ВЛИЯНИЕ РАСТВОРИМЫХ ФАКТОРОВ МАКРОФАГОВ, ПОЛЯРИЗОВАННЫХ ЭФФЕРОЦИТОЗОМ, НА НЕЙРОНАЛЬНУЮ ПЛОТНОСТЬ ВО ФРОНТАЛЬНОЙ КОРЕ И ГИППОКАМПЕ МЫШЕЙ В МОДЕЛИ СТРЕСС-ИНДУЦИРОВАННОЙ ДЕПРЕССИИ

Ращупкин И.М.[1], Амстиславская Т.Г.[2], Маркова Е.В.[1], Останин А.А.[1], Шевела Е.Я.[1]

[1] ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия
[2] ФГБНУ «Научно-исследовательский институт нейронаук и медицины», г. Новосибирск, Россия

Резюме. В последние десятилетия наблюдается неуклонный рост депрессивных расстройств, занимающих важное место в структуре причин нетрудоспособности. В основе патогенеза депрессии лежит нейровоспаление, ассоциированное с нарушением взрослого нейрогенеза. Важно отметить, что нейровоспаление, является частично обратимым, при этом ведущая роль в запуске и регуляции нейровосстановительных процессов отводится макрофагам/микроглии, характерными свойствами которых является гетерогенность и пластичность. При этом оппозитными состояниями активации макрофагов являются классически активированные М1 и альтернативно активированные М2-макрофаги, характеризующиеся, соответственно, про- и противовоспалительной активностью. Смещение баланса в сторону макрофагов с М2-фенотипом рассматривается в последние годы в качестве новой терапевтической стратегии в коррекции психо-неврологических расстройств. Одним из индукторов М2-фенотипа макрофагов является эффероцитоз. Ранее нами был разработан оригинальный протокол генерации макрофагов человека в условиях дефицита ростовых / сывороточных факторов, в котором ключевым моментом формирования М2-фенотипа является эффероцитоз. Получаемые таким образом макрофаги (M2(LS), LS – Low Serum) экспрессируют М2-ассоциированные маркеры и характеризуются активной продукцией ростовых и проангиогенных факторов (IGF-1, VEGF, BDNF, EGF, FGF-basic и др.), способных подавлять воспаление и стимулировать нейрорегенерацию/нейропластичность. В модели стресс-индуцированной депрессии был показан антидепрессантный

Адрес для переписки:
Ращупкин Иван Михайлович
ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии»
630099, Россия, г. Новосибирск, ул. Ядринцевская, 14.
Тел.: 8 (383) 236-03-29.
Факс: 8 (383) 222-70-28.
E-mail: ct_lab@mail.ru

Address for correspondence:
Ivan M. Rashchupkin
Research Institute of Fundamental and Clinical Immunology
14 Yadrintsevskaya St
Novosibirsk
630099 Russian Federation
Phone: +7 (383) 236-03-29.
Fax: +7 (383) 222-70-28.
E-mail: ct_lab@mail.ru

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эффект растворимых факторов указанных М2-макрофагов, проявляющийся в снижении депрессивно-подобного поведения и снижении уровня провоспалительных цитокинов в отдельных структурах головного мозга. Однако влияние факторов М2(LS) на нейрогенез оставалось неизученным. В настоящей работе, которая является продолжением вышеупомянутого исследования, проанализировали влияние интраназального введения факторов М2(LS) макрофагов на нейрональную плотность в различных областях мозга – фронтальной коре и гиппокампе мышей в модели стресс-индуцированной депрессии. Полученные результаты показали, что нейрональная плотность во фронтальной коре, а также CA1 и CA3 зонах гиппокампа после терапии растворимыми факторами М2(LS) была значимо выше, чем у депрессивноподобных животных и сопоставима с таковой у интактных животных. Полученный результат может свидетельствовать о нейрорегенеративной активности М2(LS) макрофагов в модели стресс-индуцированной депрессии, который опосредуется через растворимые факторы и проявляется в повышении плотности нейронов во фронтальной коре и гиппокампе.

