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Research Article

Key Transcription Factors Linking Macular Degeneration and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) and age-related macular degeneration (AMD) have certain pathologic features in common. Chronic oxidative stress and neuroinflammation result in aggregate protein deposits, extracellular drusen in AMD, extracellular and intracellular amyloid in AD, and intracellular tau in AD, and mitochondrial proteosomal pathway damage in both. Along with risk factors: aging, smoking, hypertension, hypercholesterolemia, obesity, arteriosclerosis, unhealthy diet, chronic anticholinergic use, and latent herpetic infection, three transcription factors, NRF-2 (nuclear factor-erythroid 2) and NFKB (nuclear factor kappa B) which regulate cellular detoxification from oxidative stress and innate cellular immunity, respectively, and PGC-1α (peroxisome receptor gamma coactivator), which is the master of mitochondrial biogenesis and antioxidant control, seem to play a major role in disease progression of AMD and AD . Neuropathology and protein marker changes related to imbalances in NRF-2, NFKB, and PGC-1α illustrate neurodegenerative and vision loses commensurate with NRF-2 and PGC-1α deficiencies and NFKB excess. Examining these transcription factors in more detail may provide insights into slowing the progression of AD and AMD.

Introduction

The global prevalence of AMD in 2020 is projected to be 196 million people [1] and that of Alzheimer's disease was 50 million in 2017 [2]. Chronic oxidative stress and neuroinflammation from aging, injury, and individual risk factors (smoking, hypertension, arteriolosclerosis, obesity, dietary indiscretion, chronic anti-cholinergic use, and latent infection) in AMD and AD contribute to toxic protein deposits, loss of homeostatic protein clearance, and progressive neurodegeneration [3-11].

Neuroinflammation also provokes persistent immune response, which participates in further brain and macular damage. However, studies using anti-inflammatory therapy in AD and in AMD have yielded small, mixed or inconclusive results [12-15].

Toxic protein accumulation: in AMD, drusen, (lipoprotein deposits between the basal lamina and the retinal pigment epithelial layer, RPE) and lipofuscin (from inefficient protein clearance) [3,4,13] and in AD, extracellular and intracellular amyloid and complement and intracellular tau, (because of breakdown of the blood-brain barrier from reactive oxygen species, inflammation, or local or systemic infection), may be slow burners in chronic inflammation and its sequelae [5,6,16] However, cognitive issues, (memory and learning) in AD may precede amyloid plaque and tau fibrillar aggregates by months or longer [5]. For that matter, in AMD despite impaired lysosomal degradation, lipofuscin accumulation, defects in the ubiquitin protein clearance, and mitochondria dysfunction [3], many ophthalmologists can attest to the fact that visual loss may take years to manifest itself clinically. So, the relationship of the protein deposits to the chronology of clinical AD and AMD is not quite linear.

Similarly, in AD, the ubiquitin, functioning as beta amyloid "gatekeeper", controlling beta amyloid traffic from intracellular compartments to the cell surface is affected by higher levels of beta amyloid cleaving enzyme (BACE) and affects amyloid levels and proteosomal stability and function [3]. So, both in AMD and AD declining mitochondrial function, proteosomal protein degradation and clearance can result in more profound aging and degenerative changes associated with greater homeostatic imbalance. (Figure 1) However, are these associated intracellular ageing breakdown phenomenon or root causes of AD and AMD?

(Figure 1) RPE, retinal pigment epithelium and neurons in AD, Alzheimer's disease and AMD, age related macular degeneration.

Mitochondria: e-chain, TCA cycle, ATP, Noxa A1 [NADPH], Ucp3, Calcium, Hi/Lo Energy, Respiration, Metabolism, Mito DNA < with age, Ox /Stress/Anti-oxidants, Mito proteins +lipids, Damage, Repair, Mitophagy, Autolysosome, Bcl2 (for Caspace and Apoptosis).

Miscoded, Misfolded, Aggregated proteins, Lipoproteins, lipofuscin, drusen (AMD), complement, Tau, amyloid, (AD) adducts, antibodies, autoantibodies, Autophagy Lysosome Pathway, Autophagosome, Lysosome,

Modifiers: (1) Sirtuins 1,2: up-regulator, down-regulator of acetylation/deacetylation and other epigenetic histone stabilizers; (2) Transcription
Factors: NRF-2, NFKB, and PGC-1a: major protective framework oxidative stress and inflammation.

