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Differential hepatic protein tyrosine nitration of mouse due to aging – Effect on mitochondrial energy metabolism, quality control machinery of the endoplasmic reticulum and metabolism of drugs

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ABSTRACT

Aging is the inevitable fate of life which leads to the gradual loss of functions of different organs and organelles of all living organisms. The liver is no exception. Oxidative damage to proteins and other macromolecules is widely believed to be the primary cause of aging. One form of oxidative damage is tyrosine nitration of proteins, resulting in the potential loss of their functions. In this study, the effect of age on the nitration of tyrosine in mouse liver proteins was examined. Liver proteins from young (19–22 weeks) and old (24 months) C57/BL6 male mice were separated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and electroblotted onto nitrocellulose membranes. Proteins undergoing tyrosine nitration were identified using anti-nitrotyrosine antibody. Three different protein bands were found to contain significantly increased levels of nitrotyrosine in old mice (Wilconxon rank-sum test, $p < 0.05$). Electrospray ionization liquid chromatography tandem mass spectrometry (ESI-LC–MS/MS) was used to identify the proteins in these bands, which included aldehyde dehydrogenase 2, Aldehyde dehydrogenase family 1, subfamily A1, ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit, selenium-binding protein 2, and protein disulfide-isomerase precursor. The possible impairment of their functions can lead to altered hepatic activity and have been discussed.

1. Introduction

Aging is a universal phenomenon observed in all living organisms but the detailed physiological mechanisms implicated with aging is still not clear. Evidently, aging leads to progressive loss of functions of various organs accompanied by increasing mortality and disability. The effect of age observed in the structure and function of liver include increase in serum and biliary cholesterol, decrease in the rate of liver regeneration, and decreased ability to metabolize drugs. This leads to many health problems including coronary disease, gallstones and inability to tolerate pharmaceuticals. Unfortunately, high prevalence of different diseases such as arthritis, hypertension, cancer, diabetes and stroke due to aging leads to high use of medications in older people. Although there are distinct benefits of appropriate medications, the harmful effects of such medications in older people are well documented. In fact, the occurrence of adverse drug reactions correlates with age (for references see [1]).

Recent research has attempted to determine the physiological mechanism underlying the development of the aging process. One well-established theory of aging is the free radical theory originally proposed by Harman [2]. According to this theory, reactive oxygen species (ROS) such as superoxide radical, hydrogen peroxide, singlet oxygen and hydroxyl radical interfere with normal physiological functions by oxidizing proteins, lipids and other biomolecules. ROS are generated endogenously, as by product of metabolic processes, and exogenously, from pollutants, radiation, and other sources (for references see [3]).

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In addition to ROS, reactive nitrogen species (RNS) also oxidatively modify macromolecules and have been implicated in aging and age-associated diseases [4]. Like ROS, RNS are generated both endogenously and exogenously, and they include nitric oxide and peroxynitrite [4]. Nitric oxide is a naturally occurring messenger molecule that plays a key role in blood flow, inflammation, and neurotransmission, but is cytotoxic in excess [5]. It may be absorbed from exogenous sources such as cigarette smoke, or synthesized endogenously by neutrophils and macrophages [5]. In addition to auto oxidation, a reaction between nitric oxide and superoxide anion synthesizes peroxynitrite [4]. Although it has been proposed [6] that peroxynitrite leads to the formation of 3-nitrotyrosine, it must be mentioned that the importance of peroxynitrite in nitrotyrosine formation is somewhat contested [7,8].

In fact, Ischiropoulus [9] has suggested that tyrosine nitration is due to a variety of mechanism, rather than one simple pathway. Regardless of the mechanism, nitration of tyrosine is a key modification, observed in normal aging process and diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and heart failure [4,10,11]. Unfortunately, although protein tyrosine nitration can be involved in a number of pathological changes and associated with various diseases, very little is known about the specific protein targets so far.

The present study aims to find out the effect of RNS on the liver due to aging. The goal is to identify the proteins which are modified by RNS and the possible effect(s) of such modification on the function of liver.

