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Review

Changing gears in Nrf1 research, from mechanisms of regulation to its role in disease and prevention

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ABSTRACT

The "cap'n'collar" bZIP transcription factor Nrf1 heterodimerizes with small Maf proteins to bind to the Antioxidant Response Element/Electrophile Response Element to transactivate antioxidant enzyme, phase 2 detoxification enzyme and proteasome subunit gene expression. Nrf1 specifically regulates pathways in lipid metabolism, amino acid metabolism, proteasomal degradation, the citric acid cycle, and the mitochondrial respiratory chain. Nrf1 is maintained in the endoplasmic reticulum (ER) in an inactive glycosylated state. Activation involves retrotranslocation from the ER lumen to the cytoplasm, deglycosylation and partial proteolytic processing to generate the active forms of Nrf1. Recent evidence has revealed how this factor is regulated and its involvement in various metabolic diseases. This review outlines Nrf1 structure, function, regulation and its links to insulin resistance, diabetes and inflammation. The glycosylation/deglycosylation of Nrf1 is regulated by glucose levels. Nrf1 glycosylation affects its control of glucose transport, glycolysis, gluconeogenesis and lipid metabolism.

1. Overview: nuclear factor erythroid 2-like 1 (NFE2L1 or Nrf1)

Cellular responses to a range of stresses often center on common pathways and factors. The cellular responses to oxidative stress, endoplasmic reticulum stress, xenobiotic stress and inflammation involve the cap'n'collar (CNC) family of transcription factors. The CNC family of proteins includes the *Caenorhabditis elegans* skinhead-1 (Skn-1) protein [1,2], the *Drosophila melanogaster* cap'n'collar-isoform C (CncC) protein [3,4], and the vertebrate activators nuclear factor-erythroid 2 (NF-E2) p45 subunit [5], transcription factor 11 (TCF11) [6,7], locus control region-factor 1 (LCR-F1 or Nrf1β) [8,9], nuclear factor erythroid 2 like 1 (Nrf1 or NFE2L1) [5,10–14], Nrf2 (NFE2L2) [15], and Nrf3 (NFE2L3) [16–18] [Fig. 1]. It also includes the repressors, BTB and CNC homolog 1 (Bach 1) [19,20] and Bach 2 [21,22]. The CNC domain that characterizes this family of proteins binds to the Antioxidant or Electrophile Response Element (ARE or EpRE respectively); a DNA element (with the consensus sequence 5′-TGACNNNGC-3′ where N is any nucleotide) [23] found in the enhancers of promoters of many enzymes involved in antioxidant responses, xenobiotic metabolism and inflammatory responses [Table 1]. As such, target ARE genes are also tightly implicated in development and metabolism and include the catalytic heavy and the regulatory light subunit of glutamate cysteine ligase (*Gcsh* and *Gcsl*), glutathione synthetase, γ-glutamyl transpeptidase, class Alpha and Mu glutathione S-transferase (*Gst*) isoenzymes, NAD(P)H:quinone oxidoreductase 1, heme oxygenase 1, metallothionein-1 and -2 (*Mt1* and *Mt2* respectively), the heavy and light subunits of ferritin, peroxiredoxin MSP23, and leukotriene B412-hydroxydehydrogenase [24–33].

The relatively fewer studies on Nrf1, in comparison to Nrf2, have led to statements such as “nothing is known about how Nrf1 is regulated” as recently as 2010 [34]. Due to a misnomer in the literature Nrf1 (or

Abbreviations: AD1, Acidic Domain 1; AD2, Acidic Domain 2; AP-1, adaptor protein-1; ARE, Antioxidant Response Element; Bach1, BTB and CNC homolog 1; Bach 2, BTB and CNC homolog 2; BTB, broad complex, tramtrack, bric-a-brac; bZip, basic-leucine zipper; CK2, casein kinase 2; CNC, cap'n'collar; CTD, C-terminal domain; CUL2, cullin-2; DBD, DNA-binding domain; DPP, dentin phosphoprotein; DSP, dentin sialoprotein; DSPP, dentin sialophosphoprotein; Ep, electrophiles; EpRE, Electrophile Response Element; ER, endoplasmic reticulum; ERAD, endoplasmic reticulum-associated degradation; GSK3β, glycogen synthase kinase 3β; HS, hexosamine synthesis; Keap1, Kelch-like ECH-associated protein 1; LCR-F1, locus control region-factor 1; Maf, musculoaponeurotic fibrosarcoma oncogene; MCRS2, microspherule protein 2; MRE, metal response element; MSP23, murine stress protein 23; MT1, metallothionein-1; MT2, metallothionein-2; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; Neh2, Nrf2-ECH homology 2; NehL, Nrf2-ECH homology like domain; NF-E2, nuclear factor-erythroid 2; NFE2L1 or Nrf1, nuclear factor erythroid 2 like 1; NFE2L2 or Nrf2, nuclear factor erythroid 2 like 2; NF-κB, nuclear factor of kappa-light-chain-enhancer of activated B cells; NHB1, N-terminal homology box 1; NHB2, N-terminal homology box 2; Nrf1cKO, Nrf1 conditonal knockout; NST, Asn/Ser/Thr-rich domain; NTD, N-terminal domain; OGT, O-linked N-acetylglucosamine transferase; PEST, Pro/Glu/Ser/Thr-rich domain; PNGase, peptide:N-glycosidase; ROS, reactive oxygen species; RNS, reactive nitrogen species; Skn-1, *Caenorhabditis elegans* skinhead-1; TAD, transactivation domain; TCF11, transcription factor 11; TM1, transmembrane 1 domain; TMc, C-terminal transmembrane; TMi, intermediate transmembrane domain; TMp, amphipathic semihydrophobic transmembrane domain; TNF, tumor necrosis factor.

