

Supplemental Material

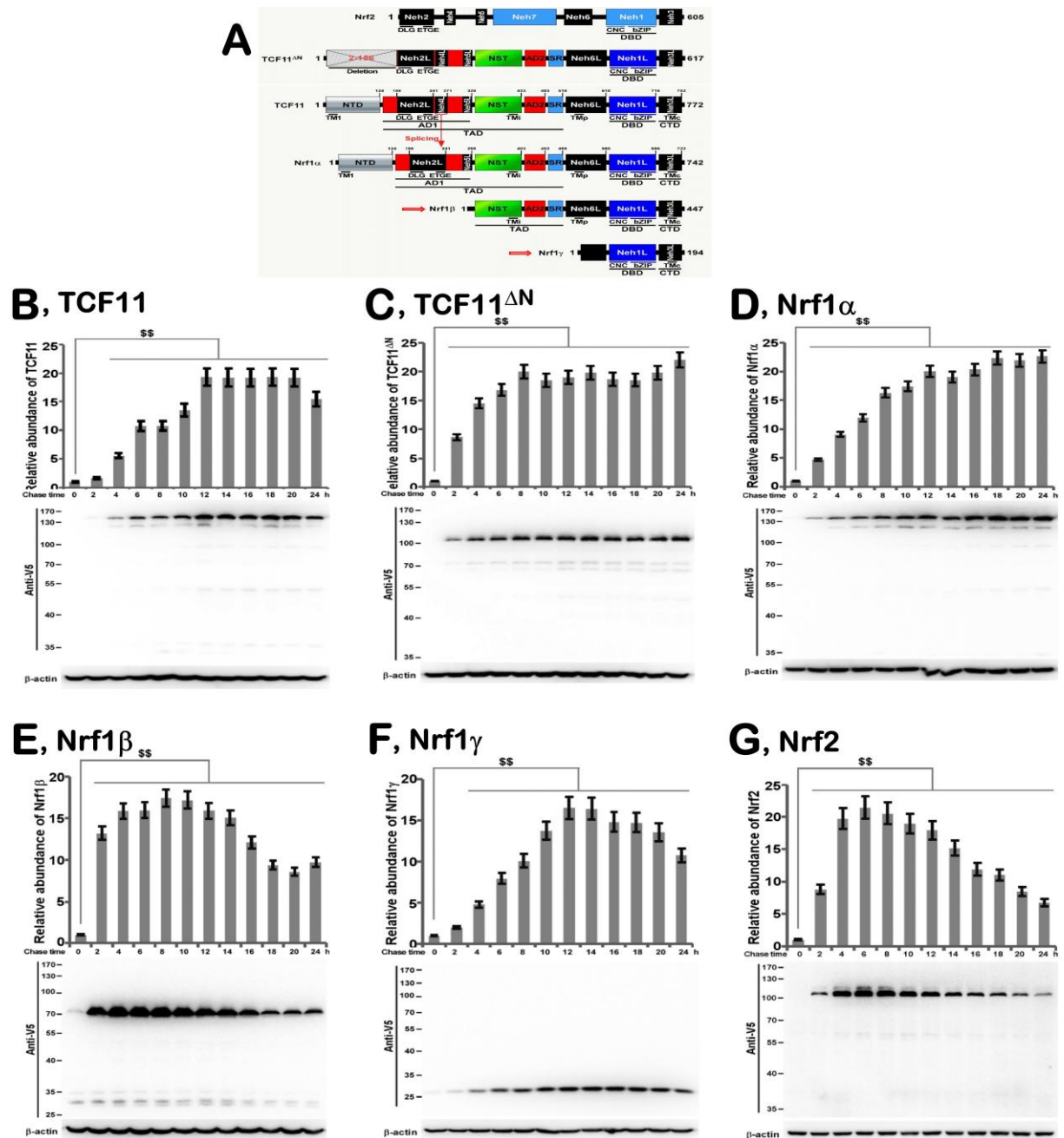
Nrf1 acts as a highly-conserved determinon for maintaining robust redox homeostasis in the eco-evo-devo process of life histories