Figure 1: RPE and Neurons in AMD and AD.

Top Blue Sphere: **Mitochonidria: Early Activities in Oxidative Stress and Inflammation**

Middle Blue Sphere: **Intermediate Activities in Oxidative Stress and inflammation**

Bottom Blue Sphere: **Key Modifiers of Chronic Oxidative Stress and Inflammation**

Lipofuscin is a highly cross-linked extracellular aggregate of oxidized proteins and lipids from mitochondrial damaged sites, which is not incorporated or degraded by proteasome or lysosomal enzymes but rather itself incorporates transition metals like iron. The iron through the Fenton reaction generates its own free radicals, which induce further retinal mitochondrial dysfunction, malondialdehyde, 4-hydroxynonenal (HNE) and advanced glycation products which enhance RPE aging and photoreceptor degeneration. [3]. In addition, lipofuscin proteins, such as malondialdehyde and HNE, which are markers of oxidative mitochondrial dysfunction, have been shown to provoke auto-immune inflammatory reaction in the retina [3, 17]. AD patients also have striking mitochondrial dysfunction, (increase in mitochondrial DNA levels) and vacuoles with lipofuscin in the neuronal cytoplasm [3,18]. Along similar lines in AD brains, malondialdehyde on electron microscopy formed "cap-like linear deposits" associated with intracellular neuronal lipofuscin [3,19].

In AD, oxidative stress markers, (lipid peroxidation, nitration, reactive carbonyls, and nucleic acid oxidation products) are elevated decades prior to amyloid deposition [3,20,21]. Increased isoprostanes (early products of unsaturated fatty acid oxidation) [3,22,23] and, in other studies, iron has been reported in the cortex and cerebellum of preclinical AD/MCI (Alzheimer's disease mild cognitive impairment) patients [3,24,25] in association with mitochondrial dysfunction [25]. As in AMD, patients with AD also seem to develop an early imbalance in iron homeostasis and mitochondrial dysfunction, [3,21-25] preceding advanced neurodegenerative change.

Thus, looking at AD and AMD from the standpoint of cumulative chronologic protein deposits of a toxic nature in the setting of mitochondrial dysfunction and impaired proteosomal clearance, there are striking similarities but as to the onset of cognitive and vision problems, it might be reasonable to view the signatures of three key protective transcription factors, NRF-2, (oxidative stress and inflammation), PGC-1α (drives mitochondrial biogenesis and antioxidant defense), and NFKB, (which controls innate immune response) for more detailed understanding of the chronology, genetics and epigenetic aspects of these diseases and their relationship to functional loss. (Figure 1) There is a recent literature with this approach, which will be the focus of this paper.

Materials and Methods

To gather data on molecular mechanisms of macular degeneration and Alzheimer's disease with respect to: definition, pathology, molecular structures of deposits, proteomics, transcription factor relationships, and homeostatic mechanisms individual and combination search meshes were run in pub med and or Google Scholar with the pertinent terms. In cases where there were differences of interpretation, additional papers were sought to try to reconcile these differences.

Results

PGC-1α and NRF-2 loss and AMD

In RPE cells, the NRF-2/ARE (nuclear factor erythroid 2/ antioxidant response element) regulates oxidative stress by, amongst other things, enabling nuclear antioxidant gene activity and antioxidant proteins [3,26]. Mice models with NRF-2 deficiency are more susceptible to oxidative damage, protein aggregation, and poor regulation of autophagy genes [27, 28].

Genetic ablation of NRF-2 and PGC-1α in mice has produced RPE (Retinal pigment epithelial) degeneration [4,29,30]. Knock out of both NRF-2 and PGC-1α also revealed profound parametric increases in: (1) ubiquitin, a key player in damaged protein removal, (2) 4-HNE, an important marker of oxidative stress, (3) damaged mitochondria, (higher numbers seen on transmission electron microscopy, TEM), (4) p62, which NRF-2 targets to reduce intracellular oxidative stress and inflammation, (5) autolysosome size (on TEM), which help remove damaged proteins, and (6) number of melanosomes, (RPE degradation products from reduced proteasome activity (as seen on TEM). [4] The insufficient rate of autophagic clearance of damaged proteins along with the higher ratio of dysfunctional mitochondria are significant contributors to AMD. [4,30,31] AMD severity has been correlated to mitochondrial DNA damage [30-32].

