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Age-related alteration in HNE elimination enzymes

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ABSTRACT

4-hydroxynonenal (HNE, 4-hydroxy-2-nonenal) is a primary α,β-unsaturated aldehyde product of lipid peroxidation. The accumulation of HNE increases with aging and the mechanisms are mainly attributable to increased oxidative stress and decreased capacity of HNE elimination. In this review article, we summarize the studies on age-related change of HNE concentration and alteration of HNE metabolizing enzymes (GCL, GST, ALDHs, aldose reductase, and 20S-proteasome), and discuss potential mechanism of age-related decrease in HNE-elimination capacity by focusing on Nrf2 redox signaling.

1. Introduction

Aerobic organisms including human beings are inevitably exposed to oxidants (frequently referred as reactive oxygen species, including H_2O_2, $O_2^{\cdot-}$,·OH, NO, ONOO) produced from either endogenous (e.g., mitochondria and NADPH oxidases) or exogenous (ultraviolet, irradiation, air pollution, pesticides) sources. To defense the harmful effects of these oxidants, the antioxidant system evolved. Redox homeostasis or the balance of oxidant and antioxidant system is essential for physiological functions, and oxidative stress occurs when the oxidant burden surpasses antioxidant capacity. Oxidative stress causes damage to proteins, lipids and nucleic acid, and disturb normal cellular function, which can lead to cell death, depending on the intensity and persistence of the stress.

The aging process is accompanied by increased oxidative stress. This is probably due to a combined effect of both an increased generation of oxidants from dysfunctional mitochondria [1–4], increased expression/activity of oxidant-producing enzymes [5–14], and a decreased capacity of antioxidant adaptation/defense [15,16]. Oxidative stress makes a substantial contribution to the aging process, with its involvement in the development of a variety of cellular hallmarks of aging, including genomic instability [17], inflammaging (which is the chronic, sterile, low-grade inflammation that develops during aging) [18,19], telomere attrition [20], epigenetic alterations [21], loss of proteostasis [22], deregulated nutrient sensing [23], mitochondrial dysfunction [24], cellular senescence [25] and stem cell aging and exhaustion [26]. In addition, oxidative stress and inflammatory pathways interact, which promote and exacerbate respective damage. Furthermore, oxidative stress is implicated in the pathogenesis and progression of almost all age-related diseases, including Alzheimer's disease, cardiovascular diseases, chronic pulmonary obstructive disease, diabetes, cataract, and cancers [27–30].

During oxidative stress, a variety of electrophiles are produced, these include 4-hydrononenal (HNE), malondialdehyde (MDA), 4-oxo-2-nonenal and acrolein. These electrophiles, especially HNE, cause various biological effects and are major contributors to oxidative/electrophilic damage, including the pathophysiological changes in the aging process. This article summarizes the aging-related increase in HNE accumulation and discusses the underlying mechanism and intervention strategy.

2. HNE production and bio-effects

HNE is a major α, β-unsaturated aldehyde derived from the decomposition of peroxidation products of omega-6 polyunsaturated fatty acids, such as arachidonic acid and linoleic acid in plasma membranes [31–35]. HNE has two functional groups; i.e. the carbonyl (-HC=O) and the double bond (C2/C3, -C=C-) groups (Fig. 1). These two functional groups enhance the electrophilicity of the molecule so that it can readily react with macromolecules including lipids, nucleic acids, and proteins. Reaction with the carbonyl group produces rapidly reversible adducts such as Schiff bases with amines. In contrast, adduct formation by Michael addition to the double bond is relatively stable. Furthermore, the -OH group on C4 contributes to the partial positive charge on C3, which along with conjugation to the carbonyl increases reactivity at C3 with nucleophiles. The most rapid non-enzyme catalyzed Michael addition is by cysteine when it is dissociated to the thiolate form (S^-)

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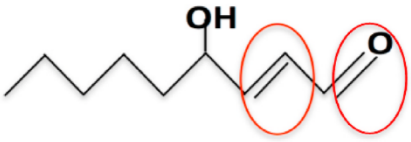