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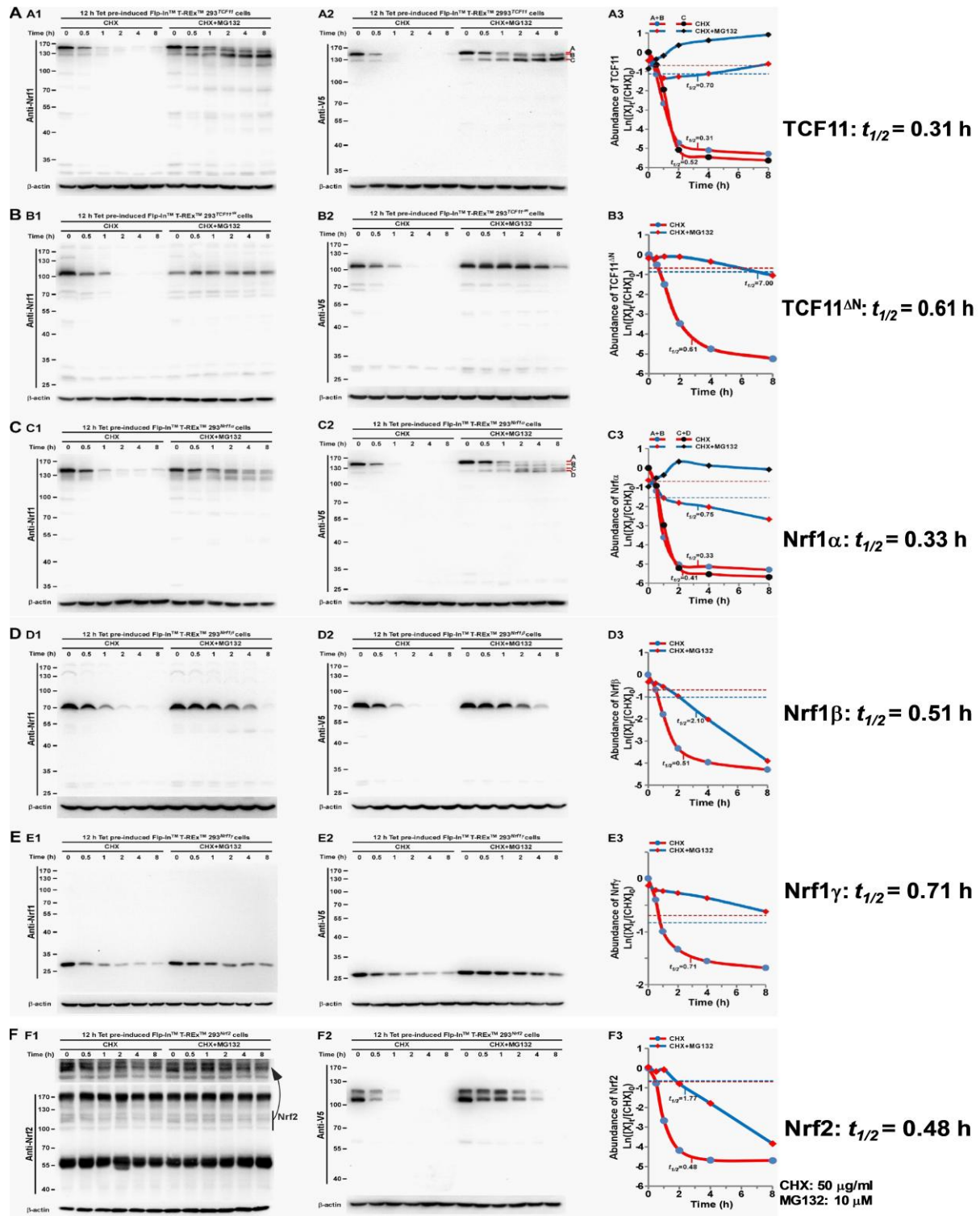
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Supplemental FIGURE S1 ● Distinct isoforms of Nrf1/TCF11, along with Nrf2, which were inducibly expressed in the tetracycline-inducible HEK293 cell system, that had been treated with tetracycline for indicated lengths of time.

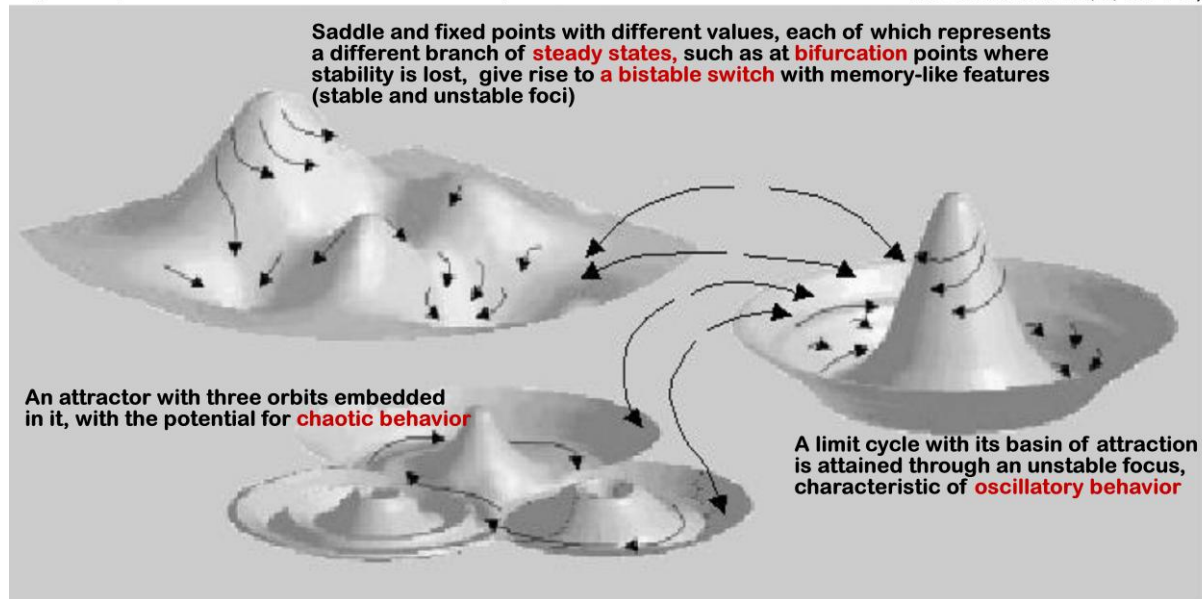


Supplemental FIGURE S2 ● The protein stability of distinct Nrf1/TCF11 isoforms along with Nrf2, which were estimated by their half-lives in the tetracycline-inducible HEK293 cell system that was pretreated with tetracycline for 12 h and then treated with CHX alone or plus MG132 for distinct lengths of chase time. The resulting data were shown graphically before calculating their half-lives.