The PGC-1 family regulates mitochondrial: biogenesis, respiration, and antioxidant defense [33-35]. Down regulation or loss of PGC-1α increases mitochondrial damage. Up regulation increases anti-oxidant genes such as SOD 2 [33-35]. The net goal of PGC-1α is for mitochondrial homeostasis [33,35].

Thus, the Nrf-2/PGC-1α double knock out mice had additive pathological changes of each transcription factor deficiency mimicking the presentation of AMD. There was: intra- and extracellular deposit accumulation, increased lipofuscin, Bruch's membrane defects, immune cell invasion, damaged mitochondria, impaired autophagy, altered pigmentation, focal photoreceptor degeneration, and ERG b wave amplitude reduction (showing effect on vision) [4].

The role of the PGC-1α and Nrf-2 knockouts in delineating many of the crucial parameters of AMD does not belie the potential contribution of genome wide [36-39] and population studies [40] (and other mice knockout studies [41] illustrating the role of complement factor H and I and HTRA in attenuating or adding to the evolution of AMD in different settings (Figure 2). With all these genes and yet others, their relationship to age, ethnicity, epigenetics, individual penetrance and protein aggregation patterns is quite enigmatic and still evolving in our understanding of AMD. Diet and exercise and other epigenetic modifiers and CFH genes may have considerable individual sparing effects in the penetrance of AMD.

AD and AMD genes in common CFH (regulates complement) and APOE (regulates lipoprotein binding to target receptors. Transcription Factors: NRF-2, PGC-1α, and NFKB: Core antioxidant, Antinflammatory, and Innate immune responses.

AD, AMD Genome Associations

AD genes: Strongest Association: APOE 4, Clusterin, (binds amyloid and reduces amyloid fibril formation) Clathrin assembly protein. AMD genes most strongly associated: CFH (402H) protective gene, APOE 2, (risk factor: increases cholesterol in retinal pigment epithelial cells) HTRA (key role in reducing heat shock oxidative stress proteins).

AD, AMD proteins in common

AD and AMD protein deposits in common: Lipofuscin (mitochondrial-proteosomal defects result in deposits). Amyloid (misfolded protein thought responsible for AD, but also protective against Oxidative stress and infections).

Complement (innate immunity; defense against microorganisms, inflammation, And cell destruction).

Figure 2: Genetics and Proteomics of AD and AMD.

NRF-2 loss and AD

Although the brain expresses low basal levels of NRF-2, even subtle changes in NRF-2 related genes may have large impact on pathophysiological pathways of AD. For example, NRF-2-encoding NFE212 haplotypes influence AD progression [5,42].

Combining NRF-2 deficiency with both amyloidopathy and tauopathy in mice, Rojo et al made a model that would mirror NRF-2 knock out with a combination of both hallmarks of human AD. However, they indicated that it is not clear what the mutual relationship of amyloidopathy and tauopathy is or what the contribution of each is to the idiopathic or sporadic forms of AD [5].

Nonetheless, Rojo et al did observe that the hippocampus of the NRF-2 knockout with amyloidopathy and tauopathy exhibited greater levels of oxidative and pro-inflammatory markers than controls early on (within the first 6 months). They pointed out this might be similar to early cognitive impairment, from early oxidative and inflammatory stress (without amyloid and tau deposition) in human AD [5,43]. In the 6-month NRF-2 knockout mice (above), acquisition and retention memory (unable to retain memory of a swim platform) was impaired even without amyloid or tau pathology deposits [5,44].

In view of the high impact of well-established familial AD genes, (Apoe 4, APP. PS1 and PS2), in the population, NRF-2 deficiency, which may have a small prevalence in younger AD patients, where presumably there are higher levels NRF-2 as compared to the aged, there may be other epigenetic, genetic or homeostatic factors operative in the protective mode. However, in the aged, where NRF-2 declines, the consequences of MCI and early AD are more penetrant [5,45,46].

