Janus kinase/signal transducer and activator of transcription pathway in schizophrenia (Review)

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Abstract. Schizophrenia is a complex mental disorder that affects cognition, emotions and behaviour. Among the signaling pathways that show dysregulation in schizophrenia is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. JAK/STAT is a pleiotropic pathway that plays key roles in multiple cellular functions. A brief overview of dysregulated signaling in schizophrenia is provided in the present review, focusing on the JAK/STAT pathway. Depending on the disease stage, dysregulation of signaling pathways causes inflammation, which is a key factor in the onset and maintenance of schizophrenia. The dysregulated JAK/STAT signaling pathway is implicated in schizophrenia through numerous processes, including neuro- and gliogenesis, synaptic plasticity and microglia activation. Research on JAK/STAT pathway components can contribute to knowledge that will be translated into efficient therapeutic management strategies to improve the quality of life of patients with schizophrenia.

Contents

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1. Introduction

Schizophrenia is an incapacitating mental disorder whose etiology is multifactorial. Within this context, both genetic and environmental factors contribute to its occurrence (1). Following adversities in life (2,3), gene-environment processes (3) and epigenetic changes (4,5) may affect the expression of genes implicated in synaptic function, neurodevelopment and stress response. Such factors could potentially promote the occurrence of schizophrenia through their effects on neurotransmitters and the immune system, resulting in oxidative stress (6,7). Genetic vulnerability in combination with prenatal and perinatal risk factors (including maternal stress, viral infection, malnutrition, zinc deficiency and hypoxia) may increase the susceptibility to environmental stressors (such as childhood abuse, urbanicity, migration and substance abuse) (8,9). Similarly, it has been proposed that early-life adversity may alter the hypothalamic-pituitary-adrenal axis function, leading to a modified stress response and increased stress sensitivity to potential stressors in adolescence and adulthood (9-11), thus advancing the occurrence of schizophrenia symptoms through dopaminergic hyperactivity (12). Furthermore, prolonged exposure to stress and to glucocorticoids may result in a reduction in hippocampal volume (13) and decreased levels of brain-derived neurotrophic factor (BDNF) in patients with schizophrenia (14-19).

Despite causing major disability worldwide, and the intense research performed over the last decades on the investigation of the molecular mechanisms underlying schizophrenia, its pathophysiology remains not fully understood. Numerous questions regarding the dysregulated signaling pathways and the molecular basis of differential personalised responses to various treatments remain unanswered. The importance of genetic risk factors and key cell signaling pathways is now

confirmed; however, further research is required to fully delineate the underlying molecular mechanisms. Among the signaling pathways in schizophrenia that show dysregulation is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, a pleiotropic pathway that plays a key role in multiple cellular functions (20-22). Since its discovery >30 years ago, JAK/STAT represents one of the most conserved pathways that transmits extracellular signals from over 50 cytokines, growth factors and hormones, to the nucleus, to tightly regulate target gene transcription (23,24). The specific JAK/STAT-dependent expression programs define important cellular responses linked to cell growth, proliferation, cell cycle progression, development, apoptosis, differentiation, migration, survival and malignancy (both solid and hematologic). Furthermore, JAK/STAT plays a pivotal role in immune, inflammatory and stress responses. The family of JAK kinases is composed of four members (JAK1, JAK2, JAK3, and TYK2), while the STAT family in mammals consists of seven members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). All STATs contain a conserved structure that includes the N-terminal, the coiled-coil, the Src-homology 2 (important for STAT dimerization), the linker, the DNA-binding and the transactivation domains (21).

The JAK/STAT pathway plays a key role in inflammation, cancer and neurodegenerative diseases (25). Its importance for brain disorders highlights the necessity to elucidate how it influences the functionality of neural cells. In the present review, insights into the dysregulation of the JAK/STAT signaling pathway in neurological dysfunction and schizophrenia are provided. Inflammation and signaling dysregulation, the crosstalk of non-coding RNAs (ncRNAs) with JAK/STAT, the involvement of the JAK/STAT pathway in patient stratification, management and treatment strategies, and models/approaches to study signaling and to improve therapeutic delivery of drugs in schizophrenia are discussed.