Fig. 1. HNE structure. The two functional groups are circled in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

producing a much stronger nucleophile than a thiol or amine. HNE production is increased in oxidative stress and thus frequently used as a marker of oxidative stress. By covalently binding to and modifying proteins, HNE mediates a range of biological effects including change of various signaling pathways [36,37], disturbance of mitochondrial function, protein synthesis and function, and cell dysfunction and cell death [38–40], depending on HNE concentration and the pathophysiological context. Although HNE functions as a signaling molecule at low concentration, as the agent of oxidative damage at high concentration it is a critical mediator of pathophysiology in aging and age-related diseases.

3. Age-related increase in HNE accumulation

As lipid peroxidation constantly occurs under physiological conditions, production of HNE is an ongoing process. Most HNE in cells is present in the form of HNE-protein adducts. These adducts are relatively stable and can be retained for several hours before being degraded [41,42]. Under physiological conditions, HNE and its protein adduct are present at very low concentration in plasma and tissues in the young [31,33,35,43–45]. With aging, free HNE and HNE-protein adducts in blood and tissues are increased (Table 1). For example, aging increases HNE significantly in the brain of old versus young mice (24 mo vs 6 mo) [46,47], and by 2–3 fold in the plasma and brain of old versus young human subjects [45,48]. Based on available evidence, HNE concentration in humans starts to increase at about 50 years old, and HNE concentration in tissues of the old can be as high as ~3 fold compared to that of the young adults. Due to differences in the application of uniform measurement methods, quantitative comparison across species, ages and tissues cannot be made based on the published literature, although the qualitative increase appears to be consistent.

Due to the multiple biological effects of HNE and its roles in oxidative damage, HNE is assumed to be an important contributor of aging-related pathophysiological changes. In addition, accumulating evidence suggests that increased HNE may play a critical role in causing and/or exacerbating the pathogenesis of many age-related diseases, including Alzheimer disease [49–51], cancers [52], chronic obstructive pulmonary disease (COPD) [53], cardiovascular diseases [54], and others [40,55]. In AD, for example, HNE can cause synaptic dysfunction and neuronal death through several pathways; by conjugating/inhibiting glutamate transporter (GLT-1), it can decrease glutamate uptake and result in excitotoxicity and death of neurons [56]; by modifying enzymes involved in glycolysis, the tricarboxylic acid cycle and ATP biosynthesis, HNE can also cause dysfunctional glucose metabolism and thus decrease ATP production in the brain [57], and consequently result in dysfunction of mitochondria and endoplasmic reticulum stress (ER) and lead to neuronal death [58]. Most studies on HNE and aging, however, have focused on the association but not the cause-effect relationship.

Nonetheless, the increase in HNE accumulation with aging suggests an insufficient or less efficient capacity to eliminate/remove HNE and HNE-protein adducts produced in the older. This could be due to both increased production of HNE and decreased elimination/removal capacity. Available evidence suggests both pathways are involved. Production of oxidants and HNE in aging was discussed above. In the following, changes in HNE elimination capacity with aging is discussed.

4. HNE elimination enzymes

Cells have evolved robust mechanisms to eliminate/remove HNE and HNE-protein adducts. Free HNE is metabolized through multiple enzymes including glutathione S-transferases (GSTA4-4 and A5-8) [68–71], aldehyde dehydrogenases (ALDHs) [72,73], and aldo-keto

Table 1
Aging-related change of HNE concentration.