A geometric landscape for interpretation of redox homeostasis by distinct homeodynamic models:

- i) as a steady state with high activity;
- ii) as a bistable switch at the excitable bifurcation;
- iii) as a spontaneous oscillator with chaotic potentials.

(adapted from Lloyd D, *et al.* 2001, The Scientific World, 1, 133-145)

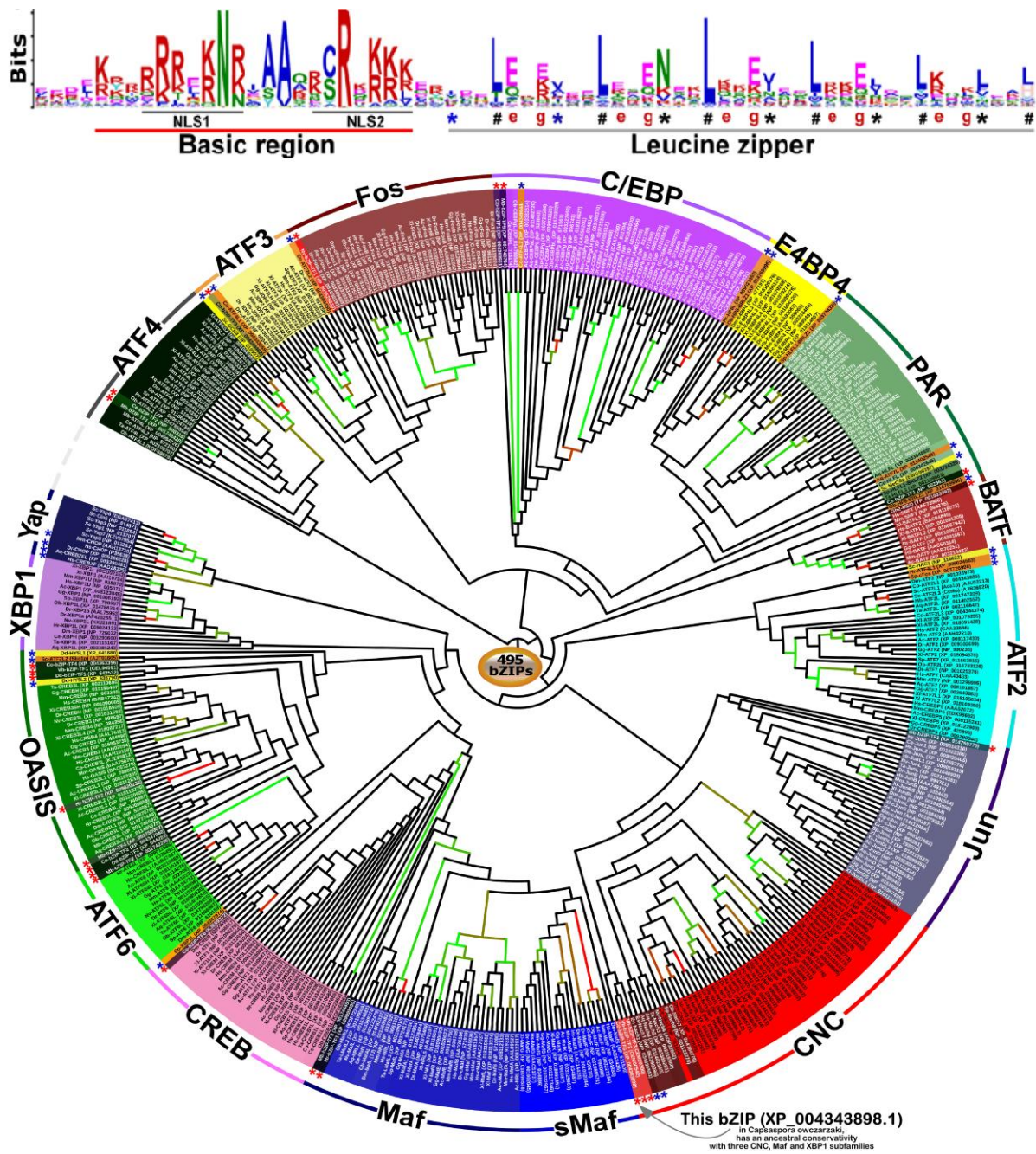


Homeostasis: a relative constancy (i.e., stable steady state) of the internal milieu at a normal physiological status; that is to say, it is as a relatively-balanced stage of dynamics with monotonic states (fixed points).

