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Alzheimer's Disease-- From Neuroinflammation & Beyond: A look into the Newer Perspectives of it

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Abstract: *Alzheimer's disease is the most common form of dementia characterised by cognitive decline & progressive memory loss. The aim of this review was to update the state of knowledge on the pathophysiological mechanisms, diagnostic methods & therapeutic approach of AD. Currently, the amyloid cascade hypothesis remains the leading theory in the pathophysiology of AD. As per this hypotheses, amyloid β deposits triggers a chemical cascade of events leading to development of AD dementia. The diagnostic procedures mostly depends on fluid based biomarkers such as those present on CSF & plasma or diagnostic imaging methods with recent development of blood based biomarkers like SIMOA (single molecule array) & mass spectrometry based assays proving superior over other assays with immunoprecipitation adding to aid in the diagnosis of AD. In addition to these PrecivityAD test for the plasma LC MS/MS assays for Aβ quantification & qualitative APOE isoform specific prototyping was used in patients with cognitive impairment. Diagnostic procedures in AD includes fluid based biomarkers such as those present in CSF, plasma & diagnostic imaging methods. The present therapeutic modalities focuses on symptom control which is mostly dependent on four types of treatment regimes – in pharmacological treatment, acetylcholinesterase inhibitors are the mainstay, pharmacological treatment under investigation which includes drugs focussed on the control of Aβ pathology & tau hyperphosphorylation ; treatment modality which mainly focuses on risk factors such as diabetes or non-pharmacological treatment aimed at preventing the development of the disease or treating symptoms through occupational therapy or psychological help. Still a lot needs to be researched into the complete domain of this neuroinflammatory disease called Alzheimer's disease with yet to know biomarkers & therapies that can prevent the progression of the pathology of AD.*

Keywords: *Alzheimers disease, senile plaques, β amyloid protein, tau protein, blood biomarkers, CSF biomarkers, immunotherapy, microglia, oligodendrocyte, acetylcholinesterase inhibitors.*

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I. Introduction

Alzheimer's disease is the commonest cause of dementia worldwide- which is characterised pathologically by the accumulation of Amyloid beta & tau protein aggregates. In current terms- there are no approved disease modifying therapies for clearance of either of these disease proteins from the brain of people with Alzheimer's disease. There is abnormality in protein aggregation with other pathological changes seen in these conditions. Both amyloid & tau proteins have detrimental effects on the function of mitochondria due to which mitochondrial function in the nervous system & rest of the body is altered early in the disease.

Mitochondrial functions :

- ATP production
- Calcium homeostasis } are affected in Alzheimers
- Mitophagy disease
- Reactive oxygen species production

** This points towards the future that mitochondrial function – maybe developed into a future biomarker for early AD.

In AD⇒cellular metabolic changes – within the brains of people with Alzheimer's disease – seen very early in the condition – which proceeds the development of both amyloid plaques & neurofibrillary tangles.

** Abnormalities has been shown in many metabolic pathways in AD – with both PNS & CNS affected.

Which function of mitochondria is affected in AD?

Significantly, how mitochondria control oxidative phosphorylation – are likely to be key in the development & progression of AD.

Alternative mitochondrial hypotheses for the etiology of AD- states that – people who inherit mitochondrial genes that predispose them to – lower mitochondrial respiration rates- are more likely to develop the condition. Mitochondria are in a constant state of flux – altering morphology & localization- depending on energy demands or metabolic stresses within the cell. Main cellular function of mitochondria – is the production of ATP via electron transport Chain(ETC). Complexes I-IV- of the respiratory chain – are coupled to the action of FOF1- ATP synthase (Complex V enzyme) – which uses the membrane potential generated by complexes I-IV to generate ATP from ADP & Phosphate. In addition, mitochondria are critical- to many other cellular functions , including maintaining cellular calcium concentrations , generation of reactive oxygen species(ROS)- for cellular signalling as a consequence of the inefficiency of the electron transport chain. Mitochondria also have a role in steroid synthesis, hormone synthesis, apoptotic signalling. Mitochondria exist in a dynamic network – altering shape in response to stress- or as result of metabolic demands of the cell. Mitochondria will fuse together – in times of increased energy demands or metabolic stress (stress induced metabolic hypoperfusion). Mitochondrial fission is less directly linked to managing ATP demands of the cell but is used as a way of identifying defective mitochondria – that needs to be removed & recycled. Mitophagy—specific form of autophagy – in which mitochondria is targetted & undergo Degradation. Parkin dependent mitophagy depends on the recruitment of Parkin – to the outer mitochondrial membrane – which leads to recruitment of PINK & eventually UBIQUITIN- to signal mitochondrial breakdown. Mitochondrial permeability transition pore (MPTP)- is formed by Cyclophilin D (Cyp D) Adenine nucleotide Translocator (ANT) & VDAC- which controls the movement of calcium & ROS out of the mitochondria. Electron transport chain disruption in AD: A microarray analysis of post-mortem frozen hippocampal samples – has revealed a global decrease in nuclear encoded Ox PHOS protein subunits &no change in mitochondrial DNA(mt DNA) encoded subunits when AD brains are compared to both aged matched controls & patients with MCI.

NEURO INFLAMMATION IN ALZHEIMER'S DISEASE

Characteristics of Aging :

- Dysregulated immune homeostasis
- Dysregulated metabolic homeostasis

} where there is

⇓

Chronic sterile low grade inflammation or inflammaging

⇓

Which involves

⇓

- cellular senescence
- immunosenescence
- mitochondrial dysfunction
- defective autophagy
- defective mitophagy
- dysregulation of the

i) Ubiquitin – proteasome system
ii) activation of the DNA damage response
iii) meta inflammation or metaflammation from chronic overnutrition or obesity
iv) gut microbiota dysbiosis

*** Due to the above mentioned events-

- there is change in circulatory immune markers including C- Reactive protein(CRP)
- IL-6
- TNFα & its soluble receptors (TNF receptor I , TNFR-I & TNFR-II)
- Vascular cell adhesion molecules I (VCAM-I)
- D- Dimer
- Sirtuin signalling

** Drawback of chronic subclinical inflammation- is that ⇒it is an essential risk factor – for increasing incidence of degenerative diseases such as AD.

Incidence:
There are about 728 million persons – aged 65 years & over in the world which will be 1.5 billion by 2050 – so this aging population would be at increased risk of inflammaging- which will increase significantly in the next decade.