Ключевые слова: макрофаги, М2-фенотип, мыши, депрессия, нейрорегенерация, нейрогенез

EFFECT OF SOLUBLE FACTORS OF MACROPHAGES POLARIZED BY EFFEROCYTOSIS ON NEURONAL DENSITY IN THE FRONTAL CORTEX AND HIPPOCAMPUS OF MICE IN A MODEL OF STRESS-INDUCED DEPRESSION

Rashchupkin I.M.[a], Amstislavskaya T.G.[b], Markova E.V.[a], Ostanin A.A.[a], Shevela E.Ya.[a]

[a] *Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*
[b] *Research Institute of Neurosciences and Medicine, Novosibirsk, Russian Federation*

Abstract. Recently, there has been a steady increase in depressive disorders, which occupy an important place in the structure of the causes of disability. In the pathogenesis of depression, an important role is played by neuroinflammation, which is associated with impaired adult neurogenesis. Notably, neuroinflammation is partially reversible, and the leading role in the initiation and regulation of neuroregeneration is given to macrophages. Opposite states of macrophage activation are classically activated M1 and alternatively activated M2 macrophages, characterized, respectively, by pro- and anti-inflammatory activity. A balance shift towards M2 macrophages has been considered as a new therapeutic strategy of psycho-neurological disorders. One of the inducers of the M2 phenotype is the efferocytosis. We have previously developed an original protocol for the generation of human macrophages under conditions of deficiency of growth / serum factors, in which M2 phenotype is formed through efferocytosis. Macrophages (M2(LS), LS – Low Serum) obtained according to this protocol express M2-associated markers, and are characterized by high production of growth and pro-angiogenic factors (IGF-1, VEGF, BDNF, EGF, FGF-basic, etc.), which can suppress inflammation and stimulate neuroregeneration / neuroplasticity. In the model of stress-induced depression, the antidepressant effect of soluble factors of M2(LS) macrophages was shown, accompanied by a decrease in the level of pro-inflammatory cytokines in certain brain structures. However, the effect of M2(LS) factors on neurogenesis remained unexplored. In the present work, which is a continuation of the aforementioned study, we analyzed the effect of intranasal administration of M2(LS) soluble factors on neuronal density in different brain areas – the frontal cortex and hippocampus – of depression-like mice. The results obtained showed that neuronal density in the frontal cortex, CA1 and CA3 zones of the hippocampus, was significantly higher in mice with intranasal administration of M2(LS) conditioned medium than in depression-like mice, and reached the level of neuronal density in intact animals. These results may indicate the neuroregenerative activity of M2(LS) macrophages in the model of stress-induced depression, which is mediated through soluble factors and manifests itself in an increase in the density of neurons in the brain.

Keywords: macrophages, M2 phenotype, mice, depression, neuroregeneration, neurogenesis

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Introduction

Macrophages (Mϕ) are one of the most important components of the innate immunity system. In the central nervous system (CNS) Mϕ are represented by microglia (resident macrophages) and Mϕ of bone marrow origin recruited from peripheral blood. The proportion of the latter increases significantly in the presence of a tissue damage or/and inflammation. Mϕ/microglia is characterized by pronounced plasticity and heterogeneity. The extreme opposite states of Mϕ activation are classically activated M1 and alternatively activated M2 cells [7]. M1 exhibit proinflammatory properties, while M2 have a pronounced anti-inflammatory activity: they promote resolution of inflammation, produce anti-inflammatory cytokines and growth factors. The role of M1 and M2 Mϕ in the CNS pathology is being actively studied. For example, the role of various Mϕ phenotypes in a model of spinal cord injury has been described in detail, the participation of activated (M1) microglia in neuroinflammation in Alzheimer's disease has been shown [9], the protective effect of M2 was found in the model of oxygen-induced retinopathy. However, most of the studies in this field of research are devoted to two opposite Mϕ phenotypes: classically activated M1 and alternatively activated M2 (i.e., M2a). At the same time, it is currently well known that Mϕ are a heterogeneous population of cells and are able to form many transition states between the described extreme states of activation in response to various stimuli from the microenvironment. In particular, toll-like receptor ligands and immune complexes are inducers of the M2b, TGF-beta, IL-10, glucocorticosteroids promote the formation of M2c, and IL-6 and adenosine contribute to M2d phenotype formation [7].

Moreover, one of the important inductors of M2 phenotype in pathology is efferocytosis – an uptake of apoptotic material [10]. Considering this, we previously developed an original protocol for the generation of M2-like Mϕ under conditions of efferocytosis [2]. This protocol is based on the cultivation of human peripheral blood monocytes under growth / serum factors deficiency, which leads to deprivation apoptosis and subsequent engulfment of apoptotic cells by Mϕ. M2(LS) (LS – Low Serum) obtained according to this protocol are characterized by low antigen-presenting and pro-inflammatory activity, and a high level of production of various neurotrophic, neuroprotective and angiogenic factors (BDNF, IGF-1, FGF-basic, EPO, VEGF and etc.) [2]. Given these data, we hypothesized that M2(LS) may exhibit neuroprotective and neuroregenerative activity. Indeed, further studies showed the stimulating effect of M2(LS) on the proliferation and differentiation of NSC-like cells *in vitro* [13].

