GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 9 (342) Сентябрь 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

GEORGIAN MEDICAL NEWS
No 9 (342) 2023

UNVEILING THE COMPLEX ROLE OF NF-KB IN ALZHEIMER'S DISEASE: INSIGHTS INTO BRAIN INFLAMMATION AND POTENTIAL THERAPEUTIC TARGETS

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Abstract.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and dementia. One of the major pathologies underlying AD is chronic neuroinflammation mediated by microglia and astrocytes in the brain. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway is a key regulator of inflammation and has been implicated in the neuroinflammatory processes associated with AD. This review comprehensively summarizes current findings on the complex role of NF-κB signalling in AD pathogenesis. The canonical and non-canonical NF-κB activation pathways are described, along with evidence from human studies and animal models demonstrating increased NF-κB activity in AD brains. The deleterious effects of NF-κB-mediated neuroinflammation are discussed, including the upregulation of inflammatory cytokines, chemokines, and enzymes that exacerbate neuronal damage over time. Targeting the NF-κB pathway is proposed as a promising therapeutic approach to dampen neuroinflammation in AD. Preclinical studies utilizing genetic or pharmacological inhibition of NF-κB are reviewed, and key challenges in translating these findings to clinical applications are analyzed. Overall, this review unveils the multifaceted contributions of NF-κB signalling to AD neuropathology and highlights anti-neuroinflammatory NF-κB modulation as a potential avenue for future AD treatments. Further research is warranted to fully elucidate the complex interactions between NF-κB and AD pathogenesis.

Key words. Alzheimer’s disease, NF-κB, Microglia, neurodegeneration, neuro-inflammation.

Introduction.

Alzheimer's disease (AD) is a progressive neurological condition that affects physical and cognitive abilities as people age [1-2]. According to the World Alzheimer's Report 2015, approximately 46.85 million people worldwide suffer from Alzheimer's disease (AD) or another form of dementia, and this number is expected to double by 2030 and potentially triple by 2050 [3-4]. Every year, more than 7.7 million new cases of dementia are reported [5]. In the United States alone, over 4 million individuals suffer from Alzheimer's disease (AD), which is a devastating and fatal neurodegenerative disorder that leads to a decline in cognitive and emotional functions.

The hippocampus, entorhinal cortex, basal forebrain, amygdala, frontal cortex, and inferior parietal cortex are crucial regions in the brain responsible for learning and memory, but in AD patients, these regions suffer from degenerating neurons and synapses [6]. The pathological hallmarks of AD include the development of neurofibrillary tangles, which are filamentous intracellular aggregates of the microtubule-associated protein tau, and plaque-like aggregates of amyloid-beta (Aβ) [7-9]. These abnormal features lead to the death of cholinergic neurons, which results in the deposition of Aβ protein and the formation of neurofibrillary tangles, hyperphosphorylated tau protein production, gliosis, and neuronal loss [8,9]. Additionally, oxidative stress, excitotoxicity, neuro-inflammation, and neurotransmitter deficiencies are all associated with the accumulation of tau tangles and extracellular Aβ deposits [10,11]. The loss of cholinergic neurons in cortical and hippocampal areas has also been linked to AD [13,14], and the way serotonergic, glutamatergic, dopaminergic, and adrenergic neurons operate is affected as well [15,16].

Microglia cells have been implicated in AD pathogenesis since the mid-1980s, and both amyloid plaques and neurofibrillary tangles have been shown to activate microglia and astrocyte cells [17]. These activated cells release pro-inflammatory cytokines, chemokines, interleukins, prostaglandins, leukotrienes, and thromboxane’s, leading to neuro-inflammatory responses that contribute to disease progression [18-20]. Aβ-sites interaction with astrocytes increases pro-inflammatory mediator secretion, further exacerbating neuro-inflammation [20]. Amyloid beta also increases nitric oxide production, causing inflammation and neuronal death [21].

When microglia are exposed to Amyloid beta, they produce inflammatory cytokines such as TNF-alpha and IL-1beta [22]. Amyloid stimulates microglia through a calcium influx-based mechanism, as per research by Landreth and colleagues [23]. Microglia expressing PS1 showed abnormal calcium homeostasis and increased inflammatory cytokine response when challenged with bacterial lipopolysaccharide (LPS) [24]. The sensitivity to LPS was higher in microglia from PS1 mutant mice than wild-type mice, indicating a negative effect of PS1 mutations and Amyloid beta on microglial cells under pro-inflammatory conditions [24,25]. These findings suggest that calcium responses may influence the neurodegenerative process in AD patients with PS1 mutations [25]. In the current review, we have discussed microglia and neuroinflammatory events and their association with Aβ and NFT pathology and cognitive decline in sporadic Alzheimer’s disease.