Specie	Age	Sex	Tissues	Detection method	Major findings	Ref.
Drosophila	3–60 days	Male and female	Head and thorax	ELISA	HNE adduct significantly increased by about 2 fold in second half of adult life, then decreased	[44]
Wistar rats	7, 15, 22, and 30 weeks	Male	Blood	Gas chromatography-mass spectrometry	Protein-bound HNE in the blood was significantly increased with aging	[59]
Fischer 344 rats	7 mo vs 24 mo	Male	Serum	MALDI-TOF-Mass spectrometry, Western blot	Free HNE was increased from about 0.3 μM to 0.7 μM, HNE-protein adducts increased by 2–3 fold	[60]
Fischer 344/NNia x Brown Norway/ BiNia rat	6 mo vs 30 mo and 36 mo	Male	Heart	Western blot	HNE-protein adducts increased by 60% at 30 m, by 80% at 36 m	[61]
Fischer 344 X Brown Norway rats	6 mo vs 33 mo	Male	Heart	Western blot	HNE-protein adducts was increased by 60% at 30 m, by 80% at 36 m	[62]
C57BL/6 mice	6 mo vs 18 mo	Male	Brain	Colorimetric assay	HNE concentration was increased by 30%	[46]
C57BL/6 mice	6 mo vs 24 mo		Hippocampus	immunohistochemistry and western blot	HNE-protein adducts was increased by 3–4 fold	[47]
B6 mice	6 mo vs 25 mo	Female	Bones	ELISA	HNE-protein adducts increased by 2–3 fold	[63]
Human	18-84 y	77 males and117 females	Blood, plasma	HPLC	Plasma HNE concentration was increased from 68.9 ± 15.0 nmol/L in the young group (up to 30 yr old) to 107.4 ± 27.3 nmol/L in the old group (older than 70 yr)	[45]
C57BL/6	3 mo vs 15 mo	Male	Lung, heart, liver, brain	Western blot	HNE-protein adduct was increased by 2–3 fold	[64]
C57BL/6	3 mo vs 22–25 mo	Male	Liver and kidney	Western blot	HNE-protein adduct was increased by 1–3 fold	[65]
Wistar rat	3 d-21 mo	Male	Skin	Immunohistochemistry	HNE in 21 m was increased by 1.3 fold compared to 3 m.	[66]
SD rat	3 mo vs 18–20 mo	Male	Brain (cortex)	Western blot	HNE-protein adduct was increased by 1.8 fold	[14]
C57BL/6 and BALB/ c	2mo-24 mo	Male	Thymus	ESI/MS/MS	HNE was increased by 2 fold in thymus and 7 fold in thymocyte	[67]

reductases (AKRs) [74–76]. HNE-protein adducts are mainly degraded through 20S proteasome [77–79].

Michael addition of glutathione (GSH), catalyzed by GST alpha isoforms especially GSTA4-4 [69], is the predominant pathway of HNE metabolism [68,70,71,80] and responsible for at least 50% of HNE degradation in cells [71,81,82]. The HNE-SG product is primarily metabolized through forming mercapturic acid in the cell, and a portion of it (e.g., 40% in hepatocyte) is rapidly and efficiently transported out the cell [71] through multidrug resistance proteins [83,84]. Other pathways lead to HNE oxidation to 4-hydroxy-2-nonenoic acid (HNA) by ALDHs [72,73] or reduction to 1,4-dihydroxy-2-nonene (DHN) by alcohol dehydrogenases [72] and AKRs [74], which further conjugates with GSH to form HNA-SG or DHN-SG and subsequently degraded through mercapturic acid pathway [80]. The ALDH superfamily includes diverse enzymes involved in aldehyde metabolism [85], many of them, including ALDH1a1, ALDH2, and ALDH3a1, have a substrate preference for HNE [86]. AKR are a superfamily of NAD(P)H linked oxidoreductases that have more than 190 members and are present in various tissues [87].

With reduction, HNE loses its ability to conjugate with proteins [88]. Even though the metabolic removal of free HNE is efficient, 2–8% of the HNE in cells appears to form conjugates with proteins [68], which are mainly degraded through 20S proteasome [77–79].