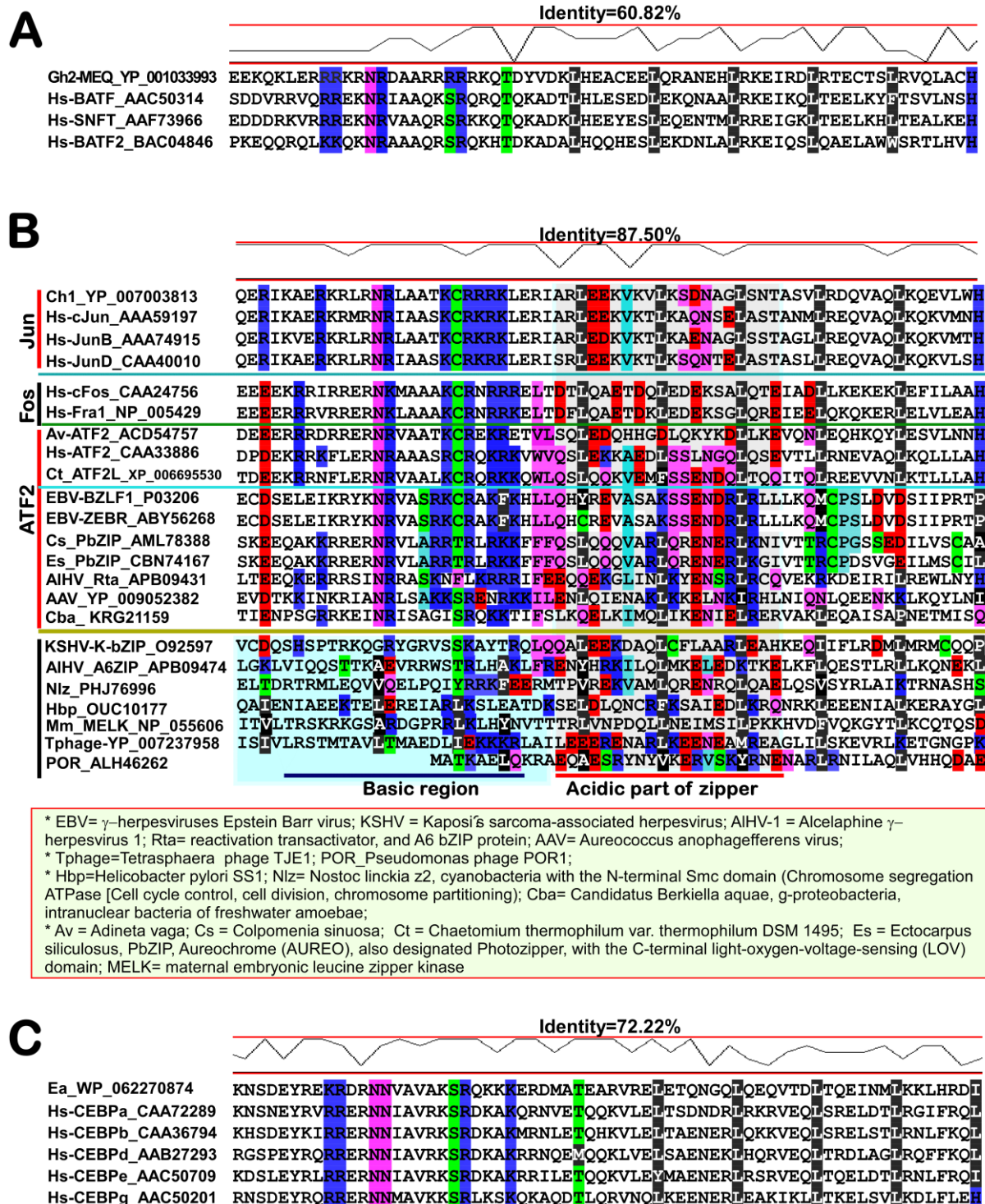
Homeodynamics: by dynamic self-organization, cell process also exhibits a capacity for bistable switching, with a threshold phenomena, and waves, gradients, mutual entrainment, and periodic or chaotic behavior.

Dynamic self-organization (to describe function in cellular systems) that arises as the spatiotemporal coherence of those emergent events resulting from the intrinsic, autonomous, dynamics of biological processes.

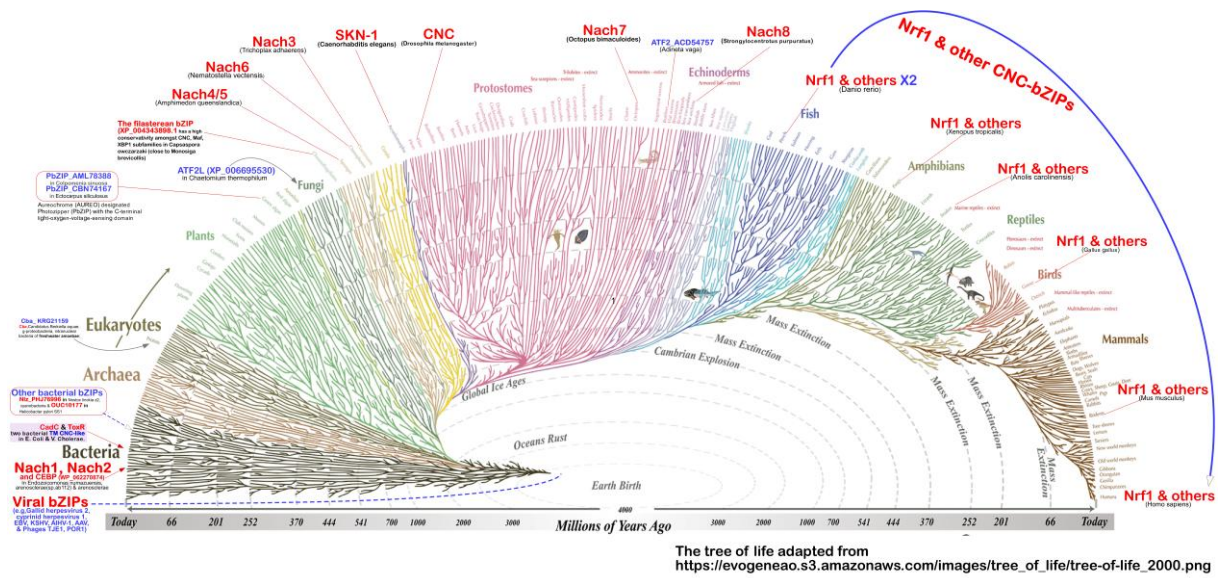
Supplemental FIGURE S3 ● A geometric landscape for interpretation of redox homeostasis by distinct homeodynamic models, which was adapted from Lloyd D, et al 2001 [182].