2. Methods

Searches across online databases, including PubMed, Google Scholar and Web of Science, were performed by employing specific keywords and their combinations [including JAK/STAT, signaling, schizophrenia, neurological dysfunction, inflammation/neuroinflammation, stress, ncRNAs (miRNAs, lncRNAs), biomarkers, therapies, organoids, nanotechnology] to identify publications relevant to this brief review. Due to space limitations, not all publications have been included. For efficient organisation, management and storage of the selected references, Zotero version 7.0.26, developed by the Corporation for Digital Scholarship, was used.

3. Inflammation and dysregulated signaling in schizophrenia

Various cell types mediate innate immunity, which participates in the defense of the immune system to various pathogens and is connected to the tightly controlled action of numerous signaling pathways, including the interferon (IFN), mitogen-activated protein kinase, JAK/STAT, interleukin (IL), chemokine receptor, and glycogen synthase kinase pathways. JAK/STAT is considered important in regulating inflammatory and immunological responses, thus promoting neuroinflammation in neurodegenerative diseases (25). Alterations to immune function have also been detected in psychosis, with increased proinflammatory cytokines in the serum of the patients, indicating activation of immune-related cells in the circulation (26).

Inflammation is considered a key factor for the onset and maintenance of schizophrenia, with a variety of cytokines being dysregulated depending on the disease stage (27-29). Cytokines, as key molecules of the immune system, control the brain/nervous system response to exogenous insults and mediate the communication of the nervous and immune systems (30). Cytokine imbalance has been detected in both blood and cerebrospinal fluid of patients with schizophrenia, particularly in T helper type 1 and type 2 cytokines, despite contradictory results in the literature (31). Infections, autoimmune diseases, and genetic predisposition are considered risk factors for schizophrenia. Furthermore, chronic stress is reported to contribute to a continued proinflammatory state that potentially promotes the disorder (31).

4. Dysregulated JAK/STAT signaling in neurological dysfunction and schizophrenia

JAK/STAT pathway in neurological dysfunction. Dysregulated cytokines bind to receptors that activate the JAK/STAT pathway, and thus are implicated in neuropsychiatric disorders through numerous processes, including neurogenesis, gliogenesis, synaptic plasticity and microglia activation (32,33). JAK/STAT signaling is reported to be linked with neurodegenerative and neuropsychiatric disorders. For example, JAK/STAT is reported to regulate many of the genes associated with epilepsy syndromes. Neurons respond to prolonged BDNF exposure, both *in vivo* and *in vitro*, by activating the JAK/STAT pathway. RNA-sequencing of neurons exposed to BDNF, in the presence or absence of JAK/STAT inhibitors, showed that the neuronal BDNF-induced JAK/STAT pathway involves more than just STAT3 phosphorylation, supporting an underlying non-canonical JAK/STAT mechanism (34). Furthermore, STAT3 plays an important role in neural function relevant to behaviour in both healthy and pathological conditions (35). However, numerous questions remain to be answered on STAT3 involvement in psychopathological neural mechanisms. Knockdown approaches suggested that STAT3 in the nuclei of the dorsal raphe (located in the midbrain and pons) controls behavioural reactivity, and serves as a functional connecting molecule between the upstream activators of STAT3, serotonergic neurotransmission and psychopathology (35). The JAK/STAT/Rho-associated coiled-coil containing protein kinase (JAK/STAT/ROCK) signaling pathway has been linked to lung-brain-related immune responses. JAK/STAT/ROCK is reported to be important for the crosstalk between uncontrolled inflammation following upper respiratory tract infections and the development of neurodegenerative diseases, providing novel avenues for the therapeutic management of the associated inflammation (36). Based on such findings, it cannot be excluded that similar mechanisms might exist in schizophrenia.

