psychosis compared with a control group (21, 49). A meta-analysis of plasma cytokine alterations suggested that TGF-β is the state marker for acute exacerbation of schizophrenia (21) and that it can be a valuable marker for psychosis (22). Recent studies have questioned these findings and did not find

a difference in the TGF-β serum levels between patients with schizophrenia and controls (50).

In our studies, we found that the IL-17 levels were decreased and that the IL-17/TGF-β ratio was significantly lower in drug naïve patients who were having their first psychotic episode. We also found that the levels of TGF-β and IL-23 were increased in all psychotic patients and that the IL-6 serum levels decreased only after antipsychotic treatment (22- 24). At the onset of illness, TGF-β most likely plays an immunosuppressive role, and IL-23 may have pathogenic effects unrelated to IL-17. In contrast to our results and those of others (51), several reports have found an increase in serum IL17 in patients whose schizophrenia is in relapse and an increased activation of Th17 cells in the first episode of schizophrenia, with a decrease in Th17 cells after risperidone treatment (50, 52). These differences may be due to the significantly shorter duration of illness in our study population, the possible predominance of IL-6 signalling pathways in later stages of schizophrenia (14), and the diverse effects of different antipsychotic drugs (21). The meta-analysis by Tourjman et al. (53) confirms our findings that TGF-β is unaffected by antipsychotic treatment (23).

Data from a pathway analysis of genome wide association study suggested that TGF-β signaling is associated with schizophrenia (54). The TGFB1+869T>C gene polymorphism is associated with schizophrenia, especially in females in the context of TGF-β and estradiol interaction (55).

TGF-β pathways and neuroplasticity in schizophrenia

TGF-β signalling is a crucial factor in neural stem cell maintenance and differentiation and determines the growth and size of the developing brain (56). Activated microglia seems to have a positive effect on the secretion of the anti-inflammatory cytokine TGF-β (57). Hyperactivity of TGF-β signalling pathways in schizophrenia is considered a neuroprotective mechanism (58). In animal models, TGF-β promotes the survival of midbrain dopaminergic neurons (59), and TGF-β over-expression increases neurogenesis in the subventricular zone (60). Additionally, TGF-β expression is induced following a variety of types of

Table 1. TGF-β role and its concentrations in schizophrenia

parameter	role	serum concentration	cerebrospinal fluid concentration	cytokines ratios	antipsychotic treatment
TGF-β	- inhibition of pro-inflammatory cytokine synthesis - inhibition of natural killer cell activity and growth of T- and B- cells - stimulation of Th17 cells in the presence of IL-6	↑ [21, 49] \ [50]	↑ [45]	IL-17/TGF-β ↓ [22]	\ [53]

↑- increased; ↓- decreased; \ - unchanged

brain tissue injury, which attenuates brain damage through anti-inflammatory, apoptotic, and excitotoxic actions and promotes angiogenesis and neuroregeneration (61).

CONCLUSION

Early interventions in schizophrenia have great importance in preserving cognitive abilities, possibly due to the neuroprotective effects of TGF-β signalling. The biological markers measured during the prodromal phase could have clinical importance in determining diagnosis, further treatment strategies, and prognosis. Targeting the TGF-β signalling pathways with new psychoactive drugs may allow the re-establishment of synaptic transmission in many neuropsychiatric disorders, including schizophrenia.

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