The roles of NFE2L1 in adipocytes: Structural and mechanistic insight from cell and mouse models

Suping Ren, China Medical University  
Yiying Bian, China Medical University  
Yongyong Hou, China Medical University  
Zhendi Wang, China Medical University  
Zhuo Zuo, China Medical University  
Zhiyuan Liu, China Medical University  
Yue Teng, Harbin Medical University  
Jingqi Fu, China Medical University  
Huihui Wang, China Medical University  
Yuanyuan Xu, China Medical University

Only first 10 authors above; see publication for full author list.

Journal Title: Redox Biology  
Volume: Volume 44  
Publisher: Elsevier Inc | 2021-08-01, Pages 102015-102015  
Type of Work: Article | Final Publisher PDF  
Publisher DOI: 10.1016/j.redox.2021.102015  
Permanent URL: https://pid.emory.edu/ark:/25593/vm003

Final published version: http://dx.doi.org/10.1016/j.redox.2021.102015

Copyright information:  
© 2021 The Authors

This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed December 6, 2023 12:22 AM EST
The roles of NFE2L1 in adipocytes: Structural and mechanistic insight from cell and mouse models

Suping Ren a,b, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Ward b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yanyan Chen e,d, Yanyan Chen a, Huihui Wang a, Yongyong Hou a, Suping Ren a, Yiying Bian a, Yongyong Hou a, Zhendi Wang a, Zhuo Zuo a, Zhiyuan Liu a, Yue Teng b, Jingqi Fu c, Huihui Wang c, Yuanyuan Xu c, Qiang Zhang d, Yan...
Following translation of Nfe2l1, multiple topovectorial processes facilitate selective post-synthetic processing of NFE2L1 in different tempo-spatial subcellular locations from the endoplasmic reticulum (ER) to the nucleus. Various genetic loss and gain of function studies of NFE2L1 over the past decades have shown that NFE2L1 has profound roles in adipose biology involving adipogenesis, lipid and glucose metabolism, thermogenesis, oxidation-reduction and proteasome homeostasis [11–14]. Besides, a single nucleotide polymorphism (SNP), rs3764400, occurring in the 5′-flanking region of the human NFE2L1 gene appears to be associated with obesity in humans [15, 16]. Thus, the study of NFE2L1 function in AT is a scientifically attractive theme with bona fide significances in normal and abnormal function.

Herein, we review data derived from cell-based studies and gene knockout (KO) mice to help synthesize the current understanding of NFE2L1 and the molecular mechanisms underlying its regulation and actions in AT biology. Further, we attempt to shed light on the isoform-specific roles of NEF2L1 in adipogenesis and adipocyte function and provide a novel insight into prevention and treatment of metabolic disorders involving AT.

2. Basics of NFE2L1 genetics and molecular biology

NFE2L1 is a member of CNC-bZIP protein family that is characterized by a highly conserved CNC-domain and a bZIP domain required for dimerization and DNA binding. NFE2L1 acts as an obligate heterodimer in formation with small musculoaponeurotic fibrosarcoma oncogene (Maf) proteins, such as MafG, MafK and MafF, for binding to DNA [17–20]. In addition, ATF/CREB proteins and c-Maf are potential partners of NFE2L1 as well [21]. NFE2L1 plays a central role in transcriptional control with genes harboring the NF-E2/AP1-like antioxidant response element (ARE)/electrophile responsive element (EpRE) site [2, 17, 19, 22, 23]. The downstream genes typically involve antioxidant response, proteasome homeostasis, genetic stability, mitochondrial respiration, inflammation, lipid metabolism and cell differentiation [2–5].

2.1. DNA structure and transcripts of mouse Nfe2l1

Based on the newest version of Ensembl Genome Browser (http://asia.ensembl.org/index.html), the mouse Nfe2l1 gene maps to the distal end of chromosome 11 [24], spans 12,554 bp DNA, and is divided into 10 exons (Fig. 1) [24]. According to the database, alternative
splicing and selective use of translation initiation codons give rise to 12 transcripts (splice variants), resulting in at least two long protein isoforms (L-NFE2L1) containing 741 and 742 amino acids (aa), as well as two short protein isoforms (S-NFE2L1) containing 453 and 583 aa [25, 26]. To distinguish these isoforms, the terminology NFE2L1-742, -741, -583 and -453 are used throughout this review.