5. Regulation of HNE elimination enzymes through Nrf2 signaling

NF-E2-related factor 2 (Nrf2) is the master transcription factor that regulates the expression of many genes involved in protection against oxidative damage and maintenance of redox homeostasis. Under basal conditions, Nrf2 activity remains low due to its constant degradation in the cytosol by 26S proteasome mediated through Keap1 and/or GSK3β/β-TrCP pathways. In response to oxidative stress, Keap1 and/or GSK3β/β-TrCP are inactivated and more Nrf2 escapes degradation [15,89], enters the nucleus, binds to the electrophile response element (EpRE) in gene promoters, and increases the transcription of target genes [15]. Details of the mechanism of Nrf2 activation can be found in review articles including [89–91].

Nrf2 signaling also regulates the cellular capacity to eliminate/remove HNE. In Nrf2 knockout mice, higher tissue HNE concentration (HNE-protein adducts) is observed under basal condition compared to age-matched wild type [92,93], and the increase of HNE in response to oxidative stress is accelerated [93–95].

Both basal and inducible expression of many enzymes involved in HNE elimination/removal are regulated through Nrf2 signaling. These include glutamate cysteine ligase (GCL) [96] and glutathione synthase [97], which synthesize GSH, the major nucleophilic compound used in the removal of HNE; GSTs [98,99] including GSTA4-4 [100]; AKRs including AKR1B1, 1B10, 1C1, 1C2, 1C3, and aldose reductase (AKR3) [76,101,102]; ALDHs including ALDH1a1, ALDH2, and ALDH3a1 [103]; and 20S proteasome [104–106]. In addition, many other antioxidant enzymes, which are indirectly involved in HNE metabolism by decreasing the original concentration of oxidants and lipid peroxidation, are also regulated by Nrf2 signaling; e.g., thioredoxin reductase [107], GSH peroxidase 2 [108], and peroxiredoxins [109,110].

The increase in Nrf2 activity and thus induction of Nrf2-regulated antioxidant genes is the most important cellular mechanism in defense against oxidative damage and maintenance of redox homeostasis. Similarly, the induction of HNE-elimination enzymes or the boost of HNE detoxification capacity in response to oxidative stress is critical for the protection against HNE toxicity. Interestingly, HNE itself is a potent activator of Nrf2 signaling and can induce the expression of Nrf2-regulated genes including those involved in HNE detoxification [96,111,112]. Thus, HNE, Nrf2 activation and the capacity of HNE detoxification form a negative feedback loop, and the alteration of any component in this loop may influence HNE concentration (Fig. 2).

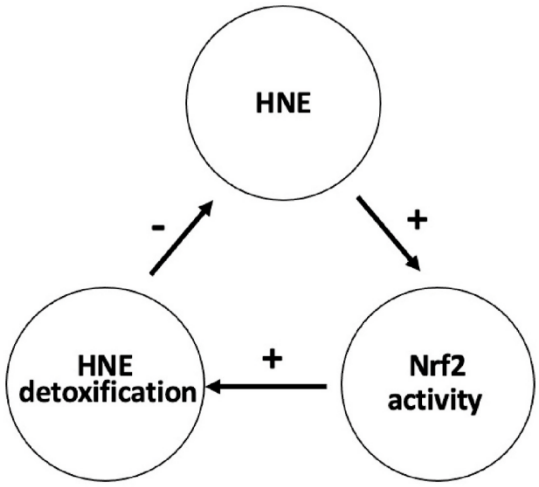

Fig. 2. Interaction of HNE, Nrf2, and HNE detoxification capacity. HNE activates Nrf2 signaling and increases the expression level of Nrf2-regulated antioxidant genes including that detoxify HNE, and subsequently decreases HNE level and protects against HNE associated damage.