In recent decades, there has been a worldwide steady increase in mental illness associated with behavioral disorders, among which depression is one of the most significant medical and social problems. Numerous studies have associated depression with a decrease in biomarkers of adult hippocampal neurogenesis, including a decrease in the number of hippocampal neurons, neural stem/progenitor cells and the hippocampal volume as well as a reduction of neurogenic niche vascularization. In turn, depression treatment is correlated with an increase in these hippocampal biomarkers suggesting a link between adult hippocampal neurogenesis and depression [12].

Limited access to brain tissues in humans makes it difficult to directly study neurogenesis and increases the significance of these studies in models of CNS pathology. One of the widely used models of chronic stress in mice that reproduces a depression-like state is a social defeat stress. Anhedonia, decreased exploratory behavior, and social avoidance are observed in animals in this model. We have previously shown that intranasal administration of soluble factors derived from M2(LS) Mϕ to depression-like mice ameliorates behavioral pattern of animals, which was accompanied by a decrease in the level of pro-inflammatory cytokines in the brain [11]. The present study continues this line of work and focuses on the effect of M2(LS) Mϕ on neuronal density in the frontal cortex and hippocampus of depression-like mice.

Materials and methods

M2(LS) Mϕ were generated from human peripheral blood mononuclear cells (PBMC), as described earlier [2]. Briefly, 3-5 × 10^6/mL PBMCs were incubated in RPMI-1640 (Biolot, St. Petersburg, Russia) supplemented with 0.05 mM 2-mercaptoethanol, 2 mM sodium pyruvate 0.3 mg/mL L-glutamine, 1% nonessential amino acids, 100 μg/mL gentamycin, 2% autoplasma and 50 ng/mL recombinant human GM-CSF (R&D Systems, USA). After 18 hours, the non-adherent cells were removed, and the adhesive cells were cultured for 7 days. The conditioned media (CM) of Mϕ was collected, centrifuged, and stored at -80 °C.

This study was performed in male mice (CBAxC57Bl/6)F1 aged 3.5-4 months, weighing 25-30 g (obtained from the husbandry of the Institute of Pharmacology and Regenerative Medicine of the Russian Academy of Sciences). The animals were kept on a standard diet with free access to water and under normal light conditions in cages of 10/cage for at least 2 weeks prior to experiments. All procedures were approved by the Bioethics Commissions of Scientific Research Institute of Neurosciences and Medicine

and Scientific Research Institute of Fundamental and Clinical Immunology.

Depression-like behavior was induced in mice (n = 17) by repeated social defeat experience in daily (20 days) agonistic interactions (sensory contact model) [6]. Then the depression-like mice were individually placed in cages to exclude agonistic interactions and subdivided into experimental and control groups. The animals from experimental group received M2(LS) CM (30 μl in each nasal passage, twice a day) for 7 days. The control group of mice received RPMI-1640 medium.

Cryosections of the frontal cortex and hippocampus of mice were obtained using a cryotome, the thickness of each slice was 30 μm. The cryosections were then stained according to the Nissl staining method. The image was captured and analyzed by semi-automatic method using a microscope (ZEISS AXioskop2, Germany) and Image Pro Plus Software 6.0 (Media Cybernetics, CA, USA). Since neurons in the studied areas (pyramidal layer of the frontal cortex, CA1 and CA3 zones of the hippocampus) are tightly packed, especially in the hippocampus, the density of cells was measured to estimate the number of neurons. The neuronal density was calculated as the percentage of an area of interest (136036 μm^2 for frontal cortex and 145907 μm^2 for hippocampus) occupied by the Nissl-stained cells.

Statistical analysis was performed using the STATISTICA software version 8.0 (StatSoft. Inc., USA). The data are presented as median (Me) and interquartile range ($Q_{0.25}$-$Q_{0.75}$). To reveal a significant difference of the values compared, the Mann–Whitney nonparametric U test was used. Values of $p < 0.05$ were considered statistically significant.