2.2. The structural domains of mouse NFE2L1

Although the exact origin of different NFE2L1 isoforms is not conclusively known, the comparison of their structural domains helps elucidate or predict their functions, regulatory relationships and mechanisms of expression and activation.

L-NFE2L1 contains nine discrete structural domains, which are NTD (N-terminal domain), AD1 (acidic domain 1), NST (asparagine/serine/threonine), AD2, SR (serine-rich), CNC, bZIP and Neh3L (Nrf2–ECH homology 3-like) and Neh6L, respectively. These domains dictate the selective post-synthetic processing of NFE2L1 to yield multiple polypeptide isoforms with distinctive and even opposing functions in regulating target gene expression (Fig. 2) [27–33]. The bZIP domain of

Table 1

<table>
<thead>
<tr>
<th>Basis of nomenclature</th>
<th>Nomenclature</th>
<th>Position on SDS PAGE/NuPAGE (kDa)</th>
<th>Amino acid length (aa)</th>
<th>Synonyms</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originally discovered and named</td>
<td>NFE2L1 [24]</td>
<td>65 [24]</td>
<td>741 [24,43]</td>
<td>Nrf1a [40], Nrf1b [2], Nrf-1 [60], p120 Nrf1 [81]</td>
<td>A full-length isoform yielded by the first translation initiation signal within the main open reading frame of alternatively spliced mRNA transcripts [38]</td>
</tr>
<tr>
<td>Nrf1 [105]</td>
<td>120 &amp; 110 [105]</td>
<td>741 [105]</td>
<td>NFE2L1 [24], Nrf1a [40], Nrf1b [2], Nrf-1 [60], p120 Nrf1 [81]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nrf1a [40]</td>
<td>120 &amp; 110 [40, 105]</td>
<td>741 [105]</td>
<td>NFE2L1 [24], Nrf1a [2], Nrf-1 [60], p120 Nrf1 [81]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P120 Nrf1 [45]</td>
<td>120 [45]</td>
<td>741 [6]</td>
<td>NFE2L1 [24], Nrf1b [40], Nrf-1 [60], Nrf1 [105], Nrf1b2 [30,106], p95 Nrf1 [81]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nrf1b [40]</td>
<td>95 [40], 100 [23]</td>
<td>583 [40]</td>
<td>Nrf1b2 [30,106], p95 Nrf1 [81]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aa, amino acid; LCR-F1, Locus control region-factor 1; MW, molecular weight; NFE2L1, nuclear factor-E2-related factor 1; Nrf1, NF-E2 related factor 1; TCF11, transcription factor 11. The symbol ~ refers to approximate.
NFE2L1 is located near the carboxyl terminus of the protein characterized by heptad repeats of leucine and hydrophobic residues within an amphipathic helical domain of 40 aa, and is preceded by 30 aa region which is rich in arginine and lysine residues [26]. N-terminal to the bZIP domain is a highly conserved 43 aa domain referred to as the “CNC” domain after the Drosophila cap-n-collar protein, which is not present in JUN, FOS or other bZIP proteins. The CNC and bZIP enable NFE2L1 to bind DNA [34]. The Neh3L region located in the C-terminal domain (CTD) at the carboxyl-end of the NFE2L1 polypeptide negatively regulates NFE2L1. AD1 and AD2 near the N-terminus are separated by NST. The SR domain located near the CNC motif of NFE2L1 positively regulates NFE2L1 but all are negatively regulated by the Neh6L domain [29, 32, 35]. The NTD determines the membrane topology of NFE2L1 [27].

### 2.3. Protein isoforms of mouse NFE2L1

The single Nfe2l1 gene can be transcribed via alternative mRNA splicing with different initiation signals. Following translation, resulting proteins undergo post-translational processing to give rise to multiple proteoforms with different length and modifications such as phosphorylation and glycosylation [23, 36]. Thus, different isoforms of NFE2L1 migrate distinctively on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) thereby displaying multiple bands with various molecular weights. Certainly, the variations of NFE2L1 on SDS-PAGE may also impacted by many other experimental factors, including the antibodies used, polyacrylamide concentration, pH value, buffer and detergent type [8, 31, 37]. Thus, given that NFE2L1 is produced and degraded in a complex way, it is easy to see confusion arising regarding the correct migratory pattern and nomenclature of different isoforms of NFE2L1. As shown in Table 1, we attempt to summarize the nomenclature of various isoforms of mouse NFE2L1.