NRF-2 deficient mouse brain with amyloidopathy and tauopathy replicated gene pathway alterations found in human elderly and AD brains. For example, Gstm1 (detoxification and oxidative stress), Kras (protein signaling), and Wdfy1 (vesicular traffic and autophagy), all regulated by NRF-2 and involved in cell signaling and inflammation, were all down regulated in the NRF-2 knockout mice. They also found Zbtb21/ANF295 upregulated, which has been implicated in Down's syndrome and cognitive deficit. The genes studied were classified in functional clusters of biological processes by GOTERM_BP_FAT, which examines the significance of enrichment of functional annotations. The genes were then compared to three cohorts of old human brain and six cohorts of AD brain. All of the NRF-2 knock out mice gene pathways were found altered in human ageing or AD brains, but some of the elderly or AD brain pathways were not found in the knock out mice. This suggests an NRF-2 knock out-group transcriptomic gene participation in the pathological process of AD [5].

NRF-2 knockout brains had lower levels of reduced glutathione and higher levels of carbonylated proteins (adducts of 2,4 dinitrophenylhydrazine, DPNH) and lipid peroxides (malondialdehyde, MDA) than controls, which point to the consequences of less control of chronic oxidative stress in the knockouts [5]. Proinflammatory markers, IL6, COX2, and iNOS were increased in NRF-2 knockouts compared with controls, consistent

with the anti-inflammatory protective effect of NRF-2. Thus, both chronic oxidative and inflammatory stress, as well as aging, appear to be more prominent in absence of NRF-2 [5].

Kaplan-Meier survival rates for NRF-2 knockouts with amyloidopathy and tauopathy showed 50% of the knockouts dying before 12 months, similar in males and females, whereas, controls reached to twenty months [6].

These same knockouts showed increased brainstem glial activation (as evidenced by increased antibody, GFAP and IBA1 staining compared with controls). Thus, NRF-2 deficiency modified immune response [6].

Nine months old NRF-2 knockouts with amyloidopathy and tauopathy mice (of the above noted research) were treated with oral gavage with vehicle or DMF, (dimethyl fumarate, an anti-oxidative and immunosuppressive) 100mg/kg every other day for six weeks. Five days after the first administration the mice were subjected to double blind motor and novel object recognition tests for memory. This was repeated once every two weeks. mRNA levels of NRF-2 target genes were analyzed by qRT-PCR.

There was a statistically significant: (1) increase in the levels of NRF-2 knock outs with DMF gavage of Ngo1, Osgin1, and Gstm1 (three oxidative stress detoxification genes), (2) reduction of astrocytosis and microgliosis (using GFAP and IBA1 antibodies in hippocampus and brainstem neurons), (3) reduction of protein levels of inflammation (less pro-inflammatory COX2, NOS2), (4) increased motor scores, and (5) increased novel object recognition scores by 2-3 fold, all in DMF gavage treated NRF-2 knockouts amyloidopathy tauopathy mice versus vehicle treated. This would suggest not only the potential role of DMF for NRF-2 activation when it is deficient in AD, but also that brain oxidative and inflammation stress, which correlates to motor, memory and immune consequences might be attenuated from full expression over time in AD with the use of pro-NRF-2 stimuli such as DMF [6].

PGC-1α, Mitochondrial Biogenesis and AD

PGC-1α, which is found in tissues with high-energy demand [47,48], such as muscle and brain, exhibits decreased expression in the brains of AD patients [49,50]. PGC-1α forms a heteromeric complex with NRF-2 and other transcription factors [51] in response to environmental stress, temperature, and nutritional status, (including insulin resistance) and could displace repressor proteins such as histone de-acetylase [52] and induce gene activation for reactive oxygen species detoxification, such as superoxide dismutase 1 and 2, catalase and glutathione peroxidase [53] PGC-1α also modulates the expression of uncouple protein 2 and uncouple 3 (See Figure 1, Ucp3, under mitochondria) which are primers of reactive oxygen species formation [54,55]. Similarly, PGC-1α controls sirtuin 1 and sirtuin 3 which reduce reactive oxygen species formation [56-58].