Role of NF-κB signalling in AD

Neuroinflammation occurs when NF-κB initiates the production of cytokines, chemokines, NO, and COX-2. This activation of microglia results in their proliferation, migration, and initiation of phagocytosis. T cells also contribute to the activation of this cascade, which generates pro-inflammatory cytokines and hazardous chemicals causing neurotoxicity. Ultimately, this leads to neuronal dysfunction and death. Neuroinflammation refers to the inflammation that occurs within the brain and spinal cord. This reaction involves the

release of cytokines, chemokines, and ROS in response to astrocytes and microglia. Microglia, which serve as the primary immune surveillance in the CNS, also produce cytokines and chemokines, similar to macrophages. These neuroinflammation responses are characterized by various pro-inflammatory cytokines, including interleukin-1, interleukin-6, TNF-, different chemokines (CXCL-1, CCL2, CCL5), nitrous oxide, PGs, and ROS. Inflammation plays a significant role in several metabolic diseases, including diabetes, atherosclerosis, and multiple sclerosis, as well as in neurodegenerative illnesses such as Alzheimer's disease (AD) [28].

The synthesis of NF-kB protein is strictly regulated in both the cytoplasm and the nucleus6. I-B family proteins, comprising I-B, I-B, and I-B (also referred to as NF-κB I, NF-kBI, and NFkB -BI, respectively), directly interact with NF-kB complexes to keep them inactive in the cytoplasm under normal physiological conditions. The NF-kB complex's nuclear localization domains are hidden by I-B proteins, which keeps the transcription complex in the cytoplasm. Toll-like receptors (TLRs), as well as cytokine receptors such as interleukin-1 receptors (IL-1Rs), TNF receptors (TNFRs), and other TNFR-like receptors, can quickly activate the NF-kB complex in response to a range of pro-inflammatory stimuli.

How to activate the neuronal NF-kb pathway

Activators

Intracellular Ca^{2+}, glutamate, NMDA, Aβ amyloid Mutation, bacterial infections, mitochondrial malfunction, saturated fat and traumatic brain injury. Elevated levels of amyloid beta protein in the brain have been observed in both animal models and AD patients, accompanied by microglia activation and microgliosis. Microglia activation is detected early in the disease course. The inflammasome, a cytosolic protein complex that activates caspase-1 to promote IL-1 production and release, has been shown by Halle et al. to be activated by internalized AD, resulting in increased production of other potentially inflammatory and neurotoxic mediators. Studies have also reported the presence of pro-inflammatory cytokines like IL-6 and TNF in greater quantities in the brains of AD patients. In addition to its direct neurotoxic effects, microglia activation also promotes amyloid beta buildup [28].

Microglial NF-κB signalling activation by Saturated fatty acid.

The activation of microglial NF-κB signalling by saturated fatty acids (SFA) was observed in both BV-2 cells and primary microglial cells. Our research showed that SFA exposure led to microglial activation, which was characterized by changes in cell shape indicative of a reactive phenotype, and an increase in the production of reactive oxygen species (ROS), nitric oxide (NO), and proinflammatory cytokines like TNF-a, IL-1b, and IL-6. This, in turn, caused the death of nearby neurons. We also found that PA administration, similar to LPS, induced an expression of IL-1b and iNOS. In addition, PA treatment activated NF-κB. Notably, blocking NF-κB activation using the inhibitor PDTC prevented the expression of iNOS, TNF-a, IL-1b, and IL-6 mRNA, as well as the production of TNF-a, IL-1b, and NO, except for IL-6. Another important observation was the inhibition of PA-induced NF-κB activation and the generation of pro-inflammatory mediators in cells treated with antiTLR4 Ab. These findings suggest that SFA can activate microglia and stimulate the TLR4-NF-κB pathway, causing the release of pro-inflammatory mediators that may contribute to the death of neurons [29].

Traumatic brain injury (TBI) induces the activation of microglial NF-κB signalling.

Activation of NF-κB is a consequence of traumatic brain injury, which can trigger self-perpetuating inflammatory responses in the brain [30,31]. In Drosophila flies affected by TBI, symptoms such as transient incapacitation, ataxia, activation of the innate immune system, neurodegeneration, and death have been observed, resembling human TBI [32,33]. In rat models, NF-κB has been found to be acutely upregulated and persistently overexpressed in the brain regions most frequently associated with post-injury atrophy [34,35].

The activation of microglial NF-κB signalling by glutamate

The overactivation of glutamate receptors in neurons can cause damage due to increased glutamate concentrations, which is a symptom of excitotoxicity. This excessive release of glutamate can activate NF-κB signalling, leading to the production of numerous proinflammatory proteins. Increased glutamate results in Ca^{2+} influx through the NMDA receptors, which activates various proteases, nitric oxide, and reactive oxygen species that damage cells. The NMDA-mediated enhanced Ca^{2+} influx stimulates NF-κB, which is translocated into the nucleus and worsens the inflammatory feedback loop [36,37].