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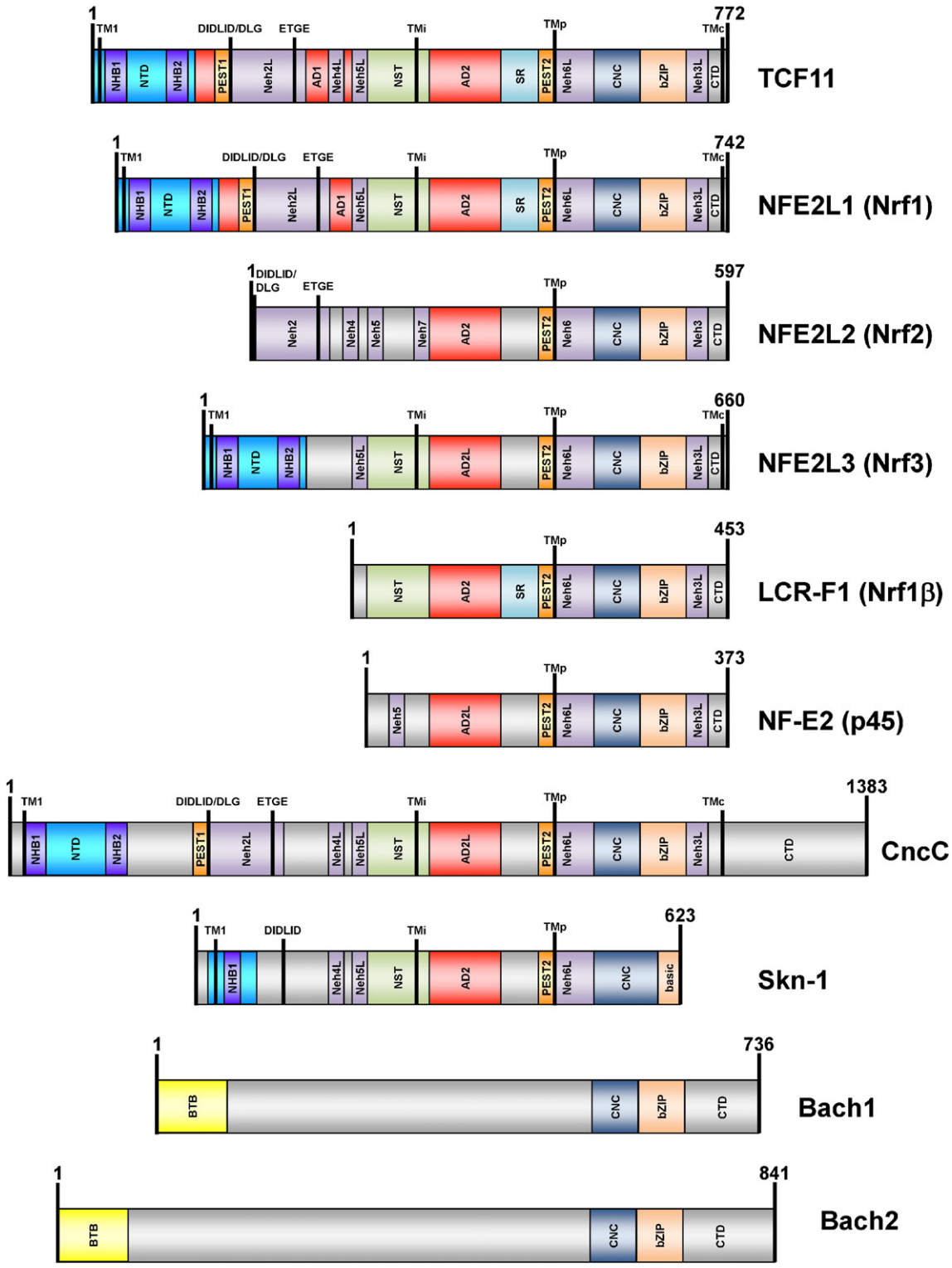

Fig. 1. The cap'n'collar family of transcription factors and their common structural domains. The human TCF11, Nrf1, Nrf2, Nrf3, LCR-F1 and NF-E2 p45 proteins are shown in comparison to the *Drosophila melanogaster* CncC and *Caenorhabditis elegans* Skn-1 proteins, as well as the Nrf2 inhibitors, Bach1 and Bach2. All family members have a cap'n'collar (CNC) and basic-leucine zipper (bZIP) domain present in the C-terminal domain (CTD) of the protein. The N-terminal domain (NTD) of many family members contains the N-terminal homology box 1 and 2 (NHB1 and NHB2 respectively) regions. Activators have Acidic Domains 1 and 2 (AD1 and AD2 respectively). The AD2L domain is present in Nrf3 only. Asn/Ser/Thr-rich (NST) and serine repeat (SR) domains are present in some, but not all, activators. The NST regions contain the sites for glycosylation in the family members that contain them. One or two Pro/Glu/Ser/Thr-rich (PEST) sequences are present in many family members. Transmembrane domains include transmembrane 1 (TM1), the intermediate transmembrane (TMi), the amphipathic semihydrophobic transmembrane (TMp) and the C-terminal transmembrane (TMc) domains. This family of proteins are also characterized by up to 7 highly conserved Nrf2-ECH homology like domain (NehL) domains (labeled Neh1L to Neh7L or Neh1 to Neh7). The DIDLID/DLG element and ETGE motif regulate protein stability in the family members in which they are found. The Nrf2 repressors, Bach1 and Bach 2, contain a broad complex, tramtrack, bric-a-brac (BTB) domains which are atypical of other CNC family member proteins. Modified from Zhang et al. 2014 [12].