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Common neurodegenerative pathways in brain aging, cognitive decline, type 2 diabetes & metabolic syndrome

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Aging and age-related diseases share several biological mechanisms, forming a finely controlled network where inflammation plays an encompassing key role. In the Central Nervous System (CNS), glial cells can modulate neuroinflammation by promoting neuronal homeostasis and limit neurodegeneration. However, age-related systemic inflammation (i.e. inflammaging) leads to additional deteriorations of both microglia and astrocytes causing an exacerbation response of these cells to stimuli. Type 2 diabetes (T2DM), a chronic metabolic disorder characterized by hyperglycemia, has also been associated with multiple organs loss, including the brain. Numerous studies have underlined direct correlations between diabetes, cognitive decline and dementia, however exact mechanisms related to neurodegeneration in T2DM remain to be elucidated. It widely recognized that aging is considered the most critical risk factor for Alzheimer's disease (AD), however there are increasing data highlighting that metabolic disorders are also strongly associated with an increased risk of AD and T2DM. Indeed, impaired glucose metabolism and mitochondrial activity are common grounds for cognitive dysfunction and AD. The Metabolic syndrome (MetS) in mid-life may accelerate the progression of AD pathogenesis by activating an increased productions neuroinflammatory biomarkers leading to amyloid pathology degeneration. There remains an intricate crosstalk between the aging process, T2DM, MetS, and neuroinflammation, thus resulting in neuronal loss and the development of cognitive impairment with an accelerated risk of AD. Future studies are needed to identify potential therapeutic benefits related to improving neuroinflammation on cognitive performance.

Key words: aging, neuroinflammation, Alzheimer's disease, type 2 diabetes; cognitive decline

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INTRODUCTION

Aging is an inevitable event in the life cycle of all organisms, characterized by progressive physiological deterioration and greater vulnerability to death.

During aging, progressive alterations of the immune system may lead to a reduced defense response to stressors [1,2] and an increased production of specific markers of low-grade chronic systemic inflammation or inflammaging [3].

Neuroinflammation may be one of the factors responsible for the increased cognitive decline and risk of Alzheimer's disease (AD) in type 2 diabetes (T2DM) [4].

Aging, as demonstrated by numerous studies, represents the most critical risk factor for AD. At the moment, there is a rapidly growing rise in AD cases worldwide. Considering that currently available drug treatments are unable to cure, the disease tends to progress irreversibly with significant socioeconomic and personal costs [5]. Interestingly, there are growing data demonstrating how metabolic alterations, such as impaired glucose metabolism and mitochondrial dysfunction are closely related to AD and T2DM, leading to cognitive decline and AD development [6].

In this commentary paper, we will analyze potential links of neuronal loss due to neuroinflammation in aging, T2DM, and MetS leading to cognitive decline and an accelerated risk of developing AD.

NEUROINFLAMMATION AND AGE-RELATED COGNITIVE DECLINE

Aging and age-related diseases share different biological mechanisms, referred as "hallmarks of aging" [7], which appear to be closely interconnected, forming a finely controlled network in which inflammation represents the "umbrella" that encompasses all these mechanisms [8].

Interestingly, the immune system reflects the exposure of each person to stress [9], and stress plays a crucial role in the deviation from good aging to disease onset [10].

In fact, aging is characterized by immunosenescence which involves a progressive impairment of immune cell function, causing reduced activity of natural and acquired immunity [1,2]. For a long time, immunosenescence has been considered a harmful phenomenon because it causes increased production of specific components of systemic inflammation, i.e., inflammaging, leading to a low-grade inflammatory state [3].

Recently, the concept of inflammaging has been revised by considering this phenomenon an adaptive process aimed at stimulating an appropriate anti-inflammatory response necessary to counterbalance environmental changes during aging [11]. The different tissues (e.g., adipose and muscle) and organs (e.g., brain and liver) contribute differently to inflammaging, comporting specific systemic effects [12,13].

The central nervous system (CNS) is composed of different cell populations with unique characteristics necessary to cooperate in properly functioning this system. In detail, neurons are highly specialized cells that play a crucial role in transmitting, processing, and storing information. On the other hand, non-neuronal cells, consisting of microglia and macroglia (i.e., astrocytes), perform other vital functions within the CNS [14].

Microglial cells are rather dynamic cells that are, in fact, the primary immune source in the CNS, tasked with participating in many vital functions ranging from vasculogenesis and neurogenesis to synapse and myelination through their motility properties, ability to release soluble factors and phagocytosis [15].