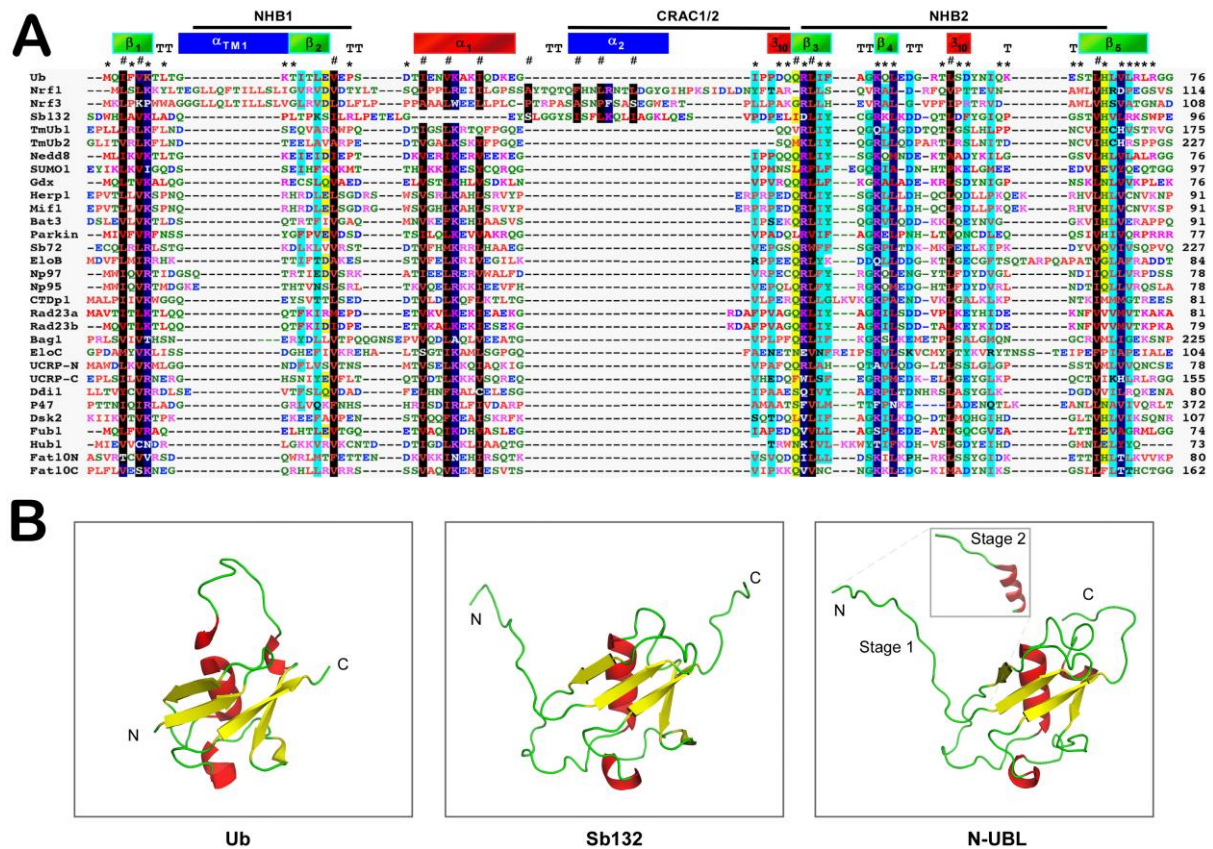
Supplemental FIGURE S4 ● The neighbor-joining phylogenetic tree of 495 bZIP factors selected from distinct species of life and viruses.