ALZHEIMER'S DISEASE:
- Chronic
- Neurodegenerative disorder
- With increasing age is the strongest non modifiable risk factor
- Presently, no effective therapies for AD

CLINICAL PRESENTATION :
Progressive deterioration of memory
Deterioration of other cognitive function
Dementia

NEUROPATHOLOGICAL HALLMARKS OF AD:
Extracellular β- amyloid plaques
Intracellular hyperphosphorylated tau(p- tau) in neurofibrillary tangles – accompanied with synaptic & neuronal loss.

Classification of Alzheimer's disease
i) Familial or early onset AD (EOAD) } both have similar pathophysiology
ii) Sporadic or late onset AD (LOAD)

3 causative genes

Presenilin 1 (PSEN1)
Presenilin 2 (PSEN2) } are involved in pathogenesis of EOAD
Amyloid precursor protein (APP) ⇓
In an autosomal dominant trait

LOAD- however comprises most AD cases (> 95% cases) ⇒ in which greatest risk factor – is the advancing age with common genetic risk factor being ⇒ an allelic variation in Apolipoprotein E.

Recent Advances : AD Genetics
⇓
Which employs genome wide association studies (GWAS)
⇓
Whole exome sequencing (WES)
⇓
Whole genome sequencing (WGS)

GWAS, WES, WGS- have defined additional genes – whose variants

contribute - to increased risk.

The variants include:

- Clusterin (CLU)
- Sortilin related receptor -1 (SORL-1)
- ATP binding cassette subfamily A member 7 (ABCA7)
- Bridging integrator 1 (BIN 1)
- Phosphatidyl inositol binding clathrin assembly protein (PICALM)
- CD 2 associated protein (CD2AP)
- Complement component(3b/4b) receptor 1 (CR1A)
- CD33 trigerrring receptor expressed on myeloid cells 2
- Phospholipase D3(PLD3)

Interestingly more than 50% of the validated gene variants – are implicated in the innate immune mechanisms & microglial functions – including the top 2 Alzheimers disease risk genes APOE & TREM.
After doing epigenomic analysis- AD GWAS loci are preferentially enriched in enhancer sequence – involved in innate immune processes as well as i) endocytosis ii)
cholesterol / sterol metabolism & synaptic function & synaptic function.
TREM2- It increases the rate of phagocytosis in microglia & macrophages
-Modulates inflammatory signalling
-controls myeloid cell number, proliferation & survival ⇒& it has been revealed that triggering TREM-2 receptors in microglial cells – is closely associated with the pathogenesis of AD.
TREM-2 ⇒modulates microglial functions in response to Aβ plaques & tau tangles
In early AD, The absence of TREM-2⇒ leads to ⇒ increased amyloid pathology – that
Progressively becomes worse owing to loss of phagocytic Aβ clearance.
In AD, TREM-2, variants – arise in part – because of their – reduced capacity to phagocytose Aβ clearance.
In AD- TREM-2 variants ⇒arise in part because of their reduced capacity to phagocytose Aβ. Evidence suggest multifactorial etiology of AD- neuroinflammation
plays a central role in its etiopathogenesis⇒ owing to the capacity of the neuroinflammation to exacerbate Aβ & tau pathologies- as evidenced by PET studies – which showed increased microglial inflammation in brains of AD patients.
Levels of proinflammatory cytokines in AD patients serum & post mortem brain are elevated & Aβ can activate the brains immune cells.
The neuronal loss due to sustained inflammation in AD patients is attributed to neuronal loss & involves – microglia, astrocytes, oligodendrocytes , mast cells, cytokines, chemokines complement which collectively play a role – in onset & progression of the disease. Early onset processes involved in etiology of the disease includes:

⇓
- Mitochondrial dysfunction
⇓
Due to it
⇓
There is altered glucose metabolism

- Oxidative stress
- Chronic hypoperfusion & neuronal cell cycle re-entry ⇒ which leads to neuronal tetrapolarization , trisomy 21 mosaicism & synapse loss - ---- these processes may synergistically interact to facilitate the neurodegenerative process in AD.

Mediators of Neuroinflammation:
Microglia: - CNS's immune cells
- Different from peripheral macrophages
- Origin: arise from yolk sac of fetal macrophages
- Unique in their capacity of self renewal

Microglia constantly survey their milieu, assess ongoing synaptic activity, mediate
synaptic prunning and clear debris & provide trophic support to neurons.
In pathological conditions, like, i) chronic stress- BBB may become compromised thus allowing peripheral haematopoietic cells – to cross into neural tissue & become part of the parenchymal microglia / macrophage pool.
In response to CNS insults – such as neuronal injury or insults – microglia become activated – to produce proinflammatory factors (M1 phenotype) or anti-inflammatory factors (M2 Phenotype) – an exquisite balance of anti-inflammatory mediators – to heal & repair tissues & proinflammatory mediators to clear cellular debris & aggregated misfolded proteins if essential for the maintenance of healthy CNS.
With advancing age, microglia acquire a activated phenotype & release pro inflammatory cytokines – such as IL-1β, TNF-∝ & IL-6.

In AD, Microglia react to pathogen associated molecular patterns (PAMPs)or danger associated molecular patterns (DAMPs) to assume a M1 phenotype- leading to an exacerbation of inflammation and an acceleration of disease progression.

In AD brain slices, activated microglia surround both extracellular Aβ plaques & neurons containing neurofibrillary tangles(NFTs)⇒ It is thought that – Aβ- activate microglia – which then secrete IL1β, IL-6 & TNF∝ as well as C-C motif ligand ⇒ which leads to recruitment of more microglia & astrocytes to the Aβ locus.

Microglia phagocytoze Aβ- through a range of cell surface receptors including CD-14, Toll like receptor2(TLR2), TLR4, α6β1 integrin, CD47 & scavenger receptors such as CD 36 . In AD- accumulation of Aβ - throughout the brain – results partly from the failure of the microglia to remove extracellular Aβ.

Initially, microglial activation may serve to eliminate Aβ- but their chronic activation – may amplify amyloid cascade & lead to neurotoxicity.

Aβ- has recently been suggested – to be an antimicrobial peptide that fibrilizes – in order to activate the innate immune defence system & protect the host from a wide range of infectious agents.