Based on the Ensembl database, four major isoforms of NFE2L1 in mice have been predicted. While the L-NFE2L1-742 is predicted to be different from L-NFE2L1-741 at the 640th to 742nd aa region, there are no published data to describe its distribution and exact function. The L-NFE2L1-741 (also termed Nrflα or Nrflαx in literature) is derived from an alternatively spliced mRNA missing exon 4 that is expressed in human transcription factor 11 (TCF11) [2, 26, 38–40]. This long isoform yields multiple bands on SDS-page with apparent MW of 140 kDa to 25 kDa via selective post-translational processing [30–32, 40]. The S-NFE2L1-583 isoform (also known as Nrflβ) is generated through an alternate promoter and contains a unique N-terminus encoded by an alternate first exon, which has an apparent MW of approximately 100 kDa on SDS-page [40–42]. The S-NFE2L1-453 isoform, also known as locus control region-factor 1 (LCRF1), p65Nrfl or Nrflβ, is encoded by an alternate transcript as documented in the Ensembl database or derived from internal ATG codon located in the transcripts encoding L-NFE2L1 [26, 35]. It lacks the N-terminal AD1 with an apparent weight of 65 kDa on SDS page [23, 30, 35, 43, 44]. Although S-NFE2L1-453 exhibits a weak transactivation activity [32, 42, 44], it was thought to be a significant dominant negative regulator of ARE-driven gene transactivation against L-NFE2L1 and/or NFE2L1 [32, 45]. In addition to the isoforms predicted by this database, other proteoforms have also been described [30, 31]. Some smaller isoforms of NFE2L1, known as Nrflγ (NFE2L1-325) and Nrfl6 (NFE2L1-194) of 36 kDa and 25 kDa, respectively, can be produced by the potential in-frame translation, as well as the selective endoproteolytic processing of longer NFE2L1 proteins [31, 32]. They can function as dominant inhibitors to down-regulate expression of NF-E2/AF1-like ARE-driven genes [32].

However, our current understanding of the expression, function, and tissue distribution of these various isoforms of NFE2L1 is woefully incomplete and inconsistent. In mice, so far as is now known, NFE2L1-741 and -742 regulate cellular adaptive antioxidant response [5, 46, 47] and are versatile in their essential roles for proteasome homeostasis [6, 7, 8], obstruction of adipogenesis [11], negative regulation of macrophage activation and M1 polarization [4]. They can also protect bone marrow-derived mesenchymal stem cells (MSCs) against arsenite-induced cytotoxicity via suppression mTRos in addition to facilitating cellular arsenic efflux [6]. NFE2L1-583 is targeted to the nucleus where it activates ARE-genes [40]. In contrast, NFE2L1-453 is a dominant negative regulator of ARE-mediated transcription in mouse [45]. Moreover, Zhang et al. have identified differential expression profiles of distinct target genes regulated by NFE2L1-741, -453, -325 alone or in their cooperation, respectively [36]. NFE2L1-325 as a putative dominant-negative inhibitor is likely to interfere with the functional assembly of active transcription factors (NFE2L1-741, NFE2L1-453, and NFE2L2), leading to down-regulation of several key genes, some of which are up-regulated by NFE2L1-741 and -453 [27, 29, 31, 32].

### 2.4. The regulation of NFE2L1

In order to act against a variety of cellular stresses, NFE2L1 is tightly regulated at several levels through distinct mechanisms. As shown in Fig. 3, after translation, L-NFE2L1 is inserted into the ER via the un cleavable NHB1 sequence [28]. Subsequently, the NHB2-connecting portions of the nascent polypeptide are translocated into the ER lumen, where the NST domain is N-glycosylated so as to become an inactive NFE2L1 glycoprotein [33]. When NFE2L1-dependent stress
L-NFE2L1 by catalyzing its polyubiquitination. Meanwhile, in the de-GlcNAcylation, phosphorylation. A variety of enzymes are identified before being translocated into the nucleus, the isoforms may undergo unidentified cytosolic protease, which may be the 26S proteasome. Lower doses of proteasomal inhibitors, it can also be suppressed by proteasome. It is noteworthy that there are paradoxical effects of proteasomal inhibition. In the nucleus, the two distinct mechanisms regulating L-NFE2L1 transcriptional activity. In the nucleus, β-TrCP and HRD1-dependent degradation is required; the ER-protected transactivation domains of β-TrCP, which is expressed in neuronal and glial precursor cells, results in motor ataxia and neurodegeneration, as well as chromatolysis in the spinal cord [67]. Kim and colleagues disrupted Nfe2l1 specifically in osteoblasts [Nfe2l1(O−)−KO] using Col1a2-Cre mice. The resulting Nfe2l1(O−)−KO mice show decreased bone size, trabecular bone, peak bone mass and mechanical strength, indicating that Nfe2l1 is involved in regulating osteir expression, osteoblast differentiation, and bone formation [68]. To investigate the role of Nfe2l1 in regulating pancreatic β-cell in vivo, we developed a line of mice where β-cell Nfe2l1 was targeted using Ins2-Cre mice. It was found that deficiency of Nfe2l1 in pancreatic β-cells disrupts glucose metabolism and ATP production in these cells leading to impaired insulin secretion, severe fasting hyperinsulinemia and glucose intolerance, suggesting that Nfe2l1 plays a key role in β-cell physiology.