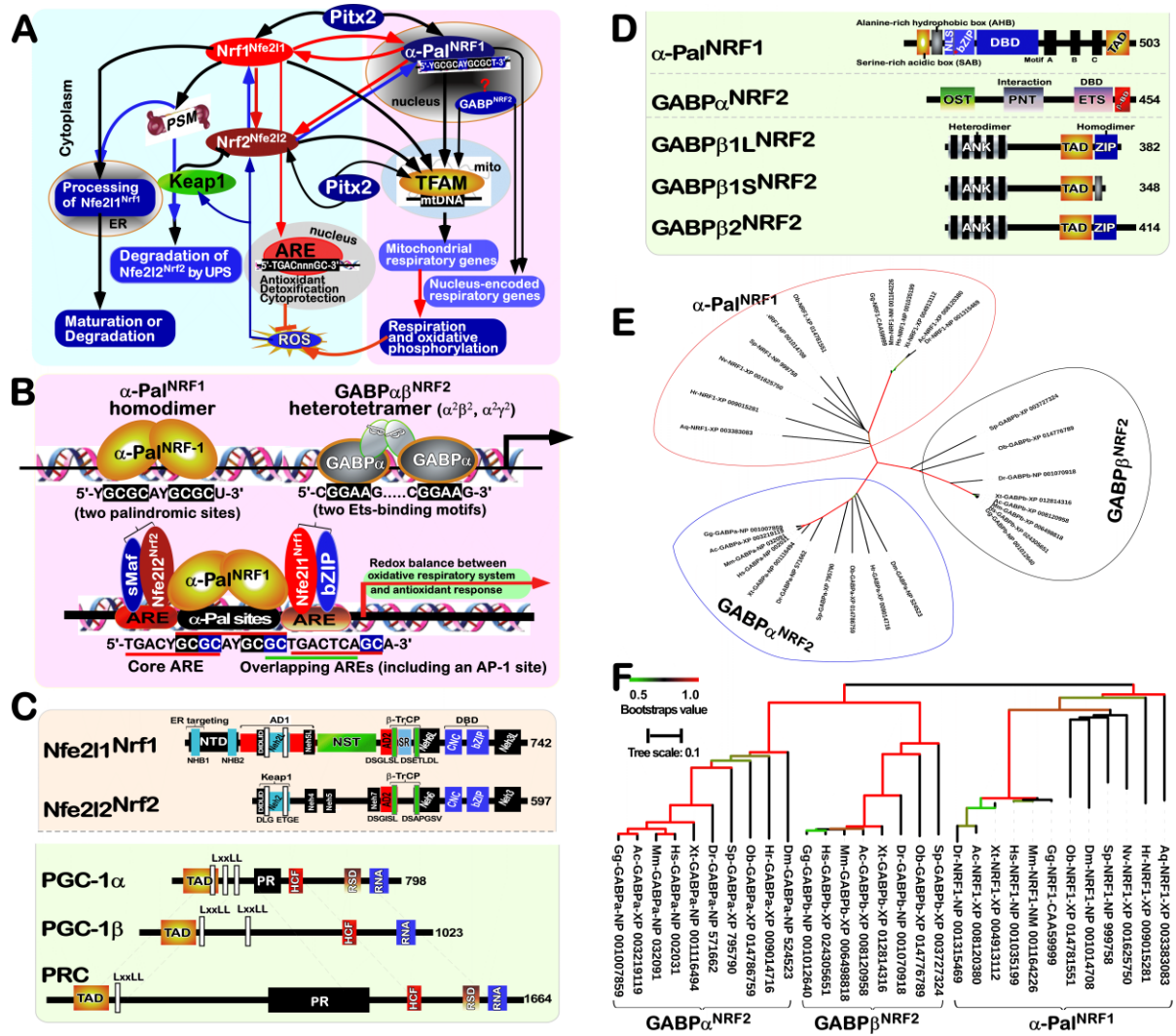
Supplemental FIGURE S5 ● Alignment of multiple amino acid sequences covering the core DNA-binding domains of those early emerged bZIP factors, along with viral and bacterial bZIP factors.



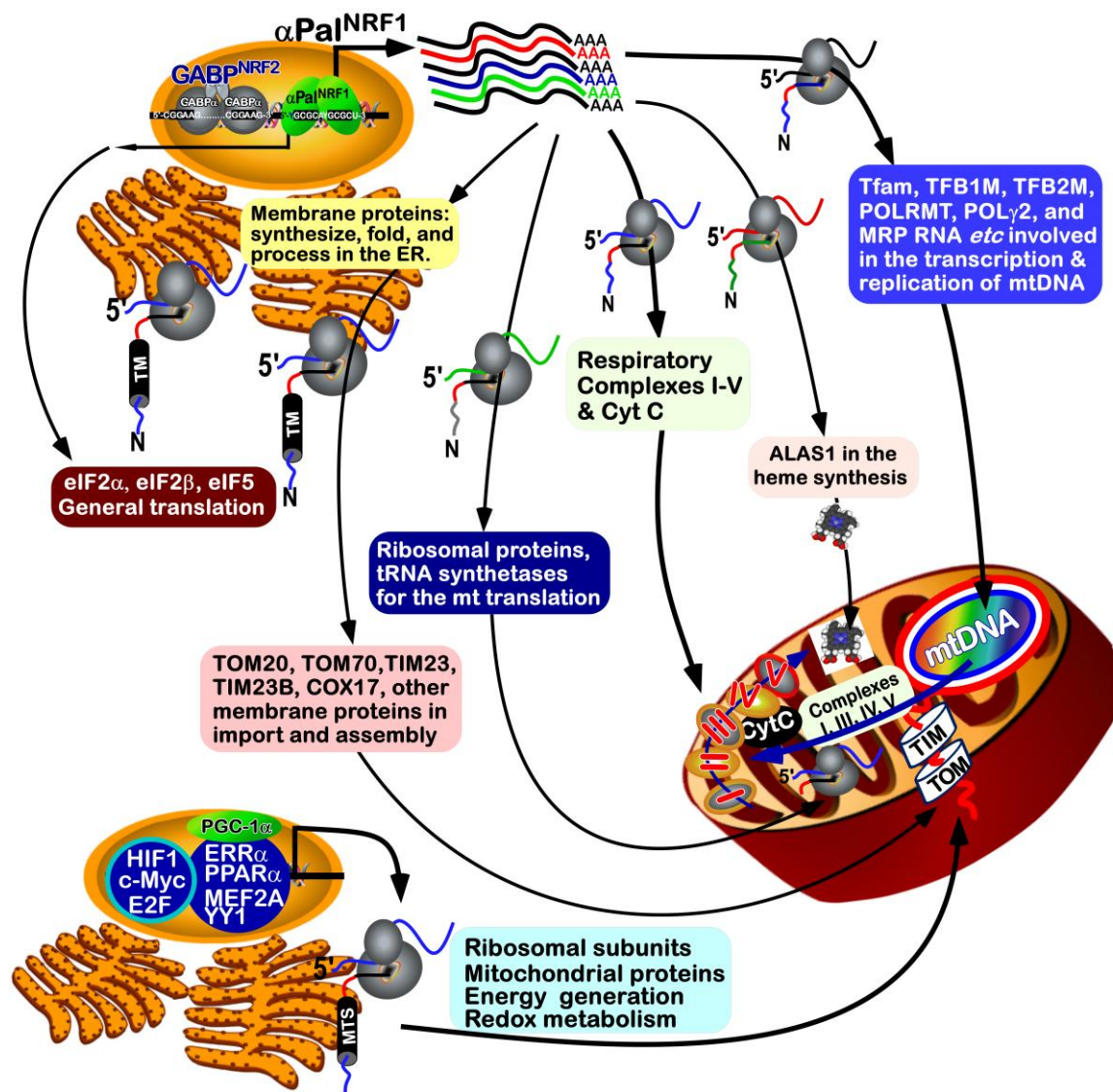
Supplemental FIGURE S6 ● All indicated CNC-bZIP factors and relevant homologues are marked on the evolutionary tree of life (adapted from online as indicated).