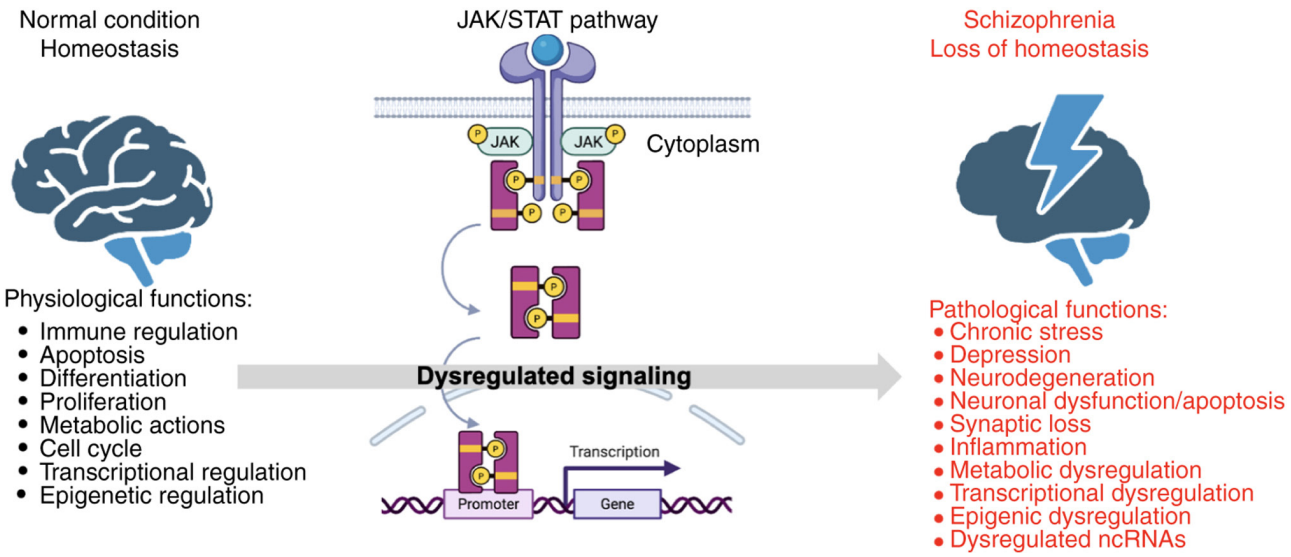

Figure 1. Dysregulation of JAK/STAT signaling pathway and other cellular functions in schizophrenia. The schematic diagram of the JAK/STAT signaling pathway is shown in the middle. The normal condition is depicted on the left, where no dysregulation is observed in the JAK/STAT pathway, and the cellular functions controlled by the JAK/STAT pathway (including inflammation, immune regulation and response, hematopoiesis, apoptosis, differentiation, proliferation, metabolic actions, cell cycle, and transcriptional and epigenetic regulation) are in homeostasis. In schizophrenia (on the right), upon dysregulation of the JAK/STAT and other pathways, metabolic, transcriptional and epigenetic dysregulation, chronic stress, depression, neurodegeneration, neuronal dysfunction and apoptosis, synaptic loss, inflammation and dysregulated ncRNAs are observed. JAK/STAT, Janus kinase/signal transducer and activator of transcription; ncRNA, non-coding RNAs. The figure was created using BioRender (https://BioRender.com).

JAK/STAT pathway in schizophrenia. The JAK/STAT1 gene expression signature has been downregulated in early psychosis and in individuals with an acute exacerbation of psychosis who require hospitalisation. By contrast, this specific expression signature was normalised in individuals with longer psychosis duration and chronic psychopathology (26). Such findings validate the importance of the JAK/STAT pathway in neurophysiological circuits that are critical for the development of psychiatric diseases, including schizophrenia.

Stress triggers inflammation through the JAK/STAT pathway, leading to neuroinflammation that causes neuronal and synaptic dysfunction, and also cognitive impairments, which are hallmarks of schizophrenia and other stress-associated neuropsychiatric disorders. Cytokines released during the stress response regulate gliogenesis, neurogenesis, and synaptic plasticity. Chronic stress sustains JAK/STAT activation, leading to the chronic inflammation observed in schizophrenia (37).