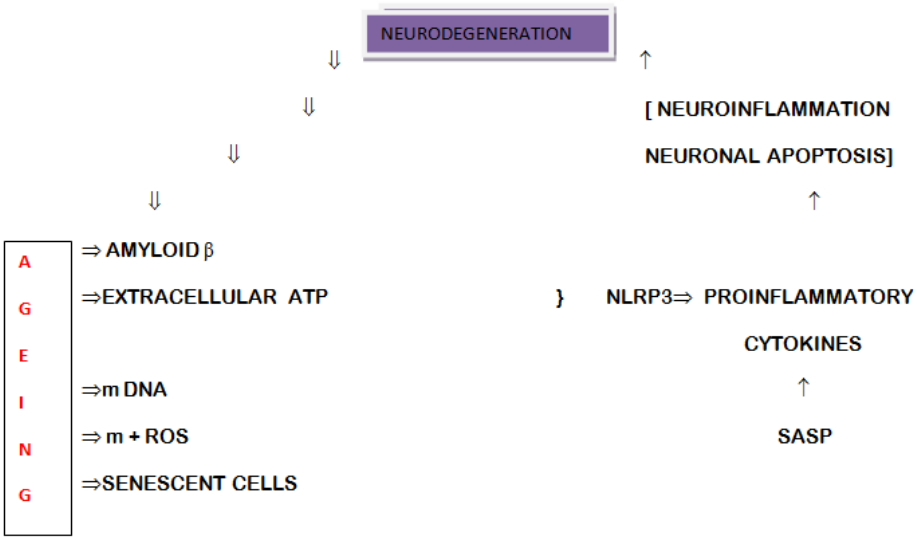

Fig: Schematic representation of the proposed causes of neuroinflammation in AD

Age related release of damage associated molecular patterns (DAMPs) ⇒such as Aβ, Extracellular ATP & cell debris – such as circulating mitochondrial DNA which are capable of interacting with the Nod like receptor protein 3 (NLRP-3) – creates a oxidative & neuroinflammatory environment – through the excessive production & release of proinflammatory cytokines & reactive oxygen & nitrogen species (RONS) In addition to that, mitochondrial reactive oxygen species (mt ROS) & senescence associated – secretory phenotype (SASP)- factors from senescent cells – which also drive senescence in nearby cells – produce proinflammatory cytokines – leading to culmination of the process by neuroinflammation & neuronal apoptosis

ASTROCYTES: - Regulate maturation of neurons & maintains functions of neurons

- They are found in various states of activation & can be neuroprotective (reducing inflammation & stimulating repair or neurotoxic – that may result in neurodegeration)

- They respond to inflammatory molecules such as cytokines & chemokines & are able to able to detect aggregated proteins such as Aβ. The astrocytes hypertrophy upon activation & upregulate glial fibrillary acidic protein (GFAP) expression.

In AD patients brains – we get reactive astrocytes – which is a distinct trait . Om post-mortem of AD patient brains ⇒ intralaminar astrocytes are atrophied - & severely disrupted in post-mortem AD brains.

When astrocytes are created from familial & sporadic AD – induced pleuripotent stem cells(iPSC) ⇒ they have an atrophic phenotype in vitro.

How the B_B- B is breached? Inhibition of Astrocytes – Aβ accumulation with increased histopathology & they are associated with cognition ⇒ which may result in breach in B_B-B leading to an infiltration of peripheral immune cells ⇒ aggravating neuroinflammation & inducing neurotoxicity – due to impairment of glucose homeostasis - & generation of altered Ca2+ signalling.

OLIGODENDROCYTES :

Main function : provide support & insulation to the axons – by forming myelin sheaths around nerve fibers.

Recent evidences suggest – potential role of Oligodendrocytes in pathogenesis & progression of AD. Oligodendrocytes are severely impaired in AD & indeed there is focal loss of oligodendrocytes resulting in a reduction of myelin proteins near Aβ plaques⇒Aβ impairs survival & maturation of Oligodendrocyte progenitor cells(OPCs) & also hampers the formation of myelin sheath. Neuroinflammation & oxidative stress – may also contribute to oligodendrocyte dysfunction & death. Myeloid cells other than microglia- like dendritic cells, monocytes& granulocytes expresses scavenger receptors (SRs)& TLRs- that facilitates phagocytosis & degradation of Aβ. Blocking transforming growth factor β signalling increases – peripheral myeloid cell infiltration into the CNS & significantly reduces the Aβ burden.

DEFECTIVE AUTOPHAGY & NEUROINFLAMMATION :

Cell degrade protein aggregates & damaged organelles by autophagy & defective mitochondria by mitophagy.

With advancing age, autophagy gradually subsides – which is linked to defective mitochondria & results in inflammaging. Damaged cellular & organelle components – that accumulate as a result of inadequate autophagy- are released as damage associated molecular patterns (DAMPs).

Dysfunctional mitochondria – that are not eliminated by mitophagy – release large amounts of mitochondrial DNA(mt DNA) into the cytosol & together with the RO, metabolites such as ATP, fatty acids, Aβ, succinate, per oxidized lipids, advanced glycation end products , altered N- glycans & HMG B1 – are also recognized as DAMP's & trigger an innate immune response by directly activating TLR9. This initiates – the transcription of proinflammatory cytokines such as IL-6, TNF∝, IL-1β & MMP-8 & activates the nod like receptor 3 protein (NLRP3) inflammasome – which is a key regulator of inflammation – to activate CASPASE 1 & facilitate IL-1β & IL-1 maturation as well as gasdermin D mediated pyroptotic cell death. These inflammatory responses – can be blocked by PRO-IL-1β in autophagosomes In addition to that- the mitochondrial derived peptide(MDP) – known as mitochondrial open reading frame of the 12-S ribosomal RNA type-C (MOTS-C) ⇒reduces inflammation by inhibiting cytokines such as TNF∝ & IL-6 , while simultaneously promoting an anti- inflammatory response.

MOTS-C stimulates ⇒IL-10, signal transducers & activators of Transcription-3(STAT-3), Aryl hydrocarbon receptor (Ahr) ⇒all of which inhibits NFκβ expression & proinflammatory cytokine production. Another mitochondrial peptide Humanin- also has anti-inflammatory effects. The chronic sterile low grade inflammation elicited – may culminate in immunosenescence & compromise neuronal function ⇒this may partly explain why dysregulated NLRP3inflammation activation is observed in AD. Eliminating damaged & dysfunctional mitochondria by mitophagy may prevent hyperinflammation – triggered by NLRP3 inflammasome activation

MITOCHONDRIAL DYSFUNCTION & IMMUNOMETABOLISM:

Mitochondrial dysfunction –with decreased oxidative phosphorylation (OX PHOS) & increased glycolysis ⇒is observed in AD microglia.

Microglia – exhibit ⇒high metabolic flexibility – to cope with their high energy demands.

Microglial activity – becomes compromised with age & especially in age related diseases- such as AD & they have low mitochondrial turnover.