Interestingly, microglia's functional "state" depends on the circumstance, i.e., the physiological conditions in which microglia cells are found depending on both the brain region and the temporal context. During aging, microglial cells change density, morphology, cytokine-producing capacity, and phagocytic capacity [16]. These age-related changes are accompanied by changes in intracellular composition, such as hypertrophy of lysosomes, endosomes, and peroxisomes and the progressive accumulation of lipofuscin, lipid droplets, and other debris [17-19]. However, the effects of age on microglia do not necessarily present themselves as a loss of these functions but rather with altered reactivity and/or a state of hyperactivation. Indeed, microglial aging is associated with the upregulation of several markers, such as MHC II antigens and CD68, CD11b/CR3, CD14, as well as pattern recognition receptors [20,21].

In general, expression of these markers, which are associated with antigen presentation, lysosome function, and recognition of pathogens and complement proteins, results in a more responsive microglia phenotype. It follows that activated microglial cells produce high levels of pro-inflammatory cytokines (e.g., tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6)), chemokines (e.g., monocyte chemoattractant protein-1 (MCP-1), reactive oxygen species (ROS) and nitric oxide (NOS) [22].

Whereas the role of anti-inflammatory cytokines (e.g., IL-10, transforming growth factor beta-1 (TGF-β1)) is to dampen microglia activation [23].

In addition, inflammatory mediators released by activated microglial cells can induce hyperactivation of astrocytes, which in turn contribute to an increased inflammatory state by aggravating neuronal damage [24].

Considering these premises, glial cells play a key role in neuronal survival and modulation of neuroinflammation, ultimately helping to promote neuronal homeostasis and limit the onset and progression of neurodegenerative diseases. In turn, systemic inflammation could influence the aging of both microglia and astrocytes by exacerbating the responses of these cells to stimuli. Sustained glial activation and inflammation may make

the brain more susceptible to injury and/or neurodegeneration, affecting cognitive decline. Indeed, it has been widely underlined that the neuroprotective functions of glia may become impaired with age while neurotoxic responses are heightened [4].

NEUROINFLAMMATION AND TYPE 2 DIABETES

Type 2 diabetes (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, which can damage multiple organs, including the brain [25]. Despite the broadly consistent link between diabetes, cognitive decline, and dementia, the underlying causes of neurodegeneration in diabetic patients remain to be elucidated. Neuroinflammation is a strong candidate to explain, at least in part, the increased cognitive decline and dementia risk in T2DM [26].

Hyperglycemia itself plays a key role in triggering a neuroinflammatory state in diabetic patients. HG leads to the formation of advanced glycation end products (AGEs), which act on RAGE to increase NF-κB activation. Activated NF-κB increases pro-inflammatory gene expression, including RAGE itself and cytokines [27]. Moreover, hyperglycemia induces oxidative stress by producing reactive oxygen species (ROS), stimulating the upregulation of inflammatory cytokines such as tumor necrosis factor (TNF), IL-1, IL-2, and IL-6 [28] and activating NF-κB pathway, resulting in damage to the blood-brain barrier (BBB) [29]. ROS directly determines structural alterations of the gap junctions and modifies the communication pathways of astrocytes by damaging the BBB [24]. BBB damaged by HG shows both thickening and increased permeability of the basement membrane, promoting endothelial cell proliferation, thus resulting in significant glucose influx into brain cells via glucose transporters [30]. Due to the high glucose levels, pericytes and astrocytes have an elevated respiratory rate, thus increasing the production of ROS and promoting oxidative stress [31]. Such alterations determine an increase in the entry of glucose into the central nervous system (CNS) [28], responsible for neuronal damage and the consequent neurodegeneration in diabetic patients [32].

In addition to hyperglycemia, Toll-like receptor 4 (TLR4) signaling pathway represents a potential link between neuroinflammation and T2DM. In diabetic patients, chronic activation of TLR4 can stimulate the production of proinflammatory cytokines such as TNF-α and IL-6 and activate PI3K, resulting in insulin resistance and impaired glucose metabolism. These alterations lead to mitochondrial dysfunction [33].

The relationship between mitochondrial dysfunction and oxidative stress has been extensively studied, while the relationship between mitochondrial dysfunction and neuroinflammation must be established. Mitochondrial dysfunction caused by HG-induced by ROS overproduction leads to upregulation of mitochondrial heat shock protein 60 (HSP60). The excess of HSP60 stimulates the production of inflammatory mediators, resulting in neuroinflammation in neurons and in astrocytes. HSP60 levels are particularly elevated in the brain cells of diabetic patients and could therefore be used as a possible future biomarker of neuroinflammation [26].

Numerous studies have tried to prevent and improve the development of cognitive and behavioral disorders associated with diabetes [34].