2. Materials and methods

2.1. Young and old mouse liver sample collection

Young (19–22 weeks) and old (24 months) C57BL//6 male mice were obtained from Harlam Sprague Dawley, Indianapolis, IN, maintained as a part of the National Institute of Aging Rodent Colonies. The mice were rested for one to two weeks at the animal facility of the Joint Sciences Department of Claremont Universities Consortium in Claremont, CA. The animals were euthanized by cervical dislocation. Livers were collected, frozen immediately, and stored in liquid nitrogen until further use. Five old and five young livers were used.

2.2. SDS–PAGE and western blot analysis

The protein samples for livers of young and old mice were prepared as described earlier for kidney and heart [12,13]. Separation of the proteins was carried out by SDS–PAGE using linear gradient polyacrylamide gels (7.5–12.5% w/v, acrylamide, Bio-Rad Laboratories) and the proteins were transferred electrophoretically onto a nitrocellulose membrane. Following blocking and washing of nitrocellulose membranes as described earlier [14], the nitrocellulose membranes were treated with (i) anti-nitrotyrosine antibody (Millipore), (ii) HRP conjugated rabbit anti-mouse antibody and (ii) Chemiluminescence detection kit (Visualizer Western Blot Detection Kit). Digital images were captured and analyzed using a CCD-based AutoChemi Bioimaging system and VisionWorksLS software (UVP, LLC, Upland, CA). Statistical significance ($p \leqslant 0.05$) for differential expression between young and old samples was carried out using the Wilcoxon Rank Sum Test.

2.3. Staining of nitrocellulose membrane, band excision and trypsin digestion

The proteins were separated by SDS–PAGE, electroblotted onto nitrocellulose membranes and stained with Memcode protein stain (Bio-Rad Laboratories). Typically, for band excision and trypsin digestion, the nitrocellulose membrane to which proteins have been transferred electrophoretically, contained one lane of young liver sample, one lane of old liver sample, one lane of prestained molecular weight marker and nine lanes of pooled liver samples. The membrane was cut through the middle of the lane containing prestained molecular weight marker and the section containing two lanes of young and old samples was developed for detection of nitrotyrosine containing proteins for western blot analysis as described above. The remaining nine lanes were developed with Memcode protein stain reagent, a total protein stain (Bio-Rad Laboratories) according to manufacturer's instruction. The protein bands corresponding to the bands showing in upregulation in protein tyrosine nitration were excised, washed, cut into small pieces and digested with trypsin (Promega, 20 μg/mL in 50 mM NH_4HCO_3, pH 8.0). The membrane was incubated overnight at 37 °C. The samples were vacuum dried, 1 mL acetone was added and the supernatant was collected. The membrane was further washed two times with 2% acetonitrile with 0.1% formic acid, vortexed and the supernatant was collected. The above supernatants containing tryptic peptides were combined, dried and stored at −20 °C.

2.4. Tandem mass spectrometry of tryptic peptides, database searching and data processing

The tryptic digested proteins were analyzed by nano-ESI-LC–MS/MS using LCQ Deca XP Proteome X System (Thermo Electron Corporation, San Jose, CA). The conditions used were described in detail [13]. The mass spectrometer was set to acquire a full MS scan between 450 and 1800 *m/z* followed by a full MS/MS scan. All MS/MS spectra were searched with SEQUEST algorithm based Bioworks 3.3 (Thermo-Fisher) against a database created by extracting mouse entries from NCBI ftp site. Proteins with four or more spectra were accepted as positive identification.

3. Results

Western blot analysis identified three bands containing nitrotyrosine containing proteins (lanes 1–10, cf. Fig. 1). Total protein present in the same extract used for Western blot analysis was detected using Memcode protein stain (cf. Fig. 2). The top two protein bands formed a doublet while the bottom band was identified as a single band. They were labeled as TT (top–top), TB (top–bottom) and B (bottom) bands. As evident from Table 1, area density analysis and a Wilcoxon rank-sum showed a significantly higher level