Activation of microglial NF-κB signalling by microbial infection.

Some viruses such as HIV-1, human T-lymphotropic virus 1 (HTLV-1), hepatitis B and C viruses, rotaviruses, influenza viruses, and respiratory syncytial viruses (RSVs) have developed mechanisms to actively stimulate the NF-κB activation to increase viral replication and prevent virus-induced apoptosis. As a result, activated NF-κB becomes essential for viral gene expression, replication, and propagation. All these viral genomes have important gene promoters with NF-κB-binding sites, and the infection's prolonged activation of both the traditional and alternative pathways of the NF-κB pathway cause excessive inflammation through the production of NF-κB-regulated pro-inflammatory cytokines and chemokines. The host superoxide-producing enzyme NOX2-containing NADPH oxidase activates the traditional NF-κB pathway in airway epithelial cells by phosphorylating I-B and RELA via RIG-I (DDX58), TRAF6, and IKK, while the kinases NIK and IKK activate the alternative NF-κB pathway, causing nuclear translocation of p52-RELB [38-43].

Alzheimer's disease and the microglial NF-κB pathway

The immune cells responsible for the CNS are called microglia [44]. The functional properties of these cells have attracted growing attention since it was discovered that microglia are the primary source of brain immune mediators. The activation of microglia has been linked to the destruction of neurons in conditions like trauma [45] and Alzheimer's disease. These cells can release cytotoxic substances, such as proteases, excitatory

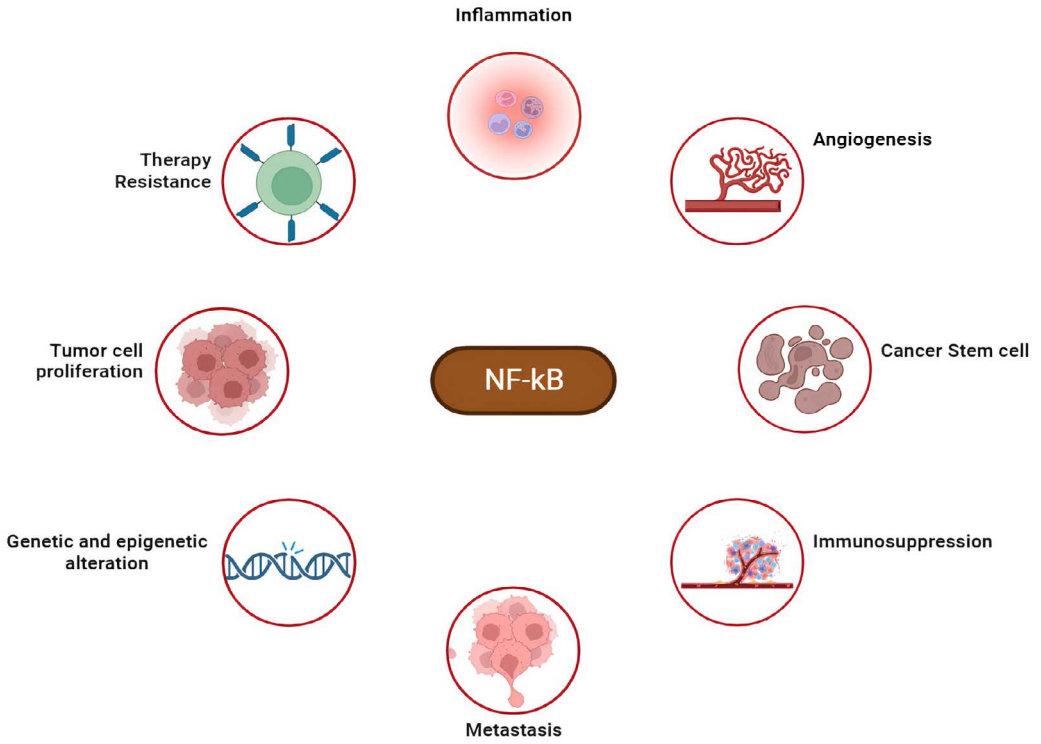

Figure 1. *Roles of NF-κB. Nuclear factor-κB (NF-κB) directly and indirectly controls inflammation, cancer cell proliferation and survival, angiogenesis, and metastasis, as well as genetic and epigenetic alterations, cancer stem cell formation, cellular metabolism and therapy resistance. NF-κB activation also induces immunosuppression via several mechanisms.*