Exposure to Aβ & tau activates – a proinflammatory phenotype – that is accompanied – by a shift of metabolic profile from OXPHOS to glycolysis. If the inflammatory process is prolonged – bioenergetic failure involving – both glycolysis & OXPHOS occurs.

** These mitochondrial perturbations – in activated microglia are propagated to other cell types including astrocytes & neurons – thus exacerbating the disease outcome.

This increased microglial glycolysis – often coupled with increased secretion of proinflammatory cytokines- exacerbates neurotoxicity & escalates ongoing neurodegeneration.

Glycolysis is upregulated- in microglial cells – during early phase of AD- coupled with increased phagocytic activity – followed by an immune tolerant phase ⇒ during which glycolysis & oxidative phosphorylation – were both disrupted with less phagocytic potential .

Microglial activities can be restored – through increasing metabolic functions – with IFNγ due to it – resulting in increased microglial clustering around Aβ plaques phagocytosis & TNFα production.

OXIDATIVE STRESS & NEUROINFLAMMATION :

Oxidative stress & neuroinflammation are the key pathologic features signatures of AD.

RONS- produced by all aerobic cells ⇒ & while they are essential signalling molecules – a redox imbalance is detrimental & plays an important role – in the inflammatory process in aging as well as in AD.

Cells of innate immunity- produces copious amounts of ROS- within the CNS⇒ it is not clears though- whether neuroinflammation induces oxidative stress – or if it is the elevated levels of ROSthat cause neuroinflammation – especially in a situation – where there is already excess oxidant production – in the face of age associated weakened antioxidant defense. Elevated RONS levels- damage primary cellular components including lipids, proteins & DNA. The biomarkers for oxidative stress malondialdehyde (MDA) , glutathione peroxidase (GSH-Px), protein carbonyl (PC)⇒ they correlate with raised levels of inflammatory cytokines - & both are associated with low cognitive performance in institutionalized elderly people. Mitochondria are the most important source of intracellular ROS- & dysfunction of mitochondria leads to significant ROS increase (Reactive oxygen species). Other mechanisms that produce ROS include

- NADPH oxidase (NOX)
- Immune activation
- Xanthine Oxidase(XO)
- Arachidonic acids (AA)metabolites

mT DNA mutations – that accumulate with age – disrupt the mitochondrial respiratory chain – which in turn leads to excessive mitochondrial ROS(mT ROS) production which accelerates – the emergence of new mT DNA mutations that leads to cellular senescence – further aggravating the inflammatory process.

CELLULAR SENESCENCE & NEUROINFLAMMATION

Stimuli such as – mitochondrial dysfunction

- Persistent DNA damage } can initiate cellular senescence
- Exposure to DAMP's

Senescent cells-accumulate with aging – secrete proinflammatory & matrix degrading molecules – as a part of a senescence associated secretory phenotype (SASP) – This SASP- linked to age related tissue inflammation & disease – SASP may account for several observed disease phenotypes in AD. The SASP- is a very heterogenous phenotype & the secreted components vary on the basis of cell types & triggering factors but generally consist of interleukins IL-1α, IL-1β & IL-6. Senescent cells are dangerous for non senescent neighbouring cells – How?? They develop a SASP& secrete cytokines, chemokines, ROS and proteases – all of these create a noxious microenvironment which promotes inflammaging.

Chemokines :

- IL-8 & growth regulated α- protein
- Growth factors (Fibroblast growth factor2 & hepatocytes growth factor)
- Metalloproteinases (interstitial collagenase- known MMP-1)
- Stromelysin -1
- Collagenase 3(also known as MMP-13)

+

Other insoluble proteins & other extracellular matrix components –

their effects are mainly paracrine but may become systemic – as some

of the soluble mediators may get into circulation.

Prominent SASP regulators include p38 MAPK, NFκβ C/ EBPβ, GATA4 & mechanistic target of rapamycin (M TOR). Senescent markers are upregulated – in the astrocytes of AD patients & Aβ elicits senescence in astrocytes invitro via ROS accompanied by p38, IL-6 & IL-8 upregulation.

Depleting human astrocytes of glutathione invitro activates SASP associated pathways (NFκβ & p38 MAPK) & IL-6 secretion. Human astrocytes is due to stress induced senescence – which becomes flattened & enlarged & adopt senescence associated heterochromatin formation (SAHF) & have elevated levels of p53, p21CIP1, p16INK4a, SA-βgal. Generally, senescent cells are cleared by NK cells & macrophages.

In aging brain, specially in the AD brain – the BBB is compromised leading to peripheral immune cell infiltration – this allows the infiltration of peripheral immune cells & possibly infectious pathogens. Microglia – are resident macrophages – but there is no evidence that they selectively kills senescent cells.

Getting rid of CNS senescent cells – would require – infiltrating CD4+ T-cells – as peripheral macrophages & appear to depend on these cells to kill senescent cells outside the CNS. As the senescent cell clearance in the CNS is limited in non aged healthy individuals – senescent cells SASP& secondary senescence may continue in the brain for several years or decades.

METAINFLAMMATION:

Late life obesity/ metabolic disease & T2DM⇒ contribute to low grade non resolving inflammation & increased risk of developing AD.

AD has been referred to as Type 3 diabetes. Adipose tissue inflammation in obesity is sterile, chronic, low grade- and it affects the metabolic control of nutrient flow in adipose tissue, liver, muscle & pancreas by inducing – insulin resistance.

Peripheral insulin resistance- leads to decreased insulin signalling in CNS that is associated with an alteration in brain metabolism- & activation of the inflammatory pathways. Due to hyperglycemia in T2DM- there is increased risk of developing AD- as there is exacerbation of microglia & astrocytes mediated neuroinflammation & neuronal injury. Individuals with increased age, obesity, T2DM, Hypercholesterolemia- are more likely to be affected by AD.

EXERCISE & INFLAMMATION

Endurance exercise (EE) – has anti inflammatory properties – that can reduce the risk of several metabolic disorders.

IL-6- secreted from skeletal muscles into circulation – inresponse to EE- are responsible for the effects. When IL-6 is secreted from skeletal muscles during endurance exercise it includes acute phase of immune response as well as glucose & lipid metabolism - & have been shown to reduce the risk & severity of many chronic diseases & benefits extend to the brain. One of the long term immunometabolic adaptations – is mediated by

energetic stress- which induces beneficial molecular adaptations in adipose tissue & immune cells. In the brain this results in upregulation of IL-10- which activates mouse microglia & astrocytes.