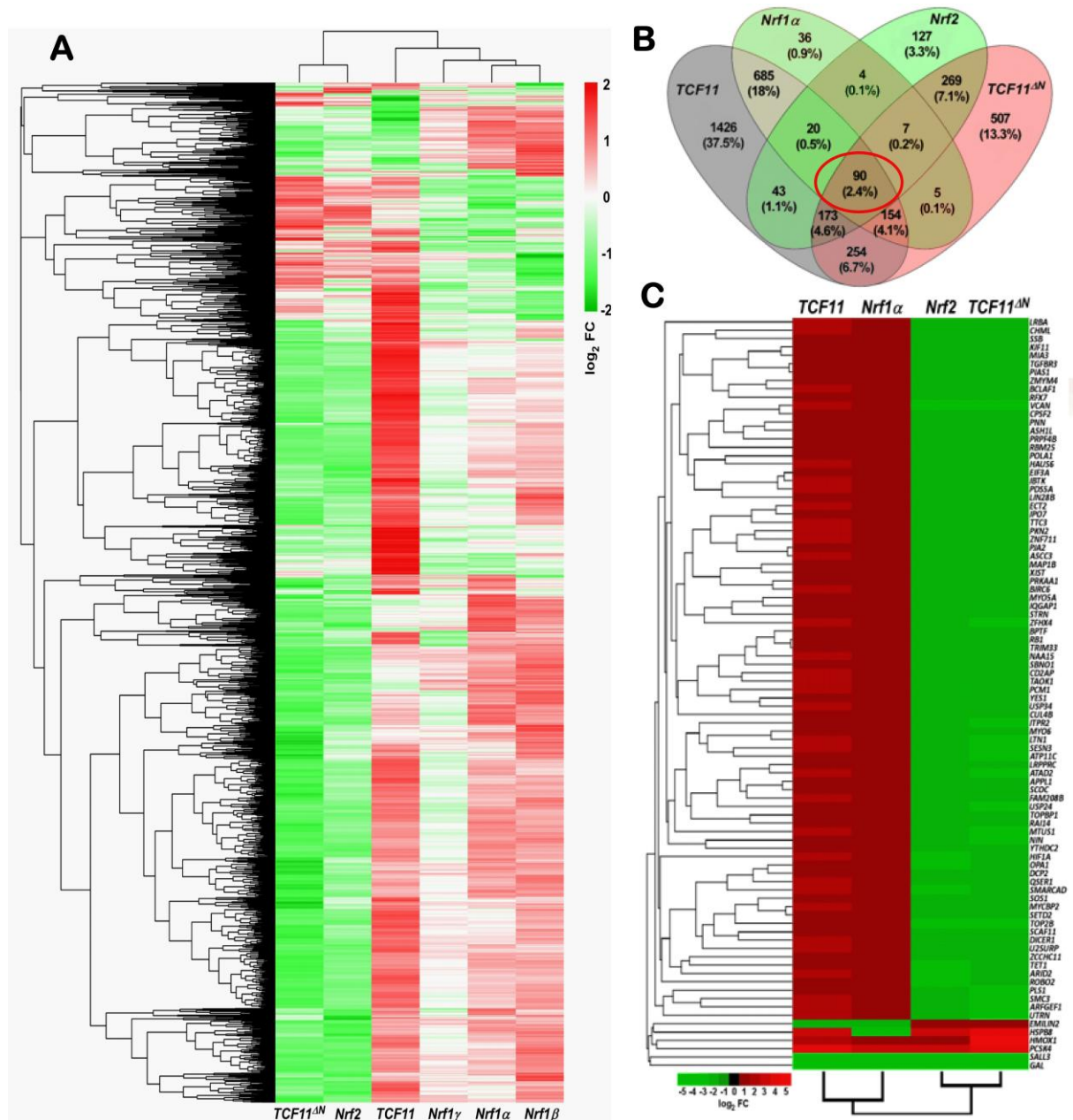
Supplemental FIGURE S7 ● Alignment of amino acid sequences from the N-terminal domains of Nrf1 and Nrf3, with all those indicated ubiquitin-like (UBL) proteins or UBL-containing proteins (A), along with structural modeling of N-UBL in Nrf1 being built (B).