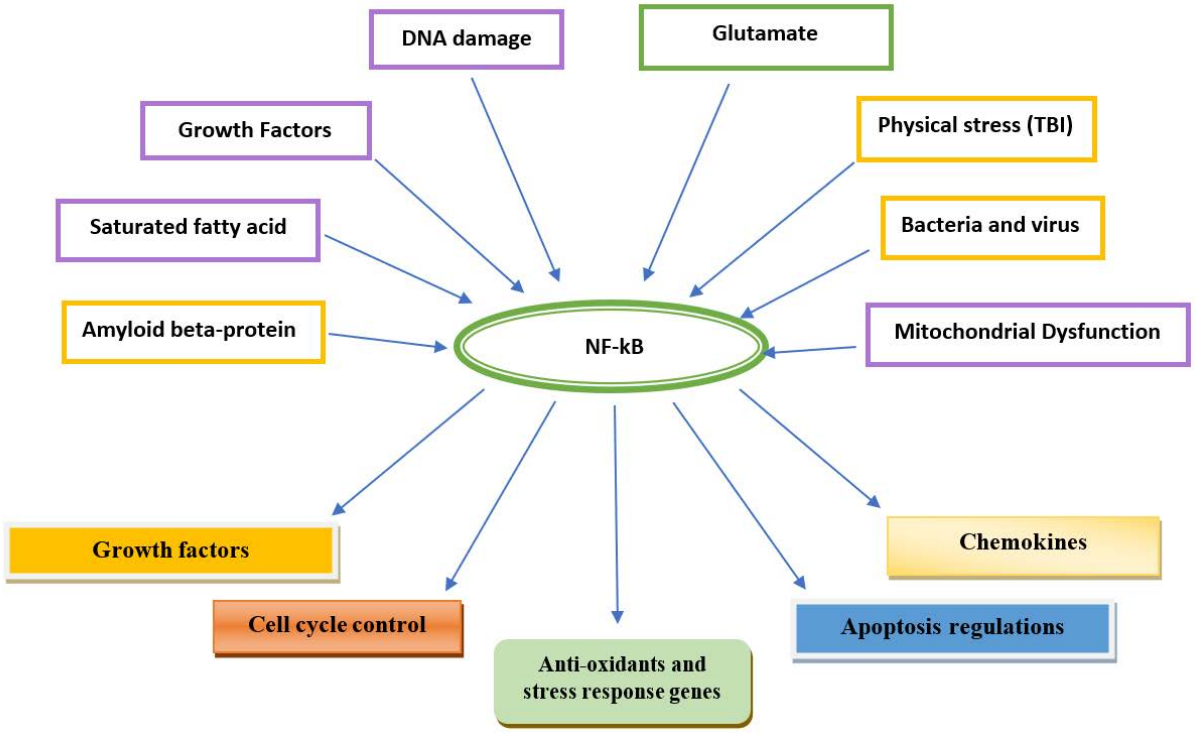

Figure 2. *Activations of NF-κB transcription factor.*

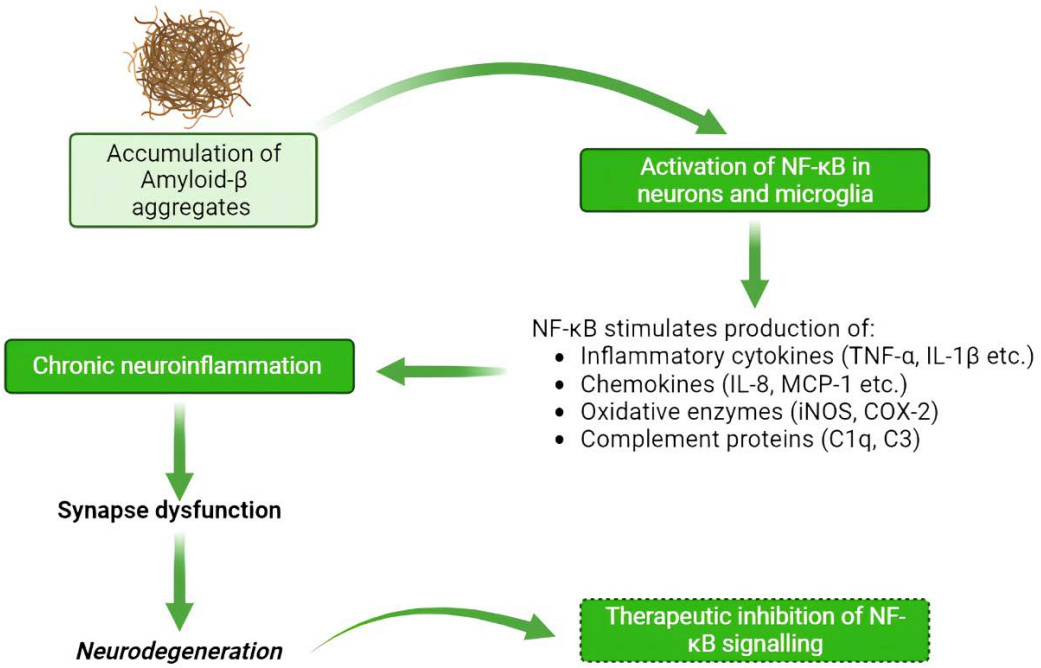

Figure 3. *Amyloid-beta aggregates trigger activation of NF-κB signaling in neurons and microglia, leading to neuroinflammatory responses that mediate synapse dysfunction, neurodegeneration, and cognitive decline. Therapeutic inhibition of NF-κB may block this deleterious cycle.*