The modulatory effects of exercise on inflammation – both centrally & peripherally have protective effect on cognitive function – maybe beneficial to the patients of AD- as it elevates the growth of circulatory growth factors (such as IGF-1) & neurotrophins (such as brain derived neurotrophic factor, BDNF)

GUT MICROBIOTA & INFLAMMATION :

Gut microbiota –less diverse with age – contains more bacteroids – compared with higher presence of Firmicutes in younger adults Corrleation ahs been established between – microbial diversity, frailty scores

environmental factors like dietary patterns – in elderly individuals.

These changes can initiate – dysbiosis & prevalence of pathogenic species in the Intestinal microbial composition – results in elevated levels of systemic proinflammatory markers(IL-6, IL-8, TNFα, CRP) – associated with the pathogenesis of AD.

The microbiota – can also modulate – events in the brain via vagus nerve activation, neuropeptide & NT release short chain fatty acids(SCFA), α-amino β methyl propionic acid (BMAA) & lipocalin -2 release. The above mentioned signals – reach the brain & influence the microglial maturation & activation, facilitating immune surveillance,

regulation of hypothalamic pituitary adrenal axis (HPA), synaptic pruning, clearance of debris.

Neurobehavioral complication – associated with peripheral infection – is facilitated by advancing age – because hippocampal processing – is more easily disrupted – when peripheral innate immune system is stimulated in older animals.

COMPLEMENT IN THE BRAIN :

Complement proteins are mainly synthesized in the liver- complement proteins & their cognate receptors & regulators are expressed throughout the CNS. If the BBB is intact – it restricts & prevents access of complement proteins from the periphery, so local production of complement is – therefore particularly important for innate immune defense in healthy brain. Even in healthy brain- there are regions –where BBB is compromised, particularly in aged normal brain –where evidence of barrier loss in & around the hippocampal area- which is more severe in AD brain. Dominant pathway of BBB breakdown inflammation – which maybe central or systemic.

BBB improvement in AD- maybe much more subtle, localized to areas of pathology affects specific transport processes eg: transport of Aβ. C3a/ C3aR signalling via intracellular Ca2+ mediates vascular endothelial cadherin junction & barrier integrity in an invitro model of the BBB.

*** Microglial reactivity – can be inhibited by inactivation of c3aR1 & this restores hippocampal & cortical volumes in aged brains – suggesting an association between impaired BBB, inflammation & neurodegeration. Complement plays complex roles in
brain homeostasis - & likely has both protective & exacerbating effects on the disease.
Evidence suggests – that complement restricts Aβ plaque formation - & aids clearance
of plaque components – but also contributes to the switch of microglia & astrocytes into activated neurotoxic cells that drive the pathology.

POSSIBLE INTERVENTION FOR NEUROINFLAMMATION IN ALZHEIMERS DISEASE
In Chronic inflammation- the initial response is not adequately resolved leading to accumulation of TNF, IFNS & IL-6 as well as

- Immune cells
- Apoptotic cell - all of them compromising final homeostasis
- Debris at the site of insult

TRAGETTING TNFα
TNFα plays a central role in initiation & maintenance of the inflammatory response. TNFα regulates

- Synaptic plasticity
- Microglial activation
- Astrocyte induced synaptic strengthening
- Glutamatergic transmission in the healthy CNS

Effects of TNFα maybe either homeostatic & pathophysiological . In AD patients - TNFα not only co-localizes with Aβ plaques in the brain – but the levels are also elevated in plasma CSF & correlate with the severity of the disease. In patients with rheumatoid arthritis – who are treated with a TNF-α blocking agent / Inhibitor like Infliximab, Rituximab, Adalilumab& recombinant fusion protein Etanercept – have a low incidence of developing AD.

SENOLYTICS:
Senescent cells secrete proinflammatory cytokines, chemokines & tissue damaging proteases- that negatively impact their surrounding microenvironment & accelerate aging & age related diseases. Senolytics are drugs – that selectively eliminate senescent cells & apparently provide beneficial effects in rodent models of
aging.
Dasatinib: A tyrosine kinase inhibitor – with BBB penetrance decreases microgliosis & is neuroprotective in pre clinical model of AD.
Quercetin: It is anaturally occuring flavinoid – ameliorates AD pathology & protects cognitive & emotional function in triple transgenic AD disease model mice.

TARGETTING THE INFLAMMASOME:
Targeting the NLRP3 inflammasome – is gaining traction as a therapeutic strategy- in inflammatory diseases. NLRP3 inflammasome – significantly contributes to neuroinflammation & age related cognitive decline & is potently activated by Aβ. Both
MCC950 – a potent inhibitor of NLRP3 & Inzomelid – another potent selective brain penetrant NLRP3 inflammasone inhibitor – are expected to move into PHASE-II trials for a range of disorders including Parkinson's , Alzheimers & MND.

TARGETTING IMMUNE CHECKPOINTS
The programmed cell death 1 receptor (an inhibitory immune checkpoint receptor [ICR]) – is expressed on the surface of activated T Cell. Together with its widely expressed ligand PD-L1, PD-1⇒ plays an important role – in maintaining immune homeostasis & self tolerance. Persistent antigen stimulation & inflammation in pathological situations- increase T-cell surface expression levels of ICRs. This leads to their interaction with their ligands – on Antigen Presenting cells(APC's) ⇒ that exhausts the T- cell inducing a hypofunctional state. This mechanism could be manipulated - to either quench or enhance the immune response as a therapeutic target- & depends on recruited immunosuppressive regulatory T-Cell(T reg). The anti PD-1/PD-L1 based immunotherapy has been effectively utilized for many cancers & is now also a therapeutic strategy in AD.
TARGETTING CD38: Daratumumab – a first in class humanized monoclonal antibody against the CD epitope – was approved & indicated for multiple myeloma- patients refractory to conventional therapy.CD 38 is a NAD glycohydrolase expressed by neurons, astrocytes, microglial cells ⇒plays an important role in euroinflammatory

& brain repair processes. Its role in AD is being evaluated

TARGETTING CD33:
CD33 has been identified by GWAS among the leading risk factors for AD. In the brain it is exclusively expressed by microglia & infiltrating macrophages, CD33 doesnot allow efficient Aβ phagocytic clearance.