6. Age-related alteration in HNE elimination capacity

With aging, expression of Nrf2 activity and expression of Nrf2-regulated genes are altered. Changes of the basal expression of Nrf2-regulated antioxidant genes with aging are inconsistent, with increased [66,113–116], decreased [65,117–120] or unchanged [121] being reported, depending on target genes, ages, species, and tissues/-cells. Nonetheless, studies have consistently observed an impaired induction of Nrf2 signaling in the old; i.e., the enhancement of Nrf2 activation and induction of Nrf2-regulated genes upon oxidative stressors declines with aging [15,114,116]. We demonstrated that tissues (lung, liver and cerebellum) of middle-aged mice (21 mo) expressed higher Nrf2 activity and higher expression of Nrf2-regulated genes (GCL, HO-1 and NQO1) compared with young adults (6 mo) under unstressed condition. Upon exposure to urban airborne nano-sized particulate matter (nPM), Nrf2 signaling is enhanced and expression of Nrf2-regulated antioxidant/detoxifying genes increased in young mice. However, in middle-aged mice, which already have higher nuclear Nrf2 activity, nPM exposure does not further activate Nrf2 signaling, nor induce the expression of Nrf2-regulated antioxidant/detoxifying genes [114,115]. Sachdeva et al. reported that retina pigment epithelial cells (RPE) from 15-mo mice expressed higher concentrations of Nrf2 target genes (NQO1, GCLM, and HO-1) compared with the RPE of younger mice (3 mo) under unstressed condition, and the RPE of older mice demonstrated impaired induction of Nrf2 signaling in response to oxidative stress induced with sodium iodate [122]. The phenomenon of aging-related increase in basal Nrf2 activity and decline in the enhancement of Nrf2 activation in response to oxidative stress is also observed in Drosophila [106,123], monkey [118], and primary human airway epithelial cells [124]. These evidences suggest an age-related increase in basal expression and decline in Nrf2-regulated antioxidant response.

Limited studies have purposely examined aging-related change of HNE-elimination enzymes. Recently, RNAseq has been widely used to determine the transcriptomic change with aging, and some data is accessible through Gene Expression Ominibus (GEO) dataset (https://www.ncbi.nlm.nih.gov/geo/). This provides a data source to analyze the change of HNE-elimination genes with aging. Based on some studies from this dataset, Table 2 briefly summarized age-related change in the basal expression of some (randomly selected) HNE-elimination genes regulated by Nrf2 signaling, including Gclc, Gsta4, Gstm2, Gstm4, Aldh2, Aldh3a1, Akr1b10, and three subunits of 20S proteasome

Table 2
Aging-related change of HNE-elimination genes in mouse tissues.

Gender	Age (m)	Tissues/cells	Age-related change	GES # and Ref.
Male	2, 9, 15, 24, 30 m	Liver, skin, blood, brain	**Gclc:** no change in brain, highest at 15 m and 24 m in other tissues. **Gsta4:** no change in brain, increase in other tissues **Gstm2:** highest at 15 m in liver, 30 m in blood, tend to increase in brain, no change in skin **Gstm4:** highest at 15 m in liver, 24 and 30 m in blood, no change in skin and brain. **Aldh2:** highest at 15 m and 24 m in brain, increase in other tissues. **Aldh3a1:** highest at 24 and 30 m in liver, 24 m in skin, 24 and 30 m in blood, and 15 m in brain **Akr1b10:** increase or tend to increase in all tissues **Psma1:** no change in skin and brain, highest at 24 m and 30 m in blood, highest at 15 m in liver. **Psmb5:** highest at 24 m and 30 m in blood, at 15 m in liver, at 2 m in skin, no change in brain. **Psmb6:** highest at 9 m in brain, at 24 m and 30 m in blood, at 9 and 15 m in liver, no change in skin.	GSE75192 [125];
Male	3, 20	Hippocampal microglia	**Gclc:** no change **Gsta4:** tend to increase **Gstm2:** increase **Gstm4:** no change. **Aldh2:** increase **Aldh3a1:** not detected **Akr1b10:** increase **Psma1:** tend to decease **Psmb5:** increase **Psmb6:** tend to decrease	GSE127542 [126]
Male	4, 22	Hippocampus	**Gclc:** increase **Gsta4:** no change **Gstm2:** no change **Gstm4:** no change **Aldh2:** tend to decrease **Aldh3a1:** increase **Akr1b10:** increase **Psma1:** tend to decease **Psmb5:** increase **Psmb6:** tend to decrease	GSE128925 [127]

Psma1, Psmb5 and Psmb6. Age-related alteration of the basal (mRNA) levels of these HNE-elimination enzymes varies, depending on gene, tissue and stage of the age. In general, an age-related increase or no change is observed for most of these genes. Obviously, more data is required to draw an absolute conclusion on the change of basal expression of HNE-eliminating genes with aging in specific tissue/cell.