Furthermore, a single-nucleotide polymorphism (SNP) in the *ZNF804A* gene has been associated with decreased transcript levels in the fetal brain and has been linked to schizophrenia and bipolar disorder. The formation of a protein complex of ZNF804A with IFN-activated STAT2 has indicated its function as a signal transducer that activates IFN-mediated gene expression programs, which are important for schizophrenia pathophysiology (38). Activation of STAT1 by signaling cascades initiated by receptors triggered by proinflammatory cytokines (such as IFNγ, IL-6, IL-2, IL-10), hypoxia, infections and peptide growth factors has also been reported to be dysregulated in schizophrenia (39). Such findings confirm the implication and importance of the dysregulated pleiotropic JAK/STAT pathway in schizophrenia, which influences several key disease-related cellular functions (Fig. 1).

5. Crosstalk of ncRNAs with the JAK/STAT pathway in schizophrenia

ncRNAs hold key roles in regulating gene expression and have been linked to neurological and neuropsychiatric disorders, including schizophrenia. ncRNAs regulate inflammation, and pro- and anti-inflammatory factors are regulated by microRNAs (miRNAs or miRs). Long ncRNAs (lncRNAs) also affect miRNAs (40). Dysregulation of ncRNAs in schizophrenia has been reported, with studies showing altered miRNA expression (including miR-132, miR-212, miR-34a/miR-34c, miR1307) and lncRNA changes in brain tissues from patients with schizophrenia (41,42). Among others, Gomafu, PINT, GAS5, IFNG-AS1, FAS-AS1, PVT1, and TUG1 have been reported as downregulated lncRNAs in schizophrenia. By contrast, MEG3, THRIL, HOXA-AS2, Linc-ROR, SPRY4-IT1, UCA1, and MALAT1 have been reported as upregulated. Furthermore, miR-30e, miR-130b, hsa-miR-130b, miR-193a-3p, hsa-miR-193a-3p, hsa-miR-181b, hsa-miR-34a, hsa-miR-346, and hsa-miR-7 have been shown to be dysregulated in blood or brain samples of patients with schizophrenia (43). Despite all these findings, the evidence for a crosstalk between ncRNAs and the JAK/STAT pathway in schizophrenia and other neuropsychiatric disorders is currently limited. ncRNAs can regulate JAK/STAT signaling by acting as downstream or upstream modulators (44). The lncRNAs AC006129.1 and RP5-998N21.4 are involved in immune responses and interact with pathways such as JAK/STAT, through the regulation of SOCS3 and STAT1, respectively (44-46).

Extensive ncRNA crosstalk with JAK/STAT pathway components is mainly documented in cancer (47). Evidence from neurological-related and other tumors shows that certain ncRNAs can regulate the JAK/STAT pathway by interacting

with pathway regulators (such as SOCS1) or by directly affecting the expression and activation of JAK/STAT proteins, thereby influencing inflammation and cell signaling (48,49). Our previous studies demonstrated significant downregulation of specific miRNAs (let-7p-5p, miR-98-5p and miR-183-5p) in patients with cancer only, and cancer with schizophrenia, when compared to patients with schizophrenia only, suggesting an oncosuppressive role for these miRNAs (50-52). Based on our findings (50-52) and the extensively studied crosstalk of ncRNAs with JAK/STAT in various malignancies (53-57), it cannot be excluded that similar crosstalk participates in mechanisms that lead to schizophrenia, a hypothesis that needs further exploration and validation in future studies.

6. JAK/STAT pathway in the therapeutic management of schizophrenia

Given the importance of the JAK/STAT pathway in neurodegenerative and neuropsychiatric diseases, the use of JAK/STAT pathway components as biomarkers for monitoring disease progression and response to therapies, or for therapeutic targeting of schizophrenia and other relevant diseases, constitutes a clinical necessity.