Results and discussion

Analysis of the relative neuronal density in the pyramidal layer of the *frontal cortex* showed that the depressive-like state was accompanied by a significant decrease in the number of pyramidal neurons compared with mice in the intact group: 16.8 (IQR 15.8-17.5%) *vs* 18.4 (IQR 17.1-21.2%) ($p < 0.05$) (Figure 1, see 2nd page of cover). Intranasal administration of RPMI-1640 medium had no effect on neuronal density, which remained significantly reduced in this area, not differing from the "depressive" control (16.8; 14.9-18.6%; $p < 0.05$). At the same time, in mice of the experimental group, intranasal therapy with soluble factors M2(LS) led to an increase in the number of neurons, reaching the level of intact animals – 19.8 (18.9-21.2%) ($p < 0.05$). In this group, neuronal density was significantly higher compared to both depression-like animals (model control) and RPMI-1640-treated mice (treatment control).

In both studied *hippocampal* zones, *CA1* and *CA3*, similar changes were observed (Figure 1, see 2nd page of cover). The development of a stress-induced depression-like state was associated with a statistically significant decrease in the number of neurons from 35.6 (29.8-41.5%) to 31.7 (26.7-34.6%) in the CA1 zone and from 41.8 (38.5-45.6%) to 34.5 (31.4-36.5%) – in the CA3 zone of the hippocampus ($p < 0.05$). Administration of RPMI-1640 failed to enhance neuronal density. In contrast, intranasal administration of M2(LS) CM led to an increase in neuronal density in both CA1 (33.6; 28.4-37.3%) and CA3 (40.3; 36.3-45.7%) areas of the hippocampus ($p < 0.05$). At the same time, the number of neurons was comparable to that in intact animals and significantly exceeded the values in the RPMI-treated mice.

Thus, the results obtained indicate that: 1) the development of a depression-like state in mice in the model of stress-induced depression is accompanied by a decrease in neuronal density in the frontal cortex and hippocampus; and 2) soluble factors of M2(LS) macrophages increase neuronal density in the studied areas of the mice brain.

The current study aims to evaluate the effect of secretory products of M2(LS) macrophages, polarized by interaction with apoptotic cells, on neuronal density in the frontal cortex and hippocampus of depression-like mice. The relative neuronal density is widely used to estimate the number of neurons in different areas of the brain, because in many areas the neurons are packed so tightly that it is often not possible to visualize individual cells. The neuronal density is an integral indicator that reflects the intensity of at least two interrelated processes: neurogenesis, on the one hand; and neuroinflammation and neurodegeneration, on the other. Accordingly, a decrease in the intensity of neuroinflammation and neurodegeneration, along with an increase in reduced neurogenesis, represent targets for therapeutic interventions in CNS pathology, in particular, in depression. An analysis of the properties of M2(LS) macrophages allows us to suggest that both of the above mechanisms may underlie the neuroregenerative activity of these cells.

Previously, we have shown a high level of production of growth and neurotrophic factors by M2(LS) Mϕ [2]. In particular, M2(LS) actively produce IGF-1, and the level of IGF-1 production by these macrophages is dozens of times higher than that of classical M1 and M2a cells [2]. The neuroprotective effects of IGF-1 have been demonstrated both *in vitro* and *in vivo* [1]. Moreover, a number of studies report the involvement of IGF-1 in the pathogenesis of depression, although the data are ambiguous. For example, Kuang et al. showed that IGF-1 injections contribute to the correction of depression-like behavior in mice in a model of chronic stress [8]. In patients with depression, the level of IGF-1 in the cerebrospinal fluid increased after antidepressant

therapy, which may indirectly indicate an IGF-1-mediated effect of antidepressants.

On the other hand, Levada et al. report a decrease in initially elevated serum IGF-1 levels in patients with major depressive disorder during antidepressant therapy, and a positive correlation between a decrease in IGF-1 and an improvement in clinical symptoms [14]. Thus, despite the lack of an unambiguous view of the role of IGF-1 in the pathogenesis of depression, there is no doubt that this factor has a significant impact on the disease course. It is very likely that it is IGF-1 in the composition of the secretory product of macrophages M2(LS) that makes a significant contribution to the antidepressant effect of macrophages observed in the present and our previous studies [11].

Another factor produced by M2(LS) at a significantly higher level than M1 and M2a Mϕ is VEGF [2]. Several recent studies demonstrate that VEGF is an angiogenic protein with neurotrophic and neuroprotective effects. Moreover, accumulating evidence has implicated VEGF in the major depression disorder pathophysiology. In particular, rodent models of stress-induced depressive-like states show significant decreases in VEGF and BDNF levels in the prefrontal cortex and hippocampus. In addition, VEGF can potentially mediate the antidepressant effects of typical antidepressants [15]. In another study, Greene et al. in a rat model of chronic stress showed that antidepressant therapy leads to an increase in the level of VEGF in the hippocampus and in peripheral blood. In addition to VEGF, IGF-1, and BDNF, other soluble factors, such as FGF-basic, EPO, EGF, etc., may also play a role in mediating the neuroregenerative effects of M2(LS) Mϕ, which is subject to further study.