As induction of HNE-eliminating enzymes is regulated through Nrf2 signaling, the decline in Nrf2 activation with aging would reduce the capacity to boost HNE detoxification in the old in response to oxidative stress, and subsequently result in exaggerated increase in HNE accumulation. Indeed, compared to the young, induction of HNE detoxification enzymes including GCL and 20S proteasome in the old is decreased upon exposure to oxidative stressors or Nrf2 activators [114–116]. The effect of Nrf2 deficiency on exaggerating HNE accumulation in oxidative stress is well demonstrated in Nrf2 knockout mice [93–95]. At present, studies on how the decline in Nrf2 activation contributes to aging-related increase in HNE accumulation under basal condition or in oxidative stress are limited.

In chronic nPM exposure models, HNE concentration was not increased in cerebellum and cerebral cortex in young mice, despite elevated inflammation [128,129], suggesting an efficient and adequate Nrf2-HNE detoxification response in the young. In contrast, old mice showed both exaggerated inflammation and lipid peroxidation in the brain upon zinc oxide nanoparticle exposure [130]. The RPE of old mice exposed to oxidative stressor (sodium iodate) exhibited greater lipid peroxidation than young mice, suggesting an inadequate protection against oxidative damage in the old [122]. In general, how the aging-related decline in Nrf2 activation contributes to HNE accumulation in the old remains unclear. In addition, aging-related change of HNE detoxification enzymes have not been examined systematically, including the changes of these enzymes in specific tissue and cell, its dependence on Nrf2 signaling, age at which the change starts, and strategy to reverse the change.

7. Potential mechanism of age-related decline in Nrf2 regulation system

The increase in basal Nrf2 activity with aging is expected as an adaptive response to increased oxidative stress. The decline in induced-Nrf2 activation with aging, on the other hand, indicates that 1) Nrf2-mediated defensive response to oxidative stress is impaired in the old, and 2) common pharmacological Nrf2 activators, which act by simulating oxidative stress, may not efficiently activate Nrf2 signaling in the old. Thus, restoring the ability to activate Nrf2 in the old is a major challenge in promoting resistance to oxidative stress.

7.1. Aging-related ceiling effect of Nrf2 activation

Multiple signaling pathways and molecules are involved in regulating Nrf2 activity, including the negative regulators Keap1-and/or GSK3β/β-TrCP in cytosol, and Bach1 in nucleus [131]. Based on evidence described above, we propose a model of aging-related change in Nrf2 signaling and the increase in HNE accumulation with aging (Fig. 3). In this model, the increase in oxidant stress and HNE accumulation during aging increases Nrf2 activity gradually through the oxidative inactivation of Keap1 and/or GSK3β/β-TrCP. Nrf2 activation reaches a plateau and is not further increased when the maximal inactivation of