JAK/STAT components as biomarkers. Components of the JAK/STAT signaling pathway have already been utilised as biomarkers of disease state. Patients with schizophrenia with poorer cognitive performance have expressed significantly higher levels of activated pSTAT1 when compared with controls, providing a biomarker of biological significance (39). Phospho-specific cell signaling epitope expression in peripheral blood mononuclear cell (PBMC) subtypes, in drug-naïve schizophrenia patients compared with controls, has identified specific disease alterations. In combination with serum immune response proteins, polygenic risk scores, drug response and side effects, such alterations have been analysed throughout the antipsychotic therapy. Among others, Stat3 (pS727), Stat3 (pY705) and Stat5 (pY694) across PBMC subtypes have been linked with schizophrenia at disease onset, and have been correlated with the type I IFN-related serum molecules CD40 and CXCL11. Alterations in Stat3 (pS727), among other molecules, predicted the development of metabolic and cardiovascular side effects following antipsychotic treatment, together with side effects and early improvements in general psychopathology scores (58). Such findings validate the importance of using PBMCs as a valuable model for detecting intracellular signaling alterations in schizophrenia for stratification of patients with differential clinical outcomes or risk for side effects of antipsychotic treatment (58). Furthermore, highly sensitive C-reactive protein, a biomarker for detecting inflammation in schizophrenia (33), has been used, and elevated levels of pro-inflammatory and anti-inflammatory cytokines have been detected in the peripheral blood of patients with first-episode schizophrenia and relapsed, when compared with healthy controls. Specifically, IL-6, IL-1, TNF, and IFN have been demonstrated to be dysregulated in schizophrenia (33). It cannot be excluded that such findings may be linked to dysregulation of the JAK/STAT pathway or can be used in combination with detected dysregulation of JAK/STAT components or relevant ncRNAs for more accurate stratification, therapeutic management, and prediction of therapeutic response in schizophrenia.

JAK/STAT targeting for therapeutic purposes. Anti-inflammatory agents inhibiting relevant signaling pathways might serve as useful treatments for inflammatory schizophrenia (33). Such agents have been effective in reducing disease symptoms and increasing the functionality of patients. Despite encouraging results, further research is needed towards the personalised approach of such treatments (33).

Small-molecule inhibitors of JAKs (jakinibs) have been safe and efficient for the treatment of diseases with underlying inflammation (rheumatoid arthritis, psoriasis, and inflammatory bowel disease) (59), and may constitute promising treatments for schizophrenia in the future.

Symptoms of depression, frequent in schizophrenia, and the antidepressant actions of current treatments have been mediated by JAK/STAT-dependent mechanisms (60). Furthermore, inflammation and oxidative stress have been targeted for the development of novel therapies for depression. The finding that the JAK/STAT pathway might mediate antidepressant-like effects of N-acetylcysteine, suggests the importance of targeting this pathway for novel and effective therapies for depression (60).

The pathogenesis of schizophrenia involves abnormal activation of microglia. Minocycline and antipsychotics have been effective in blocking the activation of microglia and thus reducing the negative symptoms of schizophrenia. When microglia cells were activated by lipopolysaccharide and treated with minocycline, haloperidol, and risperidone, various effects were detected in cytokine production and signaling pathway dysregulation. Minocycline was shown to suppress JAK2 and STAT3 activation. Risperidone and haloperidol only suppressed STAT3 activation. These findings have shed light on the underlying mechanisms of minocycline and atypical antipsychotics for the treatment of schizophrenia (61) and indicated the importance of targeting the JAK/STAT pathway.

Therapeutic agents that target the JAK/STAT pathway involve cytokine or receptor antibodies, JAK inhibitors, and STAT inhibitors, which have been applied to various cancers and autoimmune diseases. Pimozide, an antipsychotic drug belonging to the diphenylbutylpiperidine class, has been shown to inhibit the action of STAT proteins, mainly STAT3 and STAT5 (62). When pimozide was used to treat schizophrenia, the patients demonstrated a lower incidence of solid malignancies. Further studies have demonstrated that pimozide induces apoptosis and decreases metastasis through mechanisms involving STAT3, STAT5 and other molecules (63,64). As inflammation plays a major role in the onset and maintenance of schizophrenia, and the dysregulated cytokines depend on the phase of the illness (33), a wide variety of anti-inflammatory agents may inhibit subsequent pathways and have been effective for treatment. Hormonal therapies, antioxidants, omega-3 fatty acids, and minocycline have improved symptoms and everyday functioning of the patients (33); however, many questions remain to be answered on the crosstalk of such anti-inflammatory agents with the JAK/STAT pathway. Furthermore, their action in other cellular processes beyond inflammation requires further investigation and questions their efficacy for the improvement of schizophrenia. Current

therapies to mitigate inflammation in schizophrenia also include antibiotics and emerging biological agents that target specific inflammatory pathways (27,61). Additional strategies involve probiotics and advanced techniques, such as nanotechnology, to effectively deliver therapeutic agents (65). These are often used as adjunctive medication, added to traditional treatments to improve symptoms (65). The therapeutic targeting of ncRNAs to reduce inflammation is also of importance, as ncRNAs can serve as therapeutic targets in inflammation-related diseases (40), including schizophrenia.