Neurodegeneration and synaptic degradation in AD are strongly tied to impaired mitochondrial biogenesis [59]. Mitochondrial impairment is central to the progression of AD and neuronal apoptosis, [60,61] both from the standpoint of loss of energy metabolism and excess free radical formation and damage [62-66]. Several human and animal studies have correlated mitochondrial dysfunction and memory difficulties [67,68] In the aged brain, PGC-1α regulates the expression of sirtuin 3, which is an important factor in the process of aging. Patients with neurodegenerative diseases harbor low levels of PGC-1α, which leads to greater oxidative stress and mitochondrial dysfunction [69,70]. PGC-1α knockouts mice showed reduction of mitochondrial gene expression and neuronal dysfunction and others have shown that the presence of PGC-1α could improve mitochondrial dysfunction and cognitive function [71,72].

Thus, because of its manifold anti-oxidant, homeostatic metabolic, mitochondrial biogenesis roles as well as its co-opted protective gene activation roles, PGC-1α may play a significant role in the understanding of AD (Figure 2).

ω-3 Fatty Acids , NFKB and AMD

There are several studies [73-75] illustrating the protective role of long chain ω-3 fatty acids against oxidative stress and inflammation in the development of AMD. ω-3 fatty acids are comprised of linoleic acid, docosahexaenoic acid (DHA), and eicosapentaneoic acid (EPA). Linoleic acid (a short chain ω-3 fatty acid), found in e.g. flaxseed oil, is a dietary precursor to DHA and EPA and can be converted by humans to some extent to DHA, a long chain ω-3 fatty acid [73]. Otherwise fish intake provides DHA.

Higher levels of DHA are present in the retinal photoreceptor outer segments than any other tissue [76]. DHA is a central regulator of retinal membrane, visual cycle [77] transport and a precursor to the synthesis of other active molecules [78]. EPA regulates lipoprotein metabolism and suppresses inflammatory compounds that can damage Bruch's membrane and lead to choroidal neovascularization [79].

Resolvens and protectans are biosynthesized from ω-3 fatty acids EPA and DHA via cyclogenase-2 and are thought to be potent long acting anti-oxidative and anti-inflammatory molecules [80]. Neuroprotectin D, from the protectin D family has anti-apoptotic effects on oxidatively stressed retinal pigment epithelial cells [81]. NFKB protein, one of the cell's master responders to oxidative stress and immune defense [82] is retained in the cytoplasm in an inactive state, bound to inhibitory proteins IKBα, IKBβ, IKBϒ IKBε and Bcl3, also known as IKB. After oxidative stress, IKB kinase (IKK) is activated, which phosphorylates IKB proteins rendering them responsive to the ubiquitin system for protein degradation [83]. More important, however, the NFKB is moved to the nucleus where it forms activation complexes to promote various target genes which regulate acute and chronic inflammation, such as TNFα , IL-1, IL-2, IL-6, IL-8, IFNϒ, inducible NO synthase, adhesion molecules, cyclogenase-2 and CRP (c reactive protein, produced in the liver and elevated in the blood in response to acute inflammation) [82,83].

The ω-3 fatty acids can block key receptors, such as Toll 4, TNF, and prevent IKB kinase phosphorylation and attenuate exuberant NFKB transcription factor anti-inflammatory activity in RPE cells, (oxidative stress, protein misfolding and aggregation, mitochondrial/proteosomal overload, drusen, lipofuscin and

RPE/photoreceptor apoptosis) which lead to an aging macula and macular degeneration [73,84]. Thus, ω-3 fatty acids can act as a brake on the excesses of NFKB response to oxidative stress, inflammation, aging and dry AMD.