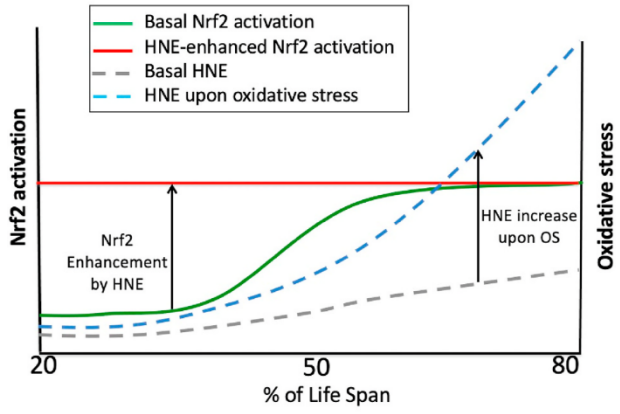

Fig. 3. Hypothetic model of aging-related decline in Nrf2 activation and accelerated HNE accumulation in response to oxidative stress. With aging, basal Nrf2 signaling is increased due to increase in oxidative stress (OS) and HNE concentration, but enhancement of Nrf2 activation upon OS (and HNE) reaches an apparent ceiling. This loss of Nrf2 enhancement permits accelerated HNE accumulation in the old upon OS.

Keap1 and/or GSK3β/β-TrCP occurs. In this model, the aging-related ceiling effect on Nrf2 activation cannot be altered by conventional strategies that target Keap1 and/or GSK3β/β-TrCP.

7.2. Bach1 and aging-related decline in Nrf2 activation

Bach1 belongs to the basic region leucine zipper protein family and is a transcription factor ubiquitously expressed [132–134]. By competing with Nrf2 for forming heterodimers with small Maf proteins and then binding EpRE, Bach1 down regulates Nrf2-regulated genes [135,136]. It is generally accepted that Bach1 acts as a brake in Nrf2 signaling and works together with Nrf2 to regulate the expression of gene expression, with the negative effect of Bach1 dominating over the positive effect of Nrf2 [137]. This is well demonstrated in models of Bach1−/− mice and Bach1 inhibition. Bach1−/− mice express higher Nrf2-regulated genes [138,139] and are protected against oxidative stress- and/or inflammation-implicated damage [132,140–143].

Bach1 expression is increased with aging [15,114,116,137], probably due to the aging-related increase in the basal Nrf2 activity, as Bach1 expression is regulated via Nrf2 signaling [144]. This suggests that Bach1 is potentially involved in the decline in Nrf2 activation and the increase in HNE accumulation with aging. Recently we demonstrated that silencing Bach1 by siRNA restored the activation of Nrf2 signaling and induction of Nrf2-regulated antioxidant genes (GCLC, GCLM, NQO1 and HO-1) in primary human bronchial epithelial (HBE) cells from donors aged 65 years and older [124]. In addition, Takada et al. found Bach1 knockout reduced aging-related increase in inflammation and the severity of aging-related and experimental osteoarthritis-like changes via increasing HO-1 [145]. These studies, although limited in numbers, suggest that Bach1 is a potential target to restore aging-related decline in Nrf2 activation. Further studies are warranted to confirm the role of Bach1 in age-related decline in Nrf2 activation and develop interventions.

8. Conclusion

The aging-related increase in HNE accumulation results from both the increase in its production and insufficient detoxification capacity in the old. Thus, to reduce HNE increase with aging, the ideal strategy is to both suppress its production and boost its detoxification. The former includes reducing risk factors that cause oxidative stress, which is difficult to accomplish, as some risk factors, such as chronological aging itself, are inescapable. As HNE detoxification is regulated through Nrf2 signaling, aging-related decline in Nrf2 activation is a barrier to boost HNE detoxification in the old. Restoring aging-related loss of Nrf2 activation can not only recover the boost of HNE detoxification capacity, but also help reduce HNE production and slow biological aging. Recent studies suggest that Bach1 is potential target to break through the apparent ceiling of Nrf2 activation in the old. However, many knowledge gaps exist for further insight of aging-related increases in HNE, the decline in Nrf2 activation, and strategies to reduce HNE and promote healthy aging. Future studies need to address important gaps needed for mechanistic analysis: At what age does HNE start to increase and the Nrf2-regulated HNE detoxification system lose its capacity to increase in response to oxidative stress? Which tissues/cells are affected? Also, does Bach1 inhibition restore Nrf2 activation and HNE detoxification in the old in vivo? Would Bach1 inhibition serve as a therapeutic intervention on age-related diseases? These questions remain to be answered.

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