It is expected that targeting the dysregulated JAK/STAT pathway alone, or in combination with the already reported anti-inflammatory therapies, or the ncRNAs regulating the JAK/STAT pathway, will contribute to the development of efficient and personalised therapeutic management approaches for schizophrenia.

7. Models and approaches to study signaling pathways in schizophrenia

Organoids. Organoid models of schizophrenia have been successfully used to study dysregulated signaling pathways, providing pioneering tools in understanding the underlying disease mechanisms. Patient-derived induced pluripotent stem cell (iPSC) organoids have been used. Such models in schizophrenia confirmed dysregulation of signaling (FGFR1) that affects cortical development (66), and dysregulation of genes functionally relevant to synapses, neurodevelopment, axonal guidance, synaptogenesis and other pathways (67-69). Such studies demonstrate the reliability of organoid models to recapitulate signaling and other pathway disruptions in schizophrenia. However, the study of the JAK/STAT signaling field, using organoid models, remains unexplored. Research using organoids is expected to address the role of JAK/STAT in schizophrenia in the near future.

Nanotechnology. Nanotechnology describes various devices, carriers, and materials that facilitate the transportation of drugs for therapeutic purposes, and includes nanomaterials and nanodevices. Nanotechnology, encompassing engineered small-scale objects that match the sizes of biomolecules, their assemblies, and cellular parts (70), provides unique opportunities to understand brain functions. Nanomaterials, acting as nano-sized lipophilic carriers, facilitate the transportation of drugs across the blood-brain barrier (71). As an example, when miR-137, which controls key cognitive and sensory processing genes that are dysregulated in schizophrenia, was encapsulated in nanoparticles, nontoxic delivery and easy incorporation into cells was achieved (72). Nanopsychiatry aims to improve agents for the treatment of psychiatric diseases through the use of nanoscaled carriers. Devices capable of detecting levels of dopamine and serotonin in patients, which could improve schizophrenia diagnostics, have already been developed. Novel nano-sized drug delivery systems, by increasing the efficacy and pharmacokinetics of traditional schizophrenia drug treatments, could improve the therapeutic landscape of this complex disease (73). The use of nanotechnology systems to study dysregulated signaling pathways, including JAK/STAT in schizophrenia, is currently limited; however, it is expected to expand in the near future and to improve the delivery of drugs targeting JAK/STAT or other pathways for the therapy of schizophrenia.

8. Conclusion

Schizophrenia, a traditionally defined brain disorder, is now known to be controlled by the periphery and the immune system. The JAK/STAT pathway plays a key role in inflammation and neurodegenerative diseases. Its importance for most brain disorders highlights the necessity to elucidate how it functionally modulates molecular pathways in neural cells. In this short review, insights into the dysregulation of the JAK/STAT signaling pathway in schizophrenia are provided. Aspects of the dysregulated signaling in inflammation, the cross-talk of ncRNAs with JAK/STAT, the involvement of JAK/STAT in therapeutic management strategies, and the models/approaches to study signaling and to efficiently deliver treatments in schizophrenia are discussed.

Future research on the dysregulated JAK/STAT signaling pathway using organoid models will generate scientific knowledge to further elucidate the pathophysiology of this complex disorder. Additionally, it is expected to provide useful biomarkers or therapeutic targets to develop novel and more efficient stratification and therapeutic management strategies for schizophrenia. Nanopsychiatry and nanotechnology are also expected to improve the delivery of drugs targeting JAK/STAT or other pathways towards efficient and personalised therapies for schizophrenia.

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ER and EK wrote and edited the manuscript. CT, JNT and DAS edited the manuscript. All authors contributed to the article, and read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in

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