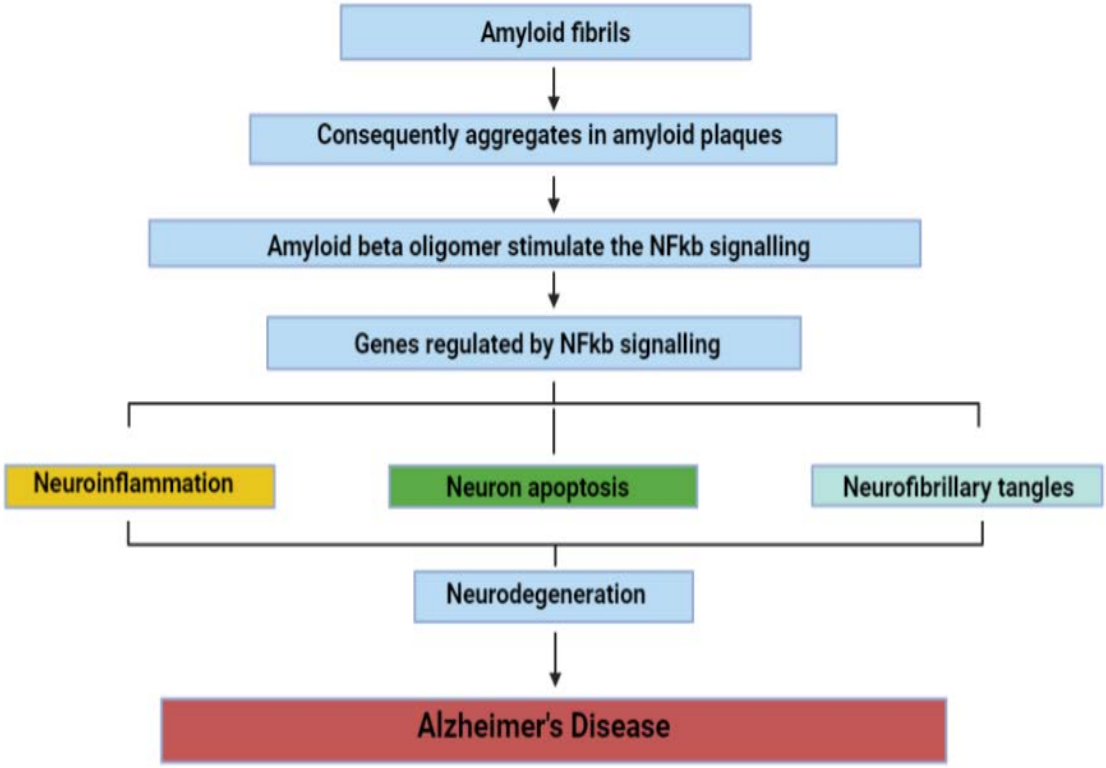

Figure 4. *Link between Alzheimer's disease and NF-κB signalling.*

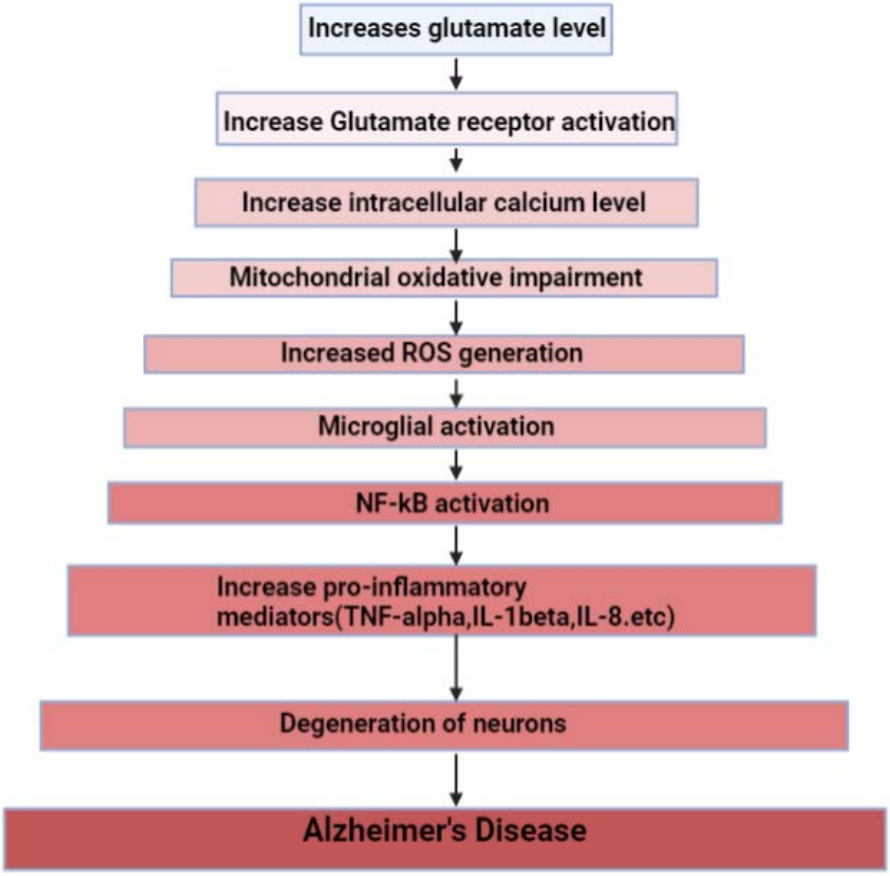

Figure 5. *Link between Glutamatergic pathway and NF-κB signalling.*

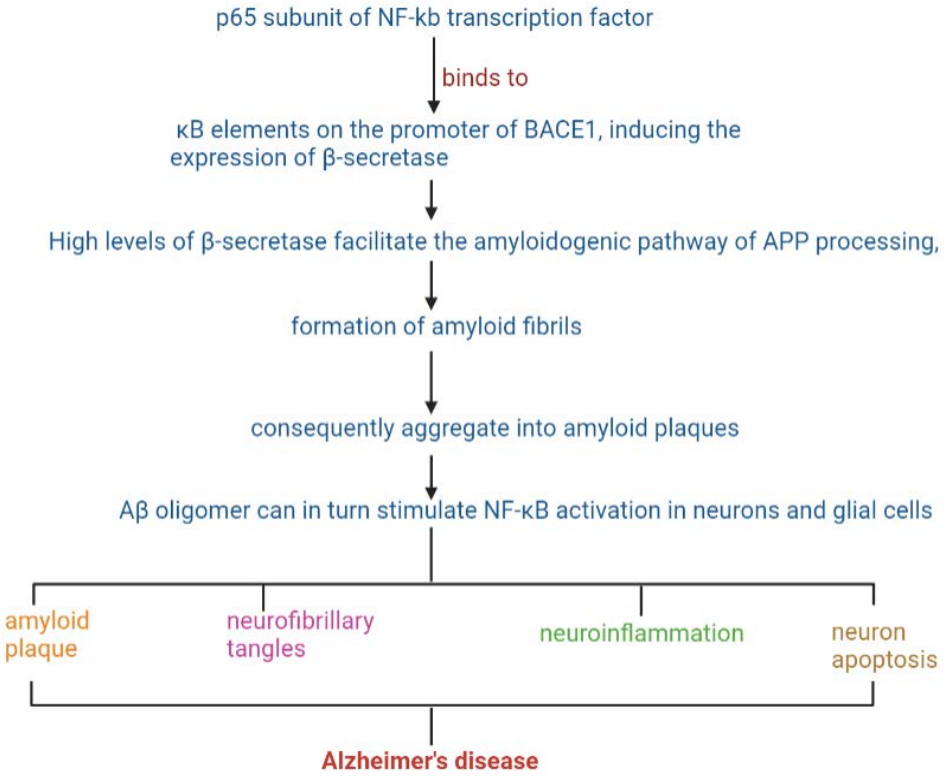

Figure 6. *Link between Secretase and NF-κB signalling.*

amino acids, arachidonic acid derivatives, cytokines, and free oxygen intermediates [46].

Activation of NF-κB can be initiated by various factors. Additionally, it is possible that autocrine and paracrine activation loops are responsible for elevated constitutive NF-κB activity. It is also hypothesized that NF-κB activation signalling is linked to synaptic events that trigger transcription. Research suggests that inducible NF-κB activity in glial or endothelial cells is essential for neuro-inflammation and is associated with secondary neuronal injury. Inflammatory processes, which are specifically regulated by increased NF-κB in glial cells, worsen several diseases, including Alzheimer's disease.