NEUROINFLAMMATION AND ALZHEIMER'S DISEASE (AD): A ROLE OF COMMON MECHANISMS RELATED TO TYPE 2 DIABETES

Studies have shown that T2DM is strongly associated with neurodegeneration in AD [35]. AD is characterized by cognitive dysfunction and progressive neurodegeneration with amyloid plaques and neurofibrillary tangles. AD is the most common cause of dementia and post-mortem brain tissue exhibits protein aggregation, mitochondrial dysfunction and neuroinflammation (Fig. 1) [36]. Recent studies have also attributed a role to the intestinal microbiota in the pathogenesis of AD. In fact, infectious agents can initiate the degenerative process by supporting chronic inflammation and leading to progressive neuronal damage and amyloid deposition[37]. Even though substantial data underlies that aging is the most critical risk factor for AD, there is continuously rising data that metabolic disturbances have been associated with AD and T2DM [38]. Indeed, altered glucose metabolism and mitochondrial activity are common soil for cognitive dysfunction and AD [6]. Metabolic alterations contributing to normal neuronal function and decreased glucose metabolism occur in AD brains [39]. A recent brain MRI study revealed the presence of AD- like functional-metabolic neurovascular coupling (NVC) in the brain of T2DM patients [40]. T2DM represents one of the key components of the Metabolic syndrome (MetS) including obesity, hypertension, and cardiovascular diseases. In a recent report, APP/PS1/Sirt3–/– mice with a superimposed MetS with amyloid pathology found that *Sirt3* gene deletion resulted in insulin resistance, neuroinflammation, plaque deposition, and microgliosis AD mouse model. The authors underlined that MetS in mid-life may interact with amyloid pathology during the cellular phase and accelerate the progression of AD pathogenesis [41]. Indeed, AD often coexists with other microvascular lesions due to hypertension, cardiovascular disease, and diabetes. Slow progressive cognitive impairment (mild cognitive impairment) is preceded by decades of prodromal

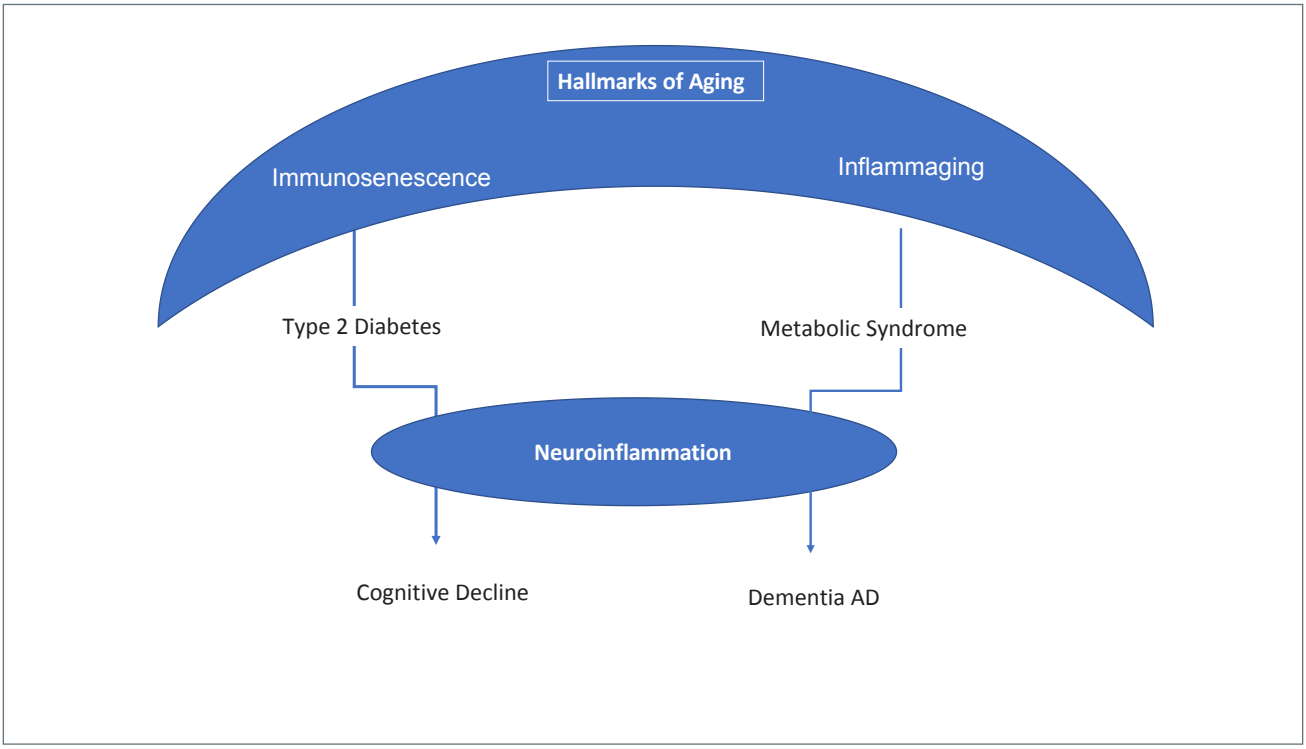

Figure 1. Neuroinflammation, as a common pathway of aging, type 2 diabetes and metabolic syndrome on cognitive decline and AD.