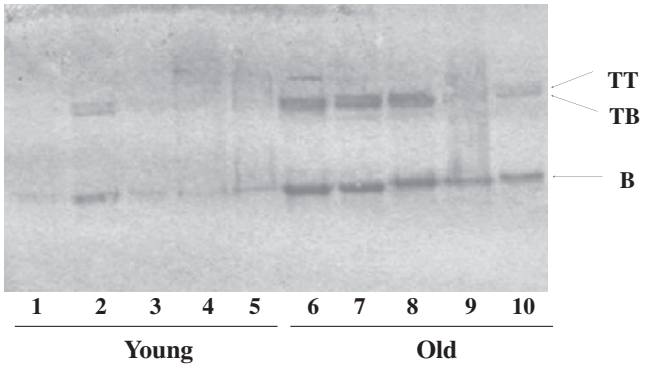

Fig. 1. Effect of aging on tyrosine nitration of proteins isolated from mouse liver. Lanes 1–5 are liver samples from five different young mice and lanes 6–10 are liver samples from five different old mice. Approx. 50 μg of protein was loaded onto each lane. Anti-nitrotyrosine antibody was used for detection of nitrotyrosine containing proteins. TT denotes top–top band, TB denotes top–bottom band and B denotes bottom band containing nitrotyrosine proteins.

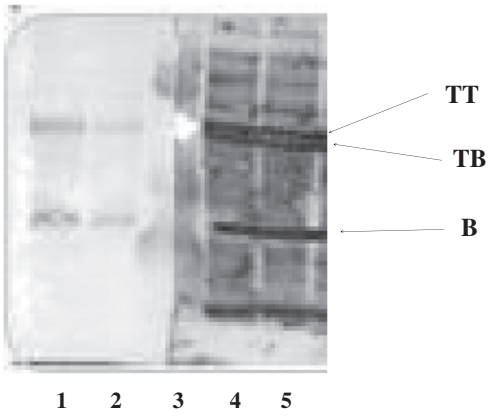

Fig. 2. Comparison of total hepatic proteins versus proteins undergoing tyrosine nitration due to aging. Lane 1 – pooled liver sample from five different old mice; lane 2 – pooled liver sample from five different young mice; lane 3 – mol. wt. standard; lanes 4 and 5 – total protein from young mouse liver stained with MemCode protein stain. The TT band, TB band and B band were excised and subjected to mass spectral analysis.

Table 1
Effect of age on the tyrosine nitration of proteins isolated from young and old mice.

Band	Fold increase (old vs. young)	*p* Value
Top–top (TT)	2.3	4.94×10^{-3}
Top–bottom (TB)	2.5	1.4×10^{-4}
Bottom (B)	3.2	5.80×10^{-7}

of tyrosine nitration of proteins in old mice when compared to young mice.

To identify the proteins which underwent higher level of nitration of their tyrosine residues due to aging, selected bands (TT, TB and B, Figs. 1 and 2) were excised, digested with tyrpsin and tryptic peptides were analyzed by LC–MS/MS. The proteins identified in these bands, total number of peptides identified, percentage of amino acid sequence covered, protein probability values, subcellular localization and the possible biological functions are summarized in Table 2A (TT band), Table 2B (TB band) and Table 3 (B band). As evident from Tables 2A, 2B and 3, protein disulfide isomerase was identified in TT band (Table 2A), ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit was identified in TB band (Table 2B) and four different proteins i.e. Aldehyde dehydrogenase 2, mitochondrial, Selenium binding protein 2, ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit and Aldehyde dehydrogenase family 1, subfamily A1 were identified in B band (Table 3).

4. Discussion

As evident from Fig. 1 and Table 1, three different protein bands (TT, TB and B) were identified to contain higher level of tyrosine nitration in case of old mice compared to young mice. Mass spectral analysis followed by tryptic digestion identified proteins such as PDIA MOUSE protein disulfide-isomerase precursor; ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit; Aldehyde dehydrogenase 2, mitochondrial; Selenium binding protein 2 and Aldehyde dehydrogenase family 1, subfamily A1 to be present in those bands.

The identification of the above proteins suggests important physiological pathways that are associated with the hepatic dysfunction due to aging. Possible alterations of the physiological pathways due to aging may involve mitochondrial energy metabolism, quality control function of the endoplasmic reticulum as well as metabolism of xenobiotics by liver and are discussed below.