NVKB and AD

The recent failure of another anti-amyloid treatment in large phase III trials for AD has suggested that alternate hypothesis for neuro-protection are necessary [85]. Beta amyloid production as an antimicrobial peptide, following exposure to neurotoxic fungi, in cell lines, nematode and rodent models [86] may be a byproduct of latter pathway immune dysregulation rather than the disease process itself. Several genes involved in innate immunity and associated with an increase in AD speak to this counter point through NFKB [87] For example, late AD onset gene TREM2, which is required for microglial amyloid clearance, is suppressed in the hippocampus by NFKB [88]. CD33, which inhibits microglial beta amyloid uptake and clearance, activates NFKB in myeloid cells [89]. CR1, whose interaction with amyloid is uncertain, is activated by microglia and is associated with increased NFKB [90]. So NFKB levels or gene/protein pathways, (in addition to or in conjunction with those of amyloid may represent a more complete method for understanding AD) and as illustrated above, may vary according to microglial, beta amyloid, and protein clearance needs, but may also be under other alternate varied gene control for anti-inflammatory/oxidative stress activities (Figures 1& 2).

Thus, NFKB is the intra-cellular trigger sensitive point for manifold activators from aging, to oxidative stress, to bacterial lipopolysaccharides, to ionizing radiation, to growth factors, to glutamate, etc. which converge on IKK kinase and result in innate immune response. The NFKB entourage sets the stage for a variety of new pathways of exploration of AD [91].

In humans, overexpression of amyloid precursor protein APP is associated with late onset AD and increases the likelihood of early AD in Down's syndrome. Beta secretase, BACE 1, cleaves APP into amyloid monomers that go on to form oligomers and plaque in neurons and vessels. BACE 1 and NFKB are increased in brains with AD, and NFKB directly increases BACE and APP gene activity [92,93].

Apoe 4 gene, which codes for cholesterol transporting protein, and is the single largest gene risk factor for AD, acts as a transcription factor for regulating NFKB expression [94]. Curiously, in early AD, the somatosensory cortex may show upregulation of NFKB, but there is reduction of NFKB in areas of more mature plaque [95,96]. So, there is a variable dynamic in NFKB expression not only relative to the presence of pathology, but also related to the time of onset and the evolution of the AD changes.

In rats, NFKB expression increases in normal aging, leading to production of neurodegenerative pro-inflammatory COX-2 and iNOS enzymes [97]. However, using anti-inflammatory Lactobacillus pentosus, plantarum C29, suppresses NFKB and restores brain derived neurotrophic factor levels and memory [98]. In rats exposed to neurotoxin, NFKB induced pro-apoptotic increases in TNF and iNOS in the hippocampus [99].

In mice, inactivating anti-aging Sirtuin genes results in chronic NFKB over expression, which significantly reduces the lifespan [100] Age related NFKB activation leads (through the chronic inflammation in microglial cells) to among other responses, epigenetic suppression of GnRH genes (gonadotropin releasing genes) in the hypothalamus [101] So NFkB with its manifold activities from amyloid production and plaque formation to glial activation, and aging seems to be vital to neurological rebalancing against the challenges of chronic oxidative stress, inflammation and protein aggregation in the development of AD.

Cross Talk between NRF2 and NFKB

Frequent changes in the levels of oxidative stress and inflammatory response necessitate an ongoing dynamic in two key cellular transcription factors NRF-2 and NFKB. Pharmacological and genetic inquiries suggest that there is a purposeful cross talk between these transcription factors leading to positive and negative effects on target gene expression. The absence of NRF2 can raise NFKB activity leading to increased cytokine production, astrogliosis, demyelination, and neuronal cell death [102-104]. Aside from its regulatory role in NRF-2-ARE pathway (nuclear active response element), Keap1 can negatively regulate IKKβ, (an essential NFKB precursor) by blocking HSP90 (heat shock protein 90) binding to IKKβ and retain lower NFKB levels of activity [105].

Both NRF-2 and NFKB are also connected through β-TrCP, a component of the E3 ligase complex (responsible for clearance of toxic proteins to proteasomes). β-TrCP controls nuclear levels of NRF-2 [106,107] The same kinase that marks NRF-2 for β-TrCP binding, GSK3β, is also involved in NFKB DNA binding [108,109]. In addition, since β-TrCP regulates NFKB response to cytokines as well as inhibition of NRF2 transcription, it can have an up-regulation effect on NFKB and a down regulation effect on NRF-2 [110].