Glial cells-mediated inflammation can exacerbate the hallmark histological features needed for Alzheimer's disease (AD) diagnosis, such as amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFT) in neurons [47]. This, in turn, promotes neuronal instability and loss [48], which creates a vicious cycle of neurodegeneration, primarily driven by NF-κB [49]. Nonetheless, the activation of NF-κB can have a dual function in either neuroprotection or neurodegeneration, depending on the cell type and/or the mix of NF-κB subunits [50]. Previous studies have shown that pro-apoptotic genes are produced that trigger neuronal death by activating p65/p50 dimers, whereas c-Rel-containing dimers control the production of genes that prevent apoptosis and promote neuronal survival. Interestingly, p65/p50 heterodimers or c-Rel can be selectively activated depending on the type of stimulus received, such as IL-1, Nerve Growth Factor (NGF), Aβ peptide, or glutamate [51,52].

NF-κB is essential in the pathophysiology of AD, as it controls several molecules that contribute to the disease's morbidity. In the following section, we will summarize the common factors involved in the pathophysiology of hyperactive NF-κB signalling in AD.

Glutamate and NF-κB in AD.

NF-κB-induced glutamate excitotoxicity triggered by amyloid oligomers is a critical component of the Alzheimer's disease (AD) neurodegenerative cascade. Aβ peptides have been found to promote glutamate receptor activation and a concomitant increase in intracellular calcium levels in human cerebral cortical neurons. Long-term increases in intracellular calcium levels lead to microtubule instability, increased tau phosphorylation by calcium-dependent kinases, reduced mitochondrial oxidative capacity, and ultimately increased reactive oxygen species (ROS) production [53,54]. A study by Lim et al. validated hippocampal astrocytes from AD patients with elevated levels of calcium and metabotropic glutamate receptor 5 (mGluR5) around Aβ plaques. According to their findings, Aβ42 raises cytosolic calcium levels by triggering calcineurin (CaN), which allows the transcription of mGluR5 under the control of the NF-κB pathway. It was also demonstrated that the dephosphorylation of B-cell lymphoma 10 (Bcl10) by CaN might have contributed to the activation of NF-κB by CaN [55]. Bcl10 ubiquitinates IKK-I, which activates the NF-κB pathway [56]. Similarly, hippocampal astrocytes stained with mGluR5 co-localize with the accumulated nuclear p65 subunit of NF-κB, supporting the notion that NF-κB and glutamate work together to promote AD-like pathology [55].

NF-κB and β-Secretase in AD.

Patients diagnosed with AD typically have high levels of NF-κB in their cerebral cortex, which is linked to elevated levels of APP cleaving enzyme-1 (BACE1). According to a previous study, the NF-κB p65 B subunit binds to the B elements on BACE1's promoter and activates the expression of β-secretase [57]. The high levels of β-secretase facilitate the amyloidogenic route of APP processing, which leads to the formation of amyloid fibrils and their subsequent aggregation into amyloid plaques [58]. Furthermore, Aβ oligomers themselves can induce NF-κB activation in glial and neuronal cells [59]. In primary and N2TN neurons, the Aβ 40 peptide was shown to strongly activate the p65/p50 dimers of NF-κB and increase the production of pro-apoptotic genes. Bax, p63, DcR2, and TANK (TRAF family member-associated NF-κB activator) are some of the genes that are induced after Aβ-40 stimulation, and they all contain B regulatory elements in their promoter regions. Additionally, Aβ 40 accelerated the formation of Aβ 42 aggregates, further accelerating the neuropathological cascade of AD [60]. Similarly, Aβ peptide has been demonstrated to cause toxicity in primary neurons and cell lines by increasing peroxide generation, a source of oxidative stress. Reactive oxygen species (ROS) are known to activate NF-κB subunits in certain cases, and our research implies an indirect relationship between Aβ peptide-mediated toxicity and NF-κB activation, which is also associated with high levels of NF-κB signalling [61].

How the NF-κB signalling pathway in the microglia can be turned off to treat Alzheimer's disease.

Microglia become activated and release inflammatory cytokines such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha) in response to AD [62]. Landreth et al. [63] found that amyloid stimulates microglia through a calcium influx-based mechanism. Current drugs approved by the US Food and Drug Administration (FDA) for the treatment of AD provide symptomatic relief, but do not significantly address the underlying causes or halt the disease's progression [64]. Research has focused on targeting the mechanisms of AD, particularly the A cascade, to prevent toxic amyloid formation [65]. An effective strategy to stop AD progression and neurodegeneration is to prevent tau pathology [66]. Furthermore, continuous use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to a significant reduction in the risk of developing AD, depending on when treatment is initiated [67].

Calcium and glutamate receptor blocker.