4.1. Perturbation of the mitochondrial energy metabolism due to aging

The protein identified in the TT band showing increased tyrosine nitration was found to contain ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit. Interestingly, oxidative modification of ATP synthase due to aging have been observed by different investigators e.g. ATP synthase has been reported to be the target of malondialdehye modification in mouse heart mitochondria [15]. Age related changes in the rat liver mitochondrial F_0F_1 ATP Synthase activity have been reported by Guerrieri et al. [16]. Recently, nitration of specific tyrosine residues in F_0F_1 ATP synthase and loss of F_0F_1 ATP synthase activity in rat liver mitochondria has been reported [17]. However, no report is available on the oxidative damage of the enzyme from mouse liver. Our results provide evidence of oxidative damage of F_0F_1 ATP Synthase in mouse liver. As evident from different tissues and animal, this is an important observation indicating the ubiquitous nature of the oxidative damage caused by aging on this key enzyme involved in the production of cellular energy. In fact, deterioration of respiratory chain function is a major contributing factor to aging.

4.2. Perturbation of endoplasmic reticulum (ER) homeostasis due to aging

Proteins are correctly folded and post-translationally modified (such as disulfide bond formation, glycosylation, etc.) in the endoplasmic reticulum by ATP dependent chaperon mediated process followed by their transfer to the cell surface or to intracellular organelles. In order to carry out these functions, the ER contains different chaperones, foldases, lectins and carbohydrate processing enzymes. The formation of disulfide bonds is a critical step in the folding of a large number of proteins that are processed by the ER. Protein disulfide isomerase (PDI) is involved with the redox dependent folding and unfolding of proteins within the ER. PDI catalyzes native disulfide bond formation through thiol-disulfide oxidation, reduction and isomerization [18] and therefore plays a key role in protein folding and quality control in the ER. Tyrosine nitration of PDI can alter its activity. In fact oxidative damage of PDI due to protein carbonylation and decline in its activity has been observed earlier in mouse liver [19–21]. The present study provides

Table 2A
Protein identified in top–top (TT) band.

Protein	GenInfo identification No. (gi No.)	Number of peptides matched	% Amino acids covered	Protein probability	Subcellular localization	Function
PDIA MOUSE protein disulfide-isomerase precursor	129729	5	15.91	3×10^{-12}	Endoplasmic reticulum lumen, melanosome, cell membrane	Catalyzing the formation, rearrangement, and breakage of disulfide bonds – at high concentration it has chaperone activity-prevents aggregation of misfolded proteins

Table 2B
Protein identified in top–bottom (TB) band.

Protein	GenInfo identification No. (gi No.)	Number of peptides matched	% amino acids covered	Protein probability	Subcellular localization	Function
ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit	31980648	4	10.78	9×10^{-11}	Mitochondrion inner membrane	Produces ATP from ADP

Table 3
Proteins identified in the bottom (B) band.

Protein	GenInfo identification No. (gi No.)	Number of peptides matched	% amino acids covered	Protein probability	Subcellular localization	Function
Aldehyde dehydrogenase 2, mitochondrial	6753036	7	18.69	8×10^{-10}	Mitochondrion matrix	Alcohol metabolism and ethanol degradation
Selenium binding protein 2	9507079	4	14.19	1×10^{-9}	Nucleus, cytoplasm	Involved in sensing reactive xenobiotics in the cytoplasm
ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit	31980648	9	24.39	3×10^{-9}	Mitochondrion inner membrane	Produces ATP from ADP
Aldehyde dehydrogenase family 1, subfamily A1	85861182	4	10.78	8×10^{-6}	Cytoplasm	Oxidation of aldehydes – substrate preference for 4-hydroxynenonal (4HNE), malondialdehyde (MDA) and retinaldehyde (RA) – also detoxifies certain drugs

evidence of additional oxidative damage of PDI due to formation of nitrotyrosine.

Protein folding in the oxidizing environment of the ER is an energy-requiring process (for references, see [22]). Due to possible loss of ATP synthase activity and PDI, there will be impairment of the function of the endoplasmic reticulum which in turn will hinder the post translational modification of various proteins that may be necessary for the proper functioning of the liver.