Overall, Nfe2l1 is ubiquitously expressed producing various protein isoforms. Nfe2l1 can be induced by stress signals from a broad spectrum of stimuli and plays an important role in regulating a range of response is required, the ER-protected transactivation domains of L-NFE2L1 are dynamically retro-translocated through an as yet unknown mechanism and repositioned from the luminal side of ER membranes into the cyto/nucleo-plasmic side, whereupon it is deglycosylated to yield an active isoform with transactivation activity [31]. It has been reported that the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retrotranslocation [8,9,37] and the AAA protein p97/VCP may provide the power to drive this dynamic retros...
cellular functions including antioxidant defense [60,63,69–71], proteasome homeostasis [7,8,64,66,72,73], inflammation [42,74], regeneration, metabolism [16,58,65,75], cellular differentiation [76–79], maintenance of chromosomal stability and genomic integrity [80]. However, the underlying mechanisms by which these unique functions of various NFE2L1 isoforms are tightly regulated at various levels are not well elucidated [81]. Further research is needed to determine exactly how the proteoforms originate, their distribution and how each isoform of NFE2L1 contributes to its unique role in regulating expression of ARE-driven cytoprotective genes against various pathophysiological stresses.

3. Adipocytes

Adipose tissue (AT), which is primarily composed of adipocytes surrounded by fibroblasts, preadipocytes, endothelial cells, nerves and immune cells, is crucial for maintaining energy and metabolic homeostasis. AT can also secrete a variety of hormones, cytokines and other factors [82,83]. There are two main types of adipocytes with distinct functions. White adipocytes (WAC) are characterized by large unilocular lipid droplets and best appreciated as repositories of lipid storage by two primary metabolic activities, lipogenesis and lipolysis. In addition, WAC can also secrete a variety of adipokines associated with satiety regulation, whole-body insulin sensitivity, and so on [15,82–84]. These cells make up the bulk of white adipose tissue (WAT) mass in mice, and populate visceral depots of AT (VAT) in the abdomen like gonadal VAT (gWAT) as well as subcutaneous depots (SAT) like inguinal WAT (iWAT). By contrast, brown adipocytes (BAC) contain large numbers of mitochondria, which account for their brown color upon visualization. They are specialized in dissipating stored chemical energy from fats in the form of heat through the actions of uncoupling protein-1 (UCP1), a brown adipose tissue (BAT)-specific protein located within the mitochondria [85–87]. UCP1 catalyzes a proton leak across the inner mitochondrial membrane, thus “uncoupling” fuel oxidation from ATP synthesis. BAT has anatomically distinct positions in depots between the scapulae, around the neck and within the chest cavity. In addition, beige adipocytes exhibiting properties of both white and brown adipocytes have been discovered. These adipocytes have abundant mitochondria, are thermogenic like BAC but are located predominately in classical subcutaneous VAT depots in mice.

Despite the functional and locational differences between white and brown adipocytes, the two cell types share many common differentiation features. All adipocytes differentiate from MSCs in a process known as adipogenesis, which is thought to occur in two stages: commitment of MSCs to preadipocytes and terminal differentiation of preadipocytes towards mature adipocytes, involving a complex integration of cytoarchitecture, the micro-environment, signaling pathways and transcription regulators. Indeed, a core adipogenic transcriptional cascade is found that preadipocytes differentiate into mature adipocytes. We work sequentially to activate peroxisome proliferator activated receptor γ (PPARγ), the master regulator of adipocyte differentiation [88–92]. However, C/EBPs may be dispensable for maintaining certain aspects of adipocyte identity once these cells have been established. For brown adipogenesis, the core program is adjoined by unique transcriptional co-regulators, including PR domain-containing 16 (PRDM16) and the transcription factor early B-cell factor-2 (EBF2), that physically interact with PPARγ to direct BAC-specific target gene expression. By contrast, PRDM16 does not affect white adipogenesis.

