

SMOKING MAY IMPACT IL-33/ST2 SIGNALING FOR BETTER COGNITIVE FUNCTIONING IN SCHIZOPHRENIA

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ABSTRACT

We found a positive correlation between serum levels of interleukin-33 (IL-33) and the Montreal Cognitive Assessment (MoCA) score in patients with stable schizophrenia, as well as with specific sub-scores. Smoking appears to decrease serum levels of soluble IL-33 receptor, a suppressor of tumorigenicity (sST2), possibly resulting in IL-33's indirect preservation of cognitive functioning.

Keywords: Schizophrenia, IL-33, ST2, cognition, smoking.

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INTRODUCTION

The interleukin-33/suppressor of tumorigenicity (IL-33/ST2) signaling pathway is involved in the regulation of T lymphocyte activity and differentiation, dendritic cell differentiation and activation, macrophage and mast cell activation, and cytokine production (1). IL-33 has a dual function and may exert pro-inflammatory or anti-inflammatory effects in the central nervous system (CNS). Its function may depend on the primary target cells, the level of IL-33/ST2 expression, the cellular context, and the cytokine milieu (2, 3, 4). IL-33 plays a neuroprotective and reparative role in the CNS by regulating the polarization of microglia and macrophages, as well as phagocytosis (5). By binding to the ST2 receptor, IL-33 promotes the activation and proliferation of microglia, the production of various cytokines, and leads to an acute inflammatory response (6). Astrocyte and oligodendrocyte precursors express IL-33 during the first postnatal week, which coincides with crucial stages of brain development (7). These findings indicate a role for IL-33 even in the absence of inflammation. IL-33 may promote neuroinflammation and cause cognitive decline in later life (8). In recent years, there has been increasing evidence for an important immunomodulatory role of IL-33 in neurodegenerative diseases (9).

Studies in animal models suggest that IL-33 improves cognition by inhibiting the inflammatory response in the hippocampus and regulating the number of excitatory synapses (10). We have also previously published results indicating that serum IL-33 levels are elevated in exacerbation and normalized in stabilization of schizophrenia (11). Additional analysis as part of a doctoral dissertation revealed that, in patients in remission, there is a positive correlation between serum IL-33 levels and the Montreal Cognitive Assessment (MoCA) score ($r = 0.401$; $p = 0.038$), as well as the sub-scores for visuospatial/executive functions ($r = 0.437$; $p = 0.023$), serial subtraction ($r = 0.428$; $p = 0.026$), and fluency ($r = 0.392$; $p = 0.043$) (12).

Furthermore, these patients are often nicotine dependent. This dual diagnosis of addiction contributes to an already compromised somatic state and poorer overall outcomes in schizophrenia (11). Extensive research links tobacco smoking to vascular damage, which contributes to the development of hypertension and atherosclerosis and increases the risk of neurodegeneration (13).

However, for the first time, we want to emphasize the underlying immunological mechanisms that could explain the short-term benefits of smoking. There is a statistically significant, moderately negative correlation between scores on the Fagerstrom scale, which assesses nicotine dependence, and serum sST2 concentrations ($r = -0.476$; $p = 0.012$) (12). Taking this into account, we propose a new cascade, suggesting that smoking may cause IL-33 to circulate more freely by decreasing sST2 levels, thereby preserving cognitive functioning (Figure 1). When circulation is oversaturated with IL-33, it may induce its downregulation. In line with our findings, a recent study provided strong evidence that cigarette smoke

leads to an overall reduction in IL-33 expression at both the transcriptomic and protein levels (14). The increase in systemic IL-33 concentration suggests its movement from the cytosol into the circulation, indicating that higher circulation levels correspond with reduced presence in cells and tissues, and *vice versa*. The proposed mechanism may not apply to patients in the acute stages of illness, those with treatment-resistant schizophrenia, or non-smoking groups.



Figure 1. Hypothesis-based model of potential smoking effects on cognition *via* IL-33/ST2 signaling. Proposed new cascade: with increasing cigarette consumption, there may be a decrease in serum levels of soluble suppressor of tumorigenicity (sST2) and, consequently, an increase in the level of free IL-33, which may affect the preservation of cognitive potential.

CONCLUSIONS

It can be concluded that IL-33 could potentially be effective in delayed neurocognitive recovery, which is of great importance for patients' daily functioning and resocialization. Data regarding cognition in patients with stabilized schizophrenia revealed that IL-33 correlated with cognitive functioning, and this pattern could be further investigated in schizophrenia. It is possible that smoking could lower sST2 levels and thus impact cognition, making circulating IL-33 more available. However, observed associations should not be considered causal and may also be bidirectional. Potential confounding factors must be taken into consideration, such as duration of illness, antipsychotic treatment, and cardiometabolic comorbidities, which may affect both cytokine profiles and cognitive functioning. In this case, the effect of smoking could be rather indirect. The currently available data should not be interpreted as a clinical recommendation, and the presented hypothesis should be thoroughly tested in the future.

LIST OF ABBREVIATIONS

IL-33/ST2: Interleukin-33/Suppressor of Tumorigenicity

CNS: Central Nervous System

sST2: soluble Suppressor of Tumorigenicity

MoCA: Montreal Cognitive Assessment

STATEMENT OF HUMAN RIGHTS

These comments are based on our previous study, which was approved by the Ethics Committee of the University Clinical Centre Kragujevac (01-7015). All participants provided written consent before any study procedures. The investigation was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

All authors contributed equally to the writing of this manuscript and have approved the final version.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

SMJ, MMB, and IPJ collaborated in collecting the related data, with all authors contributing to the conceptualization and writing of the manuscript.

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