Patients with AD who participated in clinical studies of the L-type voltage-dependent calcium channel blocker nimodipine showed small improvements in several of their symptoms [68]. Patients with severe dementia have reportedly benefited from the use of memantine, an uncompetitive NMDA receptor antagonist [69]. These findings point to a potential advantage of calcium influx-suppressing medications. However, these medications might potentially impair the way that calcium influx-dependent neurons normally function.

NSAIDs: Non-steroidal anti-inflammatory medications.

During patient clinical studies, the majority of NSAIDs were ineffective at treating AD [70]. However, early indomethacin

therapy for AD patients [71] and a post-naproxen analysis from the ADAPT (Alzheimer's disease anti-inflammatory prevention trial) research group showed promising results in preventing the development of AD [72]. Aspirin, on the other hand, proved ineffective in treating AD patients in the AD 2000 experiment and significantly raised the risk of suffering life-threatening bleeding.

β-Secretase inhibitors and modulators: The amyloidogenic APP pathway is processed at its first stages by the secretase enzymatic complex. LY2886721 (NCT01807026 and NCT01561430), MK-8931 (NCT01739348), and E2609 (NCT01600859) all successfully lower Aβ production in the cerebrospinal fluid (CSF) in people by about 80–90%. There are currently no β-secretase inhibitors on the market to treat AD [73].

α-Secretase inhibitors and modulators:

Aβ peptides are produced by the α-secretase complex, which takes part in the last phase of amyloid formation. A α-secretase inhibitor semagacestat (LY450139) reduced Aβ levels in human blood and cerebrospinal fluid (CSF). The NCT00762411, NCT01035138, and NCT00762411 clinical trials were unsuccessful and showed no efficacy against AD. In therapeutic trials with AD patients, another -secretase inhibitor called Avagacestat was equally ineffective (NCT00810147, NCT00890890, NCT00810147, NCT01079819) [74]. Active vaccination for the pathophysiology of AD In mild-to-moderate AD patients, an active immunization study was conducted using the AN-1792 Alzheimer vaccine (NCT00021723), which is a synthetic full-length Aβ-42 peptide combined with QS-21 adjuvant. However, it caused severe meningoencephalitis in about 6% of patients, so it was abandoned in Phase II trials [75]. The immunogenic Aβ-6 peptide in CAD106 functions as a B-cell epitope while preventing a T-cell response [76]. CAD106 is currently undergoing Phase II/III clinical trials in cognitively normal individuals carrying two ApoE4 genes (NCT01097096 and NCT02565511).

Novel treatment strategies:

Anti-Amyloid monoclonal antibody: Monoclonal antibodies designed to target amyloid, known as anti-amyloid MABs, are reshaping the landscape of Alzheimer's disease (AD) treatment. Notably, drugs like Aducanumab and Lecanumab are leading the charge. These medications are engineered to bind specifically to amyloid aggregates, and their early-phase trials have yielded positive outcomes. What sets them apart is their ability to target amyloid aggregates in both oligomeric and fibrillar states, a departure from conventional approaches that focus solely on amyloid monomers. These drugs, such as Aducanumab and Lecanumab, offer the potential to rejuvenate neurological function in AD patients by diminishing Aβ plaques and restoring neuronal calcium permeability [77]. The impact of these innovative therapies cannot be overstated. They provide new hope for patients who were previously confronted with the inexorable progression of AD. Moreover, these treatments represent a pioneering approach that paves the way for the development of other disease-modifying treatments and combination therapies. As we embrace these transformative therapies, it's crucial to acknowledge that they bring forth fresh challenges and opportunities for the various stakeholders in AD care. To accommodate these groundbreaking treatments, we need to foster global innovations in social and medical care. The advent of anti-amyloid MABs is a remarkable milestone, marking the dawn of a new era in addressing the formidable challenges posed by AD—a step forward in safeguarding our most invaluable global asset: the human brain [78].

Conclusion.

The development of Alzheimer's disease (AD) involves multiple factors, with inflammation being a prominent one according to several studies. A chronic inflammatory state arises from the imbalance between proinflammatory and anti-inflammatory cytokines, leading to delirium and cognitive decline. This research examines the roles of peripheral blood cells and microglia in AD pathogenesis and potential treatments for the disease. Specifically, the study reveals that microglia can be activated by factors such as SFA Amyloid beta protein, Saturated fatty acid, Traumatic Brain Injury, and microbial infection, triggering the NF-κB pathway and the release of pro-inflammatory mediators that may cause neuronal damage. One potential therapeutic approach is to inhibit NF-κB signalling, which could be achieved by blocking calcium channels or glutamate receptors, inhibiting alpha and beta secretase, and novel anti-amyloid monoclonal antibody among other strategies.

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