Chronic neuroinflammation, which plays an important role in the pathogenesis of depression, leads to an increase in neurodegenerative processes (damage to neurons and their subsequent apoptosis) and a decrease in the intensity of neurogenesis [3]. Indeed, an increased level of pro-inflammatory cytokines (IL-1β, IFNγ, IL-6, TNFα), as well as reactive oxygen species in the brain, leads to numerous disorders of neurotransmitter metabolism, contributing to the development of depressive symptoms (anhedonia, sleep disturbance, decreased motor activity, etc.). Zhang et al. showed that intracerebral injections of IFNγ reduced neurogenesis in the mouse hippocampus and contributed to the development of depression-like behavior. At the same time, microglia isolated from the hippocampus of such mice suppressed the proliferation of neural stem cells and stimulated apoptosis of immature neurons *in vitro*.

Fan et al. showed that chronic stress leading to the depression-like behavior is accompanied by an increase in the IL-1β concentration in the prefrontal cortex of the mouse brain. Moreover, the introduction of a virus with overexpression of IL-1β into the brain of mice not subjected to chronic stress also led to a shift in behavioral patterns (anhedonia, decreased motor activity). This indicates a key role of pro-inflammatory cytokines in the pathogenesis of depression. In addition, regardless of the method of inducing a depression-like state (chronic stress or IL-1 β overexpressing virus), an increased level of neuronal apoptosis in the prefrontal cortex was recorded in mice [4]. These data indicate a close relationship between a depression-like state and neuronal apoptosis.

In a number of studies, in models of chronic stress and depression-like states in rodents, neurodegenerative changes were shown in neurons in various areas of the brain (in particular, the hippocampus and prefrontal cortex): a decrease in the density of synapses, a reduction in the length and branching of dendrites, and cell loss. Hill et al. showed a direct correlation between anxiety / depression and adult neurogenesis. Activation of neurogenesis through inactivation of the pro-apoptotic gene Bax in Nestin-positive cells contributed to the reduction of anxiety and depressive behavior caused by chronic corticosterone treatment [5]. Finally, there is ample evidence of increased neurogenesis after antidepressant therapy in rodent models [12].

Conclusion

Previously, we revealed the ability of M2(LS) Mϕ to enhance neurogenesis *in vitro* through stimulation of proliferation, differentiation and survival of NSC-like cells of the SH-SY5Y line [13]. Along with this, we observed a decrease in the concentration of pro-inflammatory cytokines (IL-1β and TNFα) in the brain of depression-like mice during intranasal therapy with soluble factors of M2(LS) [11], which indicates the anti-inflammatory activity of M2(LS) Mϕ. Taken together, our data obtained earlier and presented in the current study indicate the neuroregenerative potential of macrophages polarized into the M2 phenotype by efferocytosis.

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Авторы:

Ращупкин И.М. *— лаборант-исследователь лаборатории клеточной иммунотерапии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Амстиславская Т.Г. *— д.б.н., доцент, заведующая лабораторией трансляционной биопсихиатрии ФГБНУ «Научно-исследовательский институт нейронаук и медицины», г. Новосибирск, Россия*

Маркова Е.В. *— д.м.н., доцент, заведующая лабораторией нейроиммунологии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Останин А.А. *— д.м.н., профессор, главный научный сотрудник лаборатории клеточной иммунотерапии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Шевела Е.Я. *— д.м.н., ведущий научный сотрудник лаборатории клеточной иммунотерапии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Authors:

Rashchupkin I.M., *Laboratory Assistant, Laboratory of Cellular Immunotherapy, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Amstislavskaya T. G., *PhD, MD (Biology), Associate Professor, Head, Laboratory of Translational Biopsychiatry, Research Institute of Neurosciences and Medicine, Novosibirsk, Russian Federation*

Markova E.V., *PhD, MD (Medicine), Head of Laboratory of Neuroimmunology, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Ostanin A.A., *PhD, MD (Medicine), Professor, Chief Research Associate, Laboratory of Cellular Immunotherapy, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Shevela E.Ya., *PhD, MD (Medicine), Leading Research Associate, Laboratory of Cellular Immunotherapy, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

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