Changes in AT amounts usually result from either hypertrophy or hyperplasia of adipocytes but the former is the major expansion factor in adulthood [93]. This is particularly true of WAT expansion and adipocytes. Local inflammation in response to adipocyte hypertrophy is essential for WAT expansion and subsequent remodeling [94]. However, in case of excessive adipocyte hypertrophy, such as in severe obesity, the inflammatory insult becomes persistent and may disturb energy homeostasis [95,96]. Metabolic fluxes are the primary determinants of adipocyte hypertrophy, and thus a shift in balance between influx and efflux of lipid may affect the function and fate of adipocytes. There is no doubt that in this disrupted homeostasis, lipolysis is the main contributor to lipid efflux, while lipogenesis mainly guarantees the influx.

4. Unraveling the emerging roles of NFE2L1 in AT

Given that AT functions as a key regulator of energy balance and nutritional homeostasis [97], it is worth figuring the significance of NFE2L1 in AT. To understand the biological function of NFE2L1 in AT, BAC-specific (Nfe2l1ΔBAT) [12] and adipocyte-specific Nfe2l1 (KO) mice [Nfe2l1(f)-KO] [13] have been developed by crossing Nfe2l1fl/fox mice with Ucp1-Cre and adiponectin-Cre (adipoq-Cre) mice, respectively. The data from these distinct models demonstrated that NFE2L1 plays crucial roles in adipose biology involving adipogenesis, lipid and glucose metabolism, thermogenesis, antioxidant response and proteasome homeostasis.

4.1. NFE2L1 in adipogenesis

Our group used stromal vascular fraction (SVF) cells isolated from WAT of Nfe2l1(f)-KO mice and 3T3-L1 preadipocytes with altered levels of various isoforms of NFE2L1 to study their roles in adipogenesis, a process that preadipocytes differentiate into mature adipocytes. We found that deletion of either long or all isoforms of NFE2L1 in the cells results in augmented adipogenesis. The interesting cellular phenotype from SVF cells had gender- and depot-dependent differences. Conversely, overexpression of L-NFE2L1-741, but not S-NFE2L1, in 3T3-L1 cells led to attenuated adipogenesis [11]. Mechanistic studies suggest that L-NFE2L1 might dominate over S-NFE2L1s and negatively regulates the expression of PPARG2 by directly binding to the promoter region of Pparg2 gene to repress its transcription [11]. However, we did not verify the exact roles of S-NFE2L1s in Pparg2 expression and adipogenesis. In addition, the molecular details for the suppression of Pparg2 expression by L-NFE2L1 and potential binding partners of L-NFE2L1 in the complex process remain vague.

4.2. NFE2L1 in white adipocyte

Our recent studies showed that Nfe2l1(f)-KO mice express reduced levels of multiple lipolytic genes in adipocytes, leading to adipocyte hypertrophy followed by severe inflammation, pyroptosis and insulin resistance, implicating an important role of NFE2L1 in adipocyte biology [13]. Moreover, the diminished WAT mass induced by Nfe2l1 deficiency specifically in adiponectin-expressing cells is age-, gender- and depot-dependent [98]. In line with our findings, a Ph.D. thesis from Dr. Chan’s lab also described a similar phenotype of reduced inguinal WAT mass in the adipocyte-specific Nfe2l1-KO (Nrf1 FatKO) mice they developed [99]. To further clarify the regulatory role of NFE2L1 in lipid metabolism of adipocytes and verify the mechanisms underlying the phenotype of Nfe2l1(f)-KO mice, we used protracted rosiglitazone (RGZ) treatment to create an extremely positive lipid content balance in Nfe2l1(f)-KO mice. While three weeks of RGZ treatment significantly down-regulated mRNA levels of a group of inflammation-related genes in WAT of adult Nfe2l1-flxed control mice, the adipose phenotype of Nfe2l1(f)-KO mice was aggravated showing further increased inflammation and macrophage infiltration, enhanced transcript expression related to inflammation and pyroptosis in WAT [14]. In addition, the effect of CL316243, a β3 adrenergic agonist that promotes lipolysis via a post-translational mechanism, on adipose inflammation in juvenile Nfe2l1(f)-KO mice was also studied [98]. In contrast to adult mice, 4 weeks old juvenile Nfe2l1(f)-KO mice displayed a normal fat distribution but reduced fasting plasma glycerol levels and elevated adipocyte hypertrophy and macrophage infiltration in inguinal and gonadal WAT. In addition, Nfe2l1(f)-KO mice had decreased expression of multiple
lipolytic enzymes. Follow CL316243 treatment, this phenotype is improved.