TARGETTING IL-12, IL-23
Inhibition of the IL-12 /IL-23 pathway by genetic ablation or pharmacological manipulation significantly reduces cerebral Aβ load & cognitive deficit. IL-12 & IL-23 subunit p40 production by microglia is increased in the APPPS1 AD mouse model.
Genetic ablation of the IL-12/ IL-23 signalling molecules p40, p35 or p19reduces cerebral Aβ load & the biggest effect come from ablation of p40or its receptor complex.
Antibodies against p40, IL-12 or IL-23have been developed for the prevention of treatment of AD

TARGETTING Th1 RESPONSE:
Glatiramer acetate (GA) (COPAXONE)- a synthetic analogue of myelin basic protein ⇒ the first disease modifying drug approved for the treatment of Multiple sclerosis- can be safely used to boost T- cell responses without the risk of the autoimmune disease –as it weakly cross reacts with myelin derived autoantigens . Immunisation with GA results in cerebral recruitment of prohealing, highly phagocytic monocytes (M0) & MΦ -greatly alleviating cerebral Aβ burden – reducing microgliosis & astrocytosis – resulting in increased hippocampal based cognitive functions .
GA immunisation enhances the expression of hippocampal early growth response Protein 1 (Erg1)- a protein negatively correlated with hippocampal Aβ burden GA based vaccination – could provide a new viable avenue for immunotherapy for AD

TARGETTING MICROGLIAL P2Y6
Microglial purinergic receptor – promoting their phagocytic activity & inhibiting the release of proinflammatory cytokines.

CYCLOSPORIN & TACROLIMUS
Both of them are inhibitors of Calcineurin - & are used as immunosuppressive agents- to prevent post transplant organ rejection & for the treatment of autoimmune diseases & tuberous sclerosis tumors. Cyclosporin & Tacrolimus- significantly reduce – biochemical , histopathological alterations & age related memory deficits – demonstrating their potential as therapeutic agents in cognitive dysfunctions – probably owing to their anti-amyloid , antioxidative & anti-inflammatory properties.

TARGETTING P38 MAPK
Neflamapimod (Vx-745)- developed as a disease modifying drug for AD. It is able to reduce IL-1β levels & improve patients attention & executive function.

CNS TARGETTING ANTI COMPLEMENT AGENTS:
In familial AD, which contains 3 mutations associated with familial AD
- APP SWEDISH
- MAPT P 301L
- PSEN1M 146V

ANX-M1/ANX005, a humanized IgG4 recombinant antibody against C1q – is safe at high doses (200mg/kg)- & is neuroprotective & prevents synapse loss when Aβ fibrils are injected into lateral ventricles.

NOVEL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
CSP-1103(Itanapraced)- It is a microglia modulator, that has the potential to inhibit Aβ plaque deposition – reduce tau pathology, restore normal microglial function by increasing phagocytosis & decrease the production of pro- inflammatory cytokines.

CALORIE RESTRICTION (CR)
CR has been shown to improve lipid & glucose metabolism quench inflammation & improve cardiovascular health. This is thought to be via key nutrient & stress responsive metabolic signalling pathways including IIS/ FOXO, TOR, AMPK, Sirtuin, NRF2 & Autophagy- that additionally work towards lifespan extension by CR . Ultimately, the age related proinflammatory upregulation of NFκβ, IL-β, IL-6. TNF-∝ & ROS is attenuated & beneficial effects include enhanced cognitive response

METFORMIN:
OAD- widely used to treat T2DM & metabolic syndrome. It activates AMP activated Kinase (AMPK)- enhances autophagy & mitochondrial function & quenches inflammaging.

ENDURANCE EXERCISE :
Neuroprotective agents against AD. Exercise activates continuous oxidative stress- that induces a series of counteractive mechanisms. These enhance mitochondrial function & mitigate ROS induced neurotoxicity ie, mitohormesis & this is especially important in the hippocampus – which is particularly sensitive to oxidative stress.

MELATONIN:
N- Acetyl 5 methoxytryptamine (Melatonin) – synthesized from tryptophan
– is able to activate both proinflammatory pathways.
It is also capable of suppressing proinflammatory processes including NO release, activation of cyclooxygenase, NLRP3, gas dermin D, TLR-4, m TOR signalling, cytokine released by SASP& Aβ toxicity under different conditions. In addition, it activates SIRT1 & upregulates Nrf2 while quenching NFκβ activity & the release of IL-4 & Il-10- thus shifting microglia polarization towards an M2 phenotype

RESVERATROL:
Potent natural SIRT1 activator – that helps prevent aging related decline in heart function & neuronal loss . Resveratrol-can also attenuate the phosphorylation of the mammalian target of rapamycin (mTOR) & S6 ribosomal protein – while ameliorating inflammation. A 26 week Resveratrol treatment of healthy older adult – improved memory performance & hippocampal functional connectivity. These finding suggest that SIRT1 maybe the potential target treatment of neuroinflammation & neurodegenerative disorders.

ANTIOXIDANTS:
Close association between oxidative stress & neuroinflammaging – targeting detrimental ROS at the production stage – without affecting the ROS signalling may improve immune function & ameliorate neuroinflammation Mitochondria targetted antioxidants such as (10-6' plastoquinoyl decyltriphenyl phosphonium) SKQ1, MitoQ, MITOTEMPOL & Mito Vit E- prevent apoptosis by mitigating the oxidative damage more effectively than untargeted antioxidants such as Trolox . Other such antioxidants include Tiron- which accumulate within the mitochondria – by permealizing the mitochondrial membrane & ASTAXANTHIN – a mitochondrial permeable antioxidant – that can permeate the BBB- & effective & treating macular degeneration.

PROBIOTICS:
Gut microbiota are already altered in the elderly. Therefore supplementation with specific strains of lactobacilli & bifidobacterium alongwith fructooligosaccharides maybe beneficial – they have been shown to attenuate inflammaging by downregulating IFN-γ & TNF-∝ & uploading IL-10. Alteration of the gut microbiota can induce changes in the brain activity – which raise the possibility of therapeutic intervention of the microbiome in AD & other neurological disorders. Gut flora of cognitively impaired individuals & those with brain amyloidosis have an increased abundance of pro inflammatory species E Coli/ Shigella while the abundance of anti-inflammatory species E. Rectale is reduced. Faecal samples from elderly AD Patients with AD induce a lower expression level of p- glycoprotein (a key mediator of intestinal homeostasis) in intestinal epithelial cells in vitro.

p- glycoprotein dysregulation leads to inflammatory disorders of intestine. Altered gut microbiota with disrupted intestinal hoemostasis & induced inflammation – may lead to neurodegenerative diseases like AD via the gut brain axis pathway. Thus remodelling the gut microbiota may be a novel therapeutic strategy for AD. Altering gut microbiota through probiotics – is a potential therapeutic strategy in AD.