P62, another NRF-2 target gene, modulates intracellular anti-inflammatory and anti-oxidant activities. P62, acting as protein scaffolding, can increase NRF-2 activity by mediating autophagosomal breakdown of Keap1, the key NRF-2 regulator [111] However p62 also has the ability to activate TNFα, which is a key enabler of NFKB [112]. There are also other interactions of NRF-2 and NFKB [113]. Thus, the cross talk can result in the activity of both NFKB and NRF-2 or limit the activity of one in favor of the other.

Discussion

The development and use of NRF-2 and PGC-1α mouse knockouts to study AMD [4] and NRF-2 with amyloid and tau pathology knockouts to examine AD [5, 6], provide powerful tools in our understanding of NRF-2 and PGC-1α in neurodegenerative disease. In addition to investigating protein aggregation, autophagy, proteosomal clearance, mitochondrial dysfunction, immune reaction and genomic markers after oxidative stress and chronic inflammation, the knockouts were also monitored for vision (ERG in the AMD study [4]) and motor and memory [5,6] in the AD study. Similarities of the mouse knockout studies to each other as well as to their respective comparisons to human AMD and AD are intriguing.

The highest increase in protein aggregation and oxidative stress markers in the AMD NRF-2/ PGC-1α knock out study [4] was with the combination of NRF-2 and PGC-1α gene knockouts. In the AD knock out studies [5,6] NRF-2 itself (with tauopathy and amyloidopathy) yielded significant gliosis, motor, cognitive and neuroinflammatory changes. Also, in line with other animal models, memory and learning were severely impaired as early as 6 months, preceding the appearance of amyloid and tau deposits. NRF2 deficiency in mice was quite similar to transcriptomic features found in human AD brains [6,114]

The protective role of DMF in the NRF-2 deficient mice in reducing oxidative stress and inflammatory gene activity, astrocytosis and gliosis levels, and enhancing motor and memory scores was remarkable [6]. However, in other studies with DMF, the DMF mechanism of action has been attributable to: (1) alternate pathways independent of NRF-2 [115], (i.e.: interferon ϒ reduction, IL-17 producing CD4(+) cells and induction of anti-inflammatory M2 monocytes), (2) decreased synthesis of pro-inflammatory iNOS, TNFα, IL-1β and IL-6 and activation of microglia and astrocytes [116] and (3) dimethyl fumarate causes short-lived oxidative stress, which leads to increased levels and nuclear localization of NRF-2 and a subsequent increase in glutathione synthesis and its recycling in neuronal cells [117] Future investigation examining the effects of DMF as an anti-inflammatory agent in the NRF-2 and deficient NRF-2 setting is indicated.

SIRT1 is a quiet information regulator and the mammalian homolog of the nicotinamide adenine dinucleotide, NAD deacetylase. In addition to histones for epigenetic alterations in gene expression, SIRT1 targets include transcription factors such as NFKB and PGC-1α. In vitro and in vivo studies had revealed the beneficial role of SIRT1 in regulating neural progenitors, axon elongation, dendritic branching, synaptic plasticity and endocrine function. SIRT1 has been implicated in neuroprotection in AD and traumatic brain injury [118].

Although the role of NRF-2, PGC-1α, and NFKB has been discussed here in trying to understand a more broad genomic reach of transcription factors in AMD and AD, how gene activity evidenced through genome wide association or population studies, such as complement factor H or APOE, and even epigenetic modifiers and Sirtuins tie in with transcription factors is as yet to be elicited. It is possible that an individual's transcription factors act as a metabolic/energy framework to protect the individual through the oxidative and inflammatory challenges, (smoking, dietary, exercise, sleep, infection, and adverse inherited genes) and provide some measure of a dynamic re-balancing to sustain the organism.

Conclusion

Because of their over-arching presence in the landscape of the neuro-protective/neurotoxic terrain in AMD and AD, the transcription factors NRF-2, PGC1α, and NFKB represent an alternate approach to understanding these diseases. Whether the new ideas on management derive from re-tooling anti-oxidative stress players, (e.g. up-regulating NRF-2 and/or PGC-1α or their more relevant target genes) in AMD or resetting the pro-inflammatory and immune consequences of NFKB and e.g. TNF in early AD, more in depth research of the transcription factors activity in each disease will provide greater understanding of the complex details necessary for alternate therapeutic strategies.

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Conflicts of Interest

No conflicts of interest.

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