The expression of key lipolytic genes is, at least in part, dependent on NFE2L1. Adipocyte-specific deficiency of Nfe2l1 (f)-KO mice under different treatment conditions were summarized in Table 3 [13,14,98].

Table 3

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Veh</td>
</tr>
<tr>
<td>Nfe2l1(f)-Floxed</td>
<td>Lipolysis</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Lipogenesis</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Hypertrophy</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td>–</td>
</tr>
<tr>
<td>Nfe2l1(f)-KO</td>
<td>Lipolysis</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Lipogenesis</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Hypertrophy</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

↑, increase; ↓, reduce; —, comparable.

Overall, our findings from Nfe2l1(f)-KO mice strongly indicate that NFE2L1 plays a fundamental regulatory role in the expression of a variety of lipolytic genes and thereby regulates lipid flux, WAT plasticity and global energy homeostasis (Fig. 4).

4.3. NFE2L1 in brown adipocyte

In mice, Nfe2l1 mRNA expression is more enriched in BAT than that in WAT. Cold adaptation leads to markedly higher Nfe2l1 expression in BAT and to a minor extent also in iWAT [12]. Based on the findings, Bartelt et al. carried out a series of experiments to reveal a novel guardian role of NFE2L1 in BAC function providing increased proteo-metabolite quality control for adapting to cold or obesity [12].

Under thermogenic conditions, Nfe2l1ΔBAT mice displayed lowered BAT-mediated whole-body respiration and energy expenditure. BAT also became progressively discolored and lipid-laden with ER stress, inflammation, diminished mitochondrial function, and limited proteasome subunit mRNA expression [12]. Moreover, a few findings to some extent ruled out the possibility that the BAT phenotypes of Nfe2l1ΔBAT mice are simply a reflection of a defect in the general integrity of the tissue induced by loss of Nfe2l1. Specifically, changes did not occur in UCP1 protein levels or in mRNA levels of critical BAC regulators such as Ucp1, Pparγ1a, Pparγ1b, Pparγ or Pparδ in BAT of Nfe2l1ΔBAT mice, either at 30 °C or at 22 °C. Chemical inhibition of proteasome or Nfe2l1 deficiency did not cause reduced protein levels of components of the respiratory chain in isolated mitochondria per se. Lipolysis in BAT and WAT explants remained unchanged by Nfe2l1 deletion.

Activated BAC has robust metabolic activity. Thus, a powerful proteometabolite quality control is needed to maintain the normal operation of the cells. ER is an adaptive organelle for defending homeostasis where enzymes couple nutrient-derived cues, substrates, or stress signals with coordinated changes in protein synthesis, folding, and secretion as well as lipid metabolism and trafficking [100–102]. In this process, the unfolded protein response (UPR) and the sterol response element binding protein 2 (SREBP2) sterol-sensing complex are critical, which engage metabolic and inflammatory outputs to restore homeostasis. NFE2L1 is an ER membrane sensor, which co-evolves with SREBP2 as a Yin-Yang counterbalance to stabilize ER-resident metabolic activity [103] and the downstream target genes encoding certain component of proteasome. Therefore, NFE2L1 may influences BAC profoundly through multiple pathways, including ER and oxidative stress,
findings from difficult for us to make clear explanations on the divergences in the key and the limited understanding on the transcription factor, it is still complex interactions among many pathways altered by among rather few studies available (Table 4). In addition, because of explored. The AT phenotypes induced by proteasome homeostasis, mitochondrial physiology under the states of

Abbreviations: CLS, crown-like structures; ER, endoplasmic reticulum; ND, no detection. ↑, increase; ↓, reduce; —, comparable.

proteasome homeostasis, mitochondrial physiology under the states of normal or high activity.