NUTRACEUTICALS:
The neutraceutical NT-O20 which is a proprietary brand of blueberries, green tea, vitamin D3 & carnosine – has been shown to reduce inflammation, prevent age related cognitive decline & enhance neurogenesis

ESSENTIAL VITAMINS & MINERALS :
Vitamins & minerals play major roles - in boosting the immune system to protect against certain infections & inflammation. Vitamin E supplementation enhances IL-2 production - & induces nerve T- cell proliferation.

Vitamin C is a potent – water soluble antioxidant - & plays an important role in maintaining redox homeostasis within cells & is protective against ROS released by phagocytes – so it modulates proinflammatory signalling pathways. It also augments humoral response & cell mediated immunity. By accumulating within phagocytic cell – it enhances chemotaxis & phagocytosis & is essential for apoptosis & clearance from the site of infection- of spent neutrophils by macrophages to decrease potential tissue damage. Vitamin C also also reduces inflammation by blocking the synthesis of TNF, IL-6 & IL-1β⇒& has been shown in vitro to promote IgG & IgM production. Zinc plays a key role as a structural & regulatory catalyst ion – for several enzymes & transcription factors .

Zinc deficiency results in significant decline in both adaptive & innate immune responses & promotes systemic inflammation. Zinc supplementation is associated with lower TNF-∝ levels ⇒reduce oxidative stress as well as lower incidents of infection.

Zinc deficiency activates the NFκβ pathway & release of IL-2, Il-6& TNF-∝ infection – a proinflammatory cytokine – both invivo & invitro. Zinc supplementation elicits inducible regulatory T-cell production & decreases ROs production.

FLAVONOIDS FROM EPIMEDIUM & ICARIIN

They attenuate proinflammatory response- while enhancing an anti-inflammatory response in inter alia, the hippocampus, hypothalamus, hypophysis & mitigate neuroinflammation in aging. Icariin acts via AMPK/mTOR/ ULK-1 pathway to increase neuronal autophagy & enhance brain function in aged sprague.

Vascular dysfunction & structural abnormalities in Alzheimers Disease (AD) are known to contribute to the progression of the pathology & studies have tended to ignore the role of vasculature in AD progression. 3x Tg – AD mouse model of Ad is used to examine the individual cerebral vessels and the cortical vascular network across the lifespan.

The current cerebrovascular angioarchitectural analyses demonstrate progressive alterations in individual cortical vessels as well as the vascular network of the cortex. Impaired brain clearance mechanisms may result in accumulation of aberrant proteins that defines Alzheimers Disease. The water channel protein astrocytic aquaporin 4 (AQP4) is essential for brain amyloid β- clearance- but it is more abnormally expressed in AD brains. Another protein aquaporin 5(AQP5) is found to be abundant in salivary glands suggesting that it maybe a crucial factor in gland dysfunction associated with AD. So we can conclude that AQP5 is also a significant role player in AD pathology in addition to AQP4- representing a potential target for for the treatment of AD.

Recent research on anti-AD drugs has been focussed on multi target compounds. In respect to this seven novel hybrids (RIV-BIM) conjugating the active moiety of the drug Rivastigmine (RIV) with 2- isomeric hydroxyphenylbenzimidazole (BIM) units were developed & studied . While RIV assures the inhibition of Cholinesterases, BIM provides further appropriate properties such as inhibition of amyloid β peptide (Aβ) aggregation, antioxidation & metal chelation. So RIV-BIM hybrids seems to be the potential drug candidates for AD with multi target abilities.

High density lipoproteins (HDL) play a critical role in cholesterol homeostasis .

Apolipoprotein E (ApoE) particularly the E4 allele is a significant risk factor for Alzheimer's disease but is also a key HDL- associated protein involved in lipid transport in both the periphery & central nervous system. So for the first time evidence was proved that APO-E genotype – specific alterations in HDL particles in Alzheimer's disease & an association between HDL function, size and cognitive function.

The molecular basis of amyloid toxicity in Alzheimer's disease (AD) remains controversial. Amyloid β (Aβ) oligomers promote calcium influx, mitochondrial Ca2+ overload& apoptosis in hippocampal neurons in vivo & invitro- but the primary Ca2+ entry pathways were unclear. The expression of subunits of the NMDA receptor NR1/ NR2B in HEK2 in HEK293 cells lacking endogenous NMDA receptors restored Ca2+ responses to NMDA but not to Aβ oligomers. It was concluded that Aβ oligomers promote Ca2+ entry via amyloid channels & NMDA receptors. This may recruit distant neurons intertwisted by synaptic connections, spreading excitation & recruiting further NMDA receptors & voltage gated Ca2+ channels leading to excitotoxicity & neuronal degeneration in AD. Further, it was seen that, nasal Rifampicin halts the progression of Tauopathy by inhibiting the Tau oligomer propagation in Alzheimer brain extract.

Identification of disease related genes that are common between Alzheimer's & Cardiovascular disease using blood genome – wide transcriptome analysis in which prior knowledge were utilized to identify several candidate disease related gene (DRG) sets: protein protein interactions, transcription factors, disease gene relationship databases & single nucleotide polymorphisms. Selection of respective DRG sets for AD & CVD that shows a high accuracy for disease prediction in bulk & single cell gene expression datasets. Then gene regulatory networks(GRNs) were constructed from each of the AD & CVD DRG sets to identify the upstream regulating genes. Using the GRN's two common upstream genes were identified (GPBP1 & SETDB2) between AD & CVD GRN's. So it was identified that the potential AD & CVD related genes & common