4.3. Perturbation of the metabolism of xenobiotics due to aging

We have also identified aldehyde dehydrogeases in bottom band (B band) which shows increased level of tyrosine nitration due to aging. Aldehyde dehydrogenases have broad substrate specificity. Although distributed in different tissues, these enzymes have the highest concentration in the liver. This group of enzymes catalyzes the oxidation (dehydrogenation) of aldehydes to carboxylic acids. Aldehydes are common products of xenobiotic metabolism. Oxidation of aldehydes is considered to be a detoxification reaction, since aldehydes are generally reactive molecules. There are different classes of aldehyde dehydrogenase enzymes in mammals, and two different classes, ALDH1 and ALDH2, play most important roles in the oxidation i.e. detoxification of aldehydes. The bottom band (B) which show increase in the tyrosine nitration contain both these forms of the enzymes. This can cause alteration of their activities which in turn can have adverse consequence on drug metabolism ability of an individual.

Although we have detected two different forms of aldehyde dehydrogenase in bottom band (B) with higher tyrosine nitration level, it was found that ALDH activity increases with age in male mouse liver and is influenced greatly by sex, genotype and subcellular fraction studied [23]. In case of rat, no significant difference was found for alcohol dehydrogenase activity of the young and old rat liver [24]. Although we may expect decrease in alcohol dehydrogenase activity due to tyrosine nitration, it is quite possible that such anticipated decline in activity may be overcome by increased expression of this enzyme in the liver due to aging. In fact, increased expression of ALDH2 in rat liver has been reported [25]. Such increased expression may counteract any possible decline in the activity of the enzyme(s) due to oxidative damage. In addition, we found the tyrosine nitration of two different forms of aldehyde dehydrogenase. The report on the activity of aldehyde dehydrogenase is the measurement of the activity of all different forms of the enzyme. Although nitration can lead to loss of activity of certain subtypes of aldehyde dehydrogenase, increase in activity in other forms can counteract that effect and even can lead to overall increase in activity. In addition, it has been observed earlier that oxidative damage may or may not lead to loss of activity of an enzyme [15].

In addition to aldehyde dehydrogenase, we also identified the presence of selenium binding protein 2 in the bottom band (B). It is known that this particular protein plays important role in binding with xenobiotics such as acetaminophen and involved in hepatotoxicity [26–28]. It is possible that the nitration of tyrosine residue of selenium binding protein 2 may play a significant role in hepatotoxity due to acetaminophen. Increased expression of the protein as observed in some other mouse organ such as kidney [13], may be helpful to counteract the altered activity of SBP2 due to oxidative damage. However, it will be interesting to study differential expression of this particular proteins due to aging (if any) in the mouse liver as well.

It is worth mentioning that since we found a mixture of proteins present in the bottom band (B), it is quite possible that all or some of these proteins have undergone altered tyrosine nitration level due to aging.

We compared the theoretical mol. wt. and the experimental mol. wt. of the proteins identified in three different bands (data not shown). While the proteins identified in TT and TB bands had their molecular weight comparable to their theoretical molecular weight (data not shown), the bands identified in the B band, had significantly lower mol. wt. (<50%) compared to the theoretical mol. wt. and was probably due to proteolysis. Earlier studies on proteolytic degradation of tyrosine nitrated proteins has been reported [29]. In the present investigation, aldehyde dehydrogenase 2, mitochondrial (theoretical mol. wt. 56,502 kDa), selenium binding protein 2 (theoretical mol. wt., 52,595 kDa), aldehyde dehydrogenase family 1, subfamily A1 (theoretical mol. wt. 54,433 kDa) were detected only in the B band (mol. wt. approx. 27,000 kDa) suggesting possible proteolysis of these proteins. However, PDIA MOUSE protein disulfide-isomerase precursor (theoretical mol. wt. 57,108 kDa) was detected only in the TT band and ATP synthase, H^+ transporting, mitochondrial F1 complex, β subunit

(theoretical mol. wt. 56,266 kDa) was detected in the TB band as well as B band. In our opinion, this is possibly due to preferential proteolytic cleavage of some particular nitro tyrosine proteins compared to others.

In summary, we have observed higher level of tyrosine nitration of several proteins in the liver which suggest their possible role in age associated hepatic dysfunction. Future immunoprecipitation studies using anti-nitrotyrosine antibodies and separation of the immunoprecipitate by two dimenstional gel electrophoresis prior to their mass spectrometric identification may be helpful in further identification of protein targets of tyrosine nitration due to aging.

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