At present, the role of NFE2L1 in AT has rarely been systematically explored. The AT phenotypes induced by Nfe2l1 deletion vary greatly among rather few studies available (Table 4). In addition, because of complex interactions among many pathways altered by Nfe2l1 ablation and the limited understanding on the transcription factor, it is still difficult for us to make clear explanations on the divergences in the key findings from Nfe2l1ΔBAT, Nrf1 FatKO and Nfe2l1(f)-KO mice. Considering the central role of AT in metabolic health and disease and the critical roles of NFE2L1 in many basic cellular functions in BAC and WAT, the physiological and pathophysiological roles of NFE2L1 warrant further investigations beyond the scope of the studies published.

5. Conclusion and perspectives

Accumulating data indicates that NFE2L1 plays crucial roles in adipogenesis and adipose function. We have endeavored to summarize current understandings on NFE2L1 in adipocytes and AT which are mainly obtained from Nfe2l1ΔBAT and Nfe2l1(f)-KO mice and 3T3-L1 cells. First, NFE2L1 regulates adipogenesis in an isoform-specific manner. Of particular, L-NFE2L1 serves as a distinct negative regulator of Ppara and adipogenesis. Second, NFE2L1 is a fundamental adaptive regulator of BAT thermogenic function and may act as a general cellular guardian of BAC activity. Third, NFE2L1-dependent lipolytic activity is crucial for WAT plasticity and lipid homeostasis. Because the gene knockout strategy used in the in vivo studies targets the exon 10 of the Nfe2l1 gene, a shared sequence across all the isoforms of Nfe2l1 transcripts, it is difficult, if not impossible, to determine the distinct roles of individual isoform of NFE2L1 in these models. While overexpressing individual isoform of NFE2L1 or in combinations in various cell models, such as 3T3-L1 cells, could provide informative data on the distinct roles of individual isoform of NFE2L1, it is challenging to verify their roles at AT or whole-body levels. To truly assess the isoform-specific roles of NFE2L1 in AT, conditional isoform-specific overexpressing in vivo models would be helpful.

Human and mouse Nfe2l1 genes contain multiple nucleotide polymorphisms that might affect the expression and/or function of different isoforms of NFE2L1. In addition, Nfe2l1 gene can be transcribed into multiple splice variants resulting in various protein isoforms, which may be further modified by a variety of post-translational mechanisms. While the L-NFE2L1 has been discovered as a key regulator of cellular adaptive antioxidant response, proteasome homeostasis, macrophage polarization [4] and adipogenesis [11], the exact tissue distribution and physiological function of various isoforms of NFE2L1, the short isoforms in particular, are still under investigation. Together with the findings on the linkage between gene polymorphisms of human NFE2L1 and obesity [15,16] and the crucial role of NFE2L1 in adipose function, it is time to begin to pay more attention to the under-appreciated CNC-bZIP protein for its important and novel roles regulating adipocyte function and various metabolic disorders.

Declaration of competing interest

The authors declare that they have no conflict of interest. All authors approved the final manuscript.

Acknowledgements

This research was supported in part by the National Natural Science Foundation of China: 81830099 (J.P.), 82020108027 (J.P.), 81400839 (Y.C.), 820222063 (Y.X.), 81402661 (Y.H.), 81573106 (J.P.), 82073513 (H.W.), 82003500 (Y.B.) and 81402635 (J.F.); National Key R&D Program of China: 2018YFC1101600 (J.P.); and LiaoNing Key Research and Development Guidance Plan 2019JH8/10300012 (J.P.). China Post- doctoral Management Foundation YJ20190263 (Y.B). The authors have no conflicting financial interests.

References

S. Ren et al., The Nrf1 CNC/bZIP protein is a nuclear envelope-bound transcription factor that is activated by t-butyl hydroquinone but also to enable its asparagine-glycosylation, Biochem. J. 408 (2) (2007) 161–169.


F.M. Tomlin, et al., Inhibition of NGLY1 inactivates the transcription factor Nrf2 and potentiates proteasome inhibitor cytotoxicity, ACS Gen. Sci. 3 (11) (2017) 1143–1155.


[100] K.S. Schneider, Functional Analysis of Nrf1 and Nrf2 Transcription Factors in Adipose Tissue, University of California, eScholarship, 2016.
[106] Y. Zhang, in: Molecular and Cellular Control of the Nrf1 Transcription Factor: an Integral Membrane Glycoprotein, the first ed. ed, Vdm Verlag Dr Muller Publishing House, 2009.