hub genes between these sets which may help to elucidate the shared mechanisms between these two diseases. Sporadic Alzheimer's disease (AD) is a severe disorder of unknown etiology with no definite time frame of onset. Recent studies suggest that middle age is a critical period for the relevant pathological processes of AD. There is actually dysmaturation during early development of the brain- especially insufficient glial support as a possible first hit leading to neurodegenerative processes & AD pathology manifestation later in life. There is another evidence of neurovascular uncoupling in mild Alzheimer's disease through multimodal EEG- f NIRS (functional near infra red spectroscopy) & multivariate analysis of the resting state data. Diverse role of ceramide was established in the progression & pathogenesis of Alzheimers disease. AD is the most common neurodegenerative disorder – is associated with several pathophysisological features including cellular dysfunction, failure of neurotransmission, cognitive impairment, cell death & other clinical consequences. Advanced Research on the pathogenesis of AD has elucidated a mechanistic framework & revealed many therapeutic possibilities. Among the mechanisms, sphingolipids are mentioned as distinctive mediators to be associated with the pathology of AD. Reportedly, alteration in the metabolism of of sphingolipids & their metabolites result in the dysfunction of the mitochondria, autophagy, amyloid beta regulation & neuronal homeostasis which exacerbates AD progression. Considering the importance of sphingolipids – the role of ceramide, which is a bio active sphingolipid metabolite was discussed in context of its role in development of AD wherein it was found that a defect in the synthesis pathway of ceramide & its involvement in its dysregulation of homeostasis- which finally leads to AD. Furthermore, it was established the different therapeutics proposed to modulate the ceramide pathway to maintain the ceraminde levels & prevent the disease progression. Also, direct oral anticoagulants (DOAC's) for therapeutic targeting of Thrombin which is considered to be a key mediator of cerebrovascular & neuronal dysfunction in Alzheimer's disease. DOAC's block thrombin by inhibiting its activity(dabigataran) or production (FXa inhibitors eg: Apixaba, Rivaroxaban). Therefore, DOAC use could preserve vascular integrity & brain perfusion & they thereby, could counteract vascular driven neuronal & cognitive decline in AD. A conception for clinical investigation is presented focussed on DOAC treatment of patients with diagnosed AD in early stage & low risk of major bleeding. Biomarkers are the the primary tools for clinical research, diagnostics & therapeutic monitoring in clinical trials. They provide much insightful information & while they are not clinically used routinely- they help us to understand the mechanisms of this disease. AD biomarker discovery & development of cerebrospinal fluid(CSF), amyloid beta 1-42(Aβ42), total tau(T tau) & phosphorylated tau(p tau) biomarkers & imaging technologies to the next generation of biomarkers. Also high sensitivity assay platforms for CSF Aβ 4, T-tau, p-tau & blood analysis.The recently proposed Aβ deposition/tau biomarker / neurodegeneration or neuronal injury scheme might facilitate the definition of the biological status underpinning AD & offer a common language among researchers across biochemical biomarkers & imaging. Moreover, blood based biomarkers for AD that offer scaleable alternative to CSF biomarkers through cost saving & reduced invasiveness & may provide an understanding of disease initiation & development . The development of current ATN framework for diagnosing AD represented by seven biomarkers

- CSF Aβ1-42
- Amyloid PET
- CSFp-tau
- Tau PET
- CSF T-tau
- 18 F- flourodeoxyglucose (FDG_PET)
- MRI

Regarding core CSF biomarkers, decreased CSF Aβ1-42 reflects Aβ deposition or Alzheimer's pathology , increased CSF p-tau reflects abnormal tau & high CSF t-tau indicates neurodegeneration or injury. Neurofibrillary tangle related tau has been suggested as the principal stage AD biomarker indicating the disease progression level. In blood based biomarkers for AD ultrasensitive immunoassay techniques, single molecule array(SIMOA) has enabled the detection of extremely low concentrations of promising AD biomarkers in blood at picomolar levels. Mass spectrometry based assays proved to be superior over other assays with a good receiver operating characteristic area under the curve (ROC-AUC) for Amyloid PET status compared with ELISA & SIMOA assays. Recent plasma Aβ species measured using mass spectrometry coupled with immunoprecipitation have been introduced with a close correlation with CSFAβ 42/40 ratio & amyloid PET. More recently, a high resolution mass spectrometry (MS) based blood test for Aβ conformed to the standards of Clinical Laboratory Improvement Amendments (CLIA) . In addition the Precivity AD test for plasma LC-MS/MS assays for Aβ quantification and qualitative APOE isoform specific prototyping was completed in the first phase of the Plasma test for Amyloid Risk screening study for clinical use to evaluate individuals experiencing earlycognitive impairment. Dementia remains an extremely prevalent syndrome among older

people & represents a major cause of disability & dependency. Alzheimer's disease accounts for the majority of dementia cases & stands as the most common neurodegenerative disease. Since age is the major risk factor for AD – the increase in life span not only represents a rise in the prevalence but also adds complexity to the diagnosis. Moreover, the lack of disease modifying therapies highlights another constraint. A shift from a curative to a preventive approach is imminent & we are moving towards the application of personalized medicine where we can shape the best clinical intervention for an individual patient at a given point . This new step in medicine requires the most recent tools & analysis of the enormous amounts of data where the application of AI plays a critical role on the depiction of the disease- patient dynamics, crucial in reaching early / optimal diagnosis, monitoring & intervention. Magnetic resonance imaging (MRI) & positron emission tomography (PET) have made great strides in the diagnosis & understanding of AD. The choroid plexus (CP) located in each of the four ventricles of the brain – is formed by a monolayer of epithelial cells that surrounds a highly vascularized connective tissue with permeable capillaries. These cells are joined by tight junctions forming the blood cerebrospinal fluid barrier (BCSFB) which strictly regulates the exchange of substances between the blood & CSF. The primary purpose of the CP is to secrete CSF but it also plays a role in the immune surveillance of the CNS & in removal of neurotoxic compounds from the CSF. According to the recent findings the CP is also involved in the modulation of circadian cycle & neurogenesis . In diseases such as AD, the function of CP is impaired resulting in an altered secretory barrier, transport & immune function. c-Jun N terminal kinase (JNK) plays an important role in cell death caused by various stimuli. Because the isoform JNK3 is maily expressed in the brain – it is believed to play a pivotal role in various neurodegenerative diseases including AD & Parkinson's disease (PD)- which still lacks plausible therapeutics.

II. Conclusions:

While multiple mechanisms likely contribute to the etiology & progression of the neurodegeneration in AD- the pathogenic role of neuroinflammation is now well recognized & accepted. A sedentary lifestyle & unhealthy diet – can accelerate the aging process associated chronic low grade inflammatory process linked to neurodegeneration in AD. Lifestyle changes that incorporate longterm EE regimen CR/CR mimetics & nutraceuticals or a combination of these may ameliorate – inflammaging & its progression into AD. Remodelling – the aging gut microbiota – using prebiotics or fecal transplants is likely to dampen the proinflammatory milieu & modulate the neurochemical & neurometabolic signalling pathways of the brain & protect against neuroinflammation. As there is a huge potential for therapies that modulate the neuroimmune response in AD. It is important to define inflammatory stages – to correlate to each of the AD progression phase & clarify which processes are protective & which ones are detrimental – as well as identifying suitable time modes & sites of intervention which may facilitate a focussed & functional therapeutic approach to alleviate age related stress on the intracellular organelles – tissues & systems & delay AD progression as one ages.

CONFLICTS OF INTEREST:

It is declared that there is no competing financial interests or personal relationships that could have appeared to influence the work reported on the paper.

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