cellular alterations due to neuroinflammation [19]. As previously mentioned, chronic hyperglycemia plays a critical role in neuroinflammation, and genome wide association studies (GWAS) have strongly suggested a role of the metabolic syndrome on microglia dysregulation by a defective NAD+ sirtuin pathway. Sirtuin (SIRT) proteins are a family of seven signaling proteins involved in longevity and metabolic regulation. SIRT3 is highly expressed in brain cells [42]. SIRT3's functions in peripheral tissues also indirectly affect brain function by suppressing chronic inflammation, enhancing antioxidant defense, and assisting in the generation of energy substrates for brain cells. SIRT3 is exclusively present in mitochondria and plays a significant role in metabolic adaptation by its ability to deacetylate and activate key enzymes and transcriptional regulators (i.e. NaD+). Indeed, brain tissue metabolism is high with no reserve and thus, neuroinflammation may cause cell death through mitochondrial dysfunction. There is growing data on the role of SIRT3 on neuronal death, astrocytes, and microglia. Therefore, mechanisms related to SIRT3 activity may hold an important potential for treating AD [42]. Other studies have also indicated potential mechanisms related to ameliorating neuroinflammation on cognition. Parthenolide (PTL) is a potent inhibitor of NF-κB that can cross the BBB. In just three weeks, PLT administration resulted in improved cognition in diabetic mice in Morris water maze and passive avoidance tests. Furthermore, PLT-treated rats had significantly reduced levels of TNF-α and IL-6 in the cortex and hippocampus [34].

Pioglitazone (PGT), a PPAR-γ agonist, reduced TNF-α and IL-6 levels in the prefrontal cortex of diabetic mice, improving memory and exploratory activity in behavioral tests after a 14-day treatment [43].

Hyperoside (HYP), a bioactive flavonoid glycoside, is another substance which counteracts the neuroinflammatory process, mitigating hyperlipidemia, HG, oxidative stress, cognitive dysfunction, TNF-α/NF-κB-mediated neuroinflammation and apoptosis in type 2 diabetic rats [44].

Neuroinflammation could also be prevented by the administration of vitamin D3 (Vit. D) and/or rosuvastatin (RSV). Vit. D and RSV modulate canonical/non-canonical WNT/Beta-catenin signaling, which has important roles in cell survival, synaptic plasticity [45], learning and memory [46], and restore the hippocampal balance between anti-inflammatory IL-27 and pro-inflammatory IL-23 relieving T2DM cognitive dysfunction [47].

SGLT2 inhibitors (SGLT2i) and GLP-1R agonists (GLP-1RA) are key drugs in the current therapy of diabetic patients. In pre-clinical studies, SGLT2i ameliorates cognitive dysfunction in obese and T2DM mice, reducing oxidative stress, neuroinflammation and improving neuronal plasticity and mitochondrial brain pathway [48].

In several preclinical studies, GLP-1RA reduced neuroinflammation and could be involved in therapeutic strategies to counter neurodegeneration [49].

In a clinical study, diabetic patients were treated with GLP-1RA plus metformin (MET) or MET alone for at least 12 months. Patients receiving the combination therapy had better cognitive function, as assessed by the administration of the Montreal Cognitive Assessment Test (MoCA), Mini-Mental State Examination (MMSE), Mini Nutritional Assessment (MNA), and disability tests. However, the efficacy, safety, and tolerability of GLP-1RA need to be further confirmed in other human clinical studies [50].

DPP4 (dipeptidyl peptidase-4) inhibitors and GLP-1 inhibitors are a class of drugs used to treat T2DM by increasing the levels of incretin hormones, which stimulate insulin secretion. Numerous scientific research has shown a correlation between DPP4 and GLP-1 inhibitors on neuroinflammation related to cognitive decline [51,52].

CONCLUSIONS

The aging process itself, T2DM and components of the MetS are closely related to neuroinflammation with consequent neuronal loss and development of cognitive impairment with an accelerated risk of dementia. Considering the exponential growth of older persons living longer with T2DM and MetS, future studies should be aimed at identifying potential therapeutic benefits related to correcting neuroinflammation.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AMA, BA, MA, MRR: contributed to conceptualization, supervision and final version approval; MC, IDM, MCA: contributed data collection, writing of the initial draft of the manuscript *Neuroinflammation and age-related cognitive decline* section; MC: contributed to data collection, writing of the initial draft of the manuscript *Neuroinflammation and type 2 diabetes* section; IDM, MCA: contributed to data collection, writing of the initial draft of the manuscript *Neuroinflammation and Alzheimer's disease* section.

Ethical consideration

Not applicable.

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