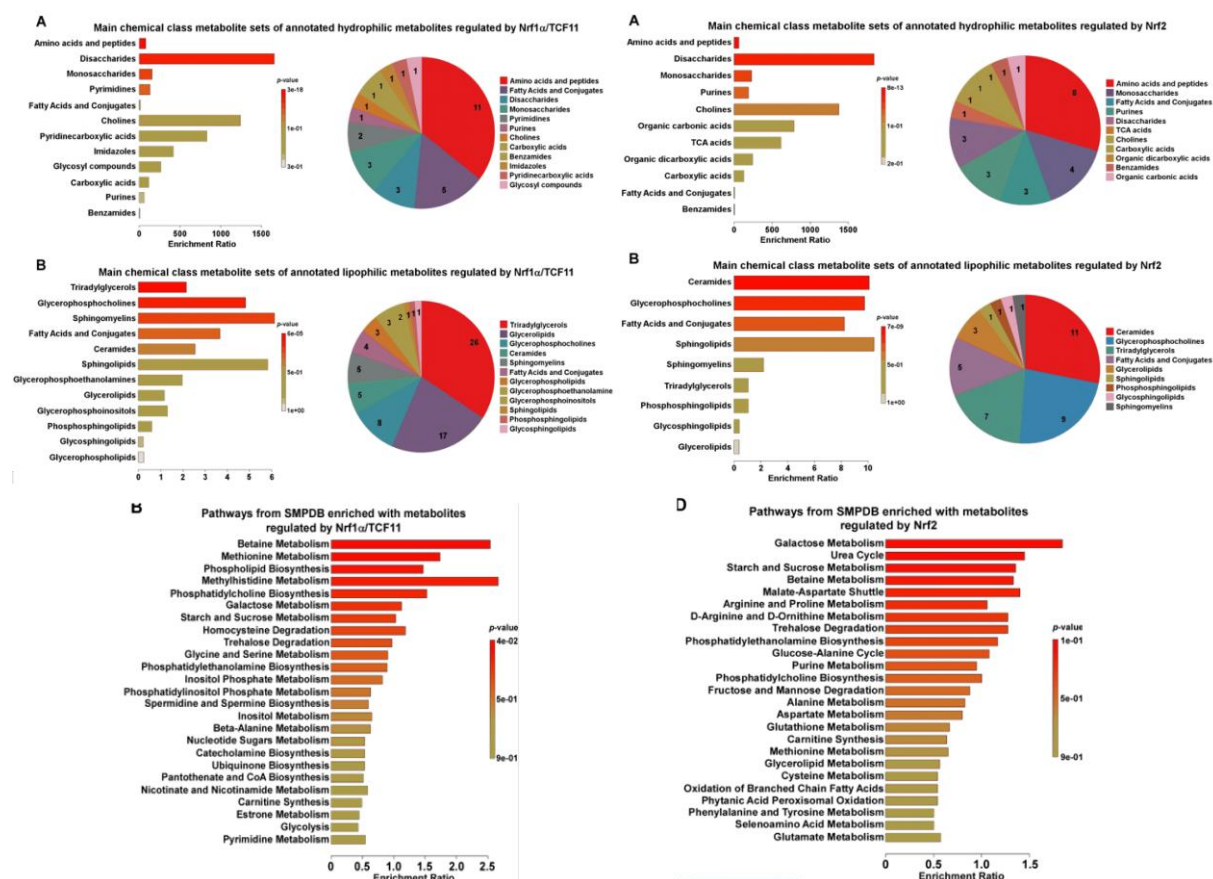
Supplemental FIGURE S8 ● Antioxidant Nrf1/2 are totally different from nuclear respiratory factors (also abbreviated often as NRF-1/2). (A) A proposed model to give a better understanding of inter-regulation between two major antioxidant factors Nrf1Nfe2l1 and Nrf2Nfe2l2 with additional two nuclear respiratory factors (also designated as α Pal^{NRF1} and GABP^{NRF2}, herein) in coordinately governing the mitochondrial biogenesis and functional homeostasis. (B) Schematic representation of directly DNA-binding of α Pal^{NRF1} and GABP^{NRF2}, alongside with Nrf1^{Nfe2l1} and Nrf2^{Nfe2l2}, to their respective consensus sequences. (C-D) Structural comparison of Nrf1^{Nfe2l1}, Nrf2^{Nfe2l2}, α Pal^{NRF1}, GABP^{NRF2}, and their co-factors PGC-1 α , PGC-1 β and PRC, all with distinct functional domains as indicated. (E, F) Two types of the neighbor-joining phylogenetic tree, revealing no homology amongst α Pal^{NRF1}, GABP^{NRF2} and GABP β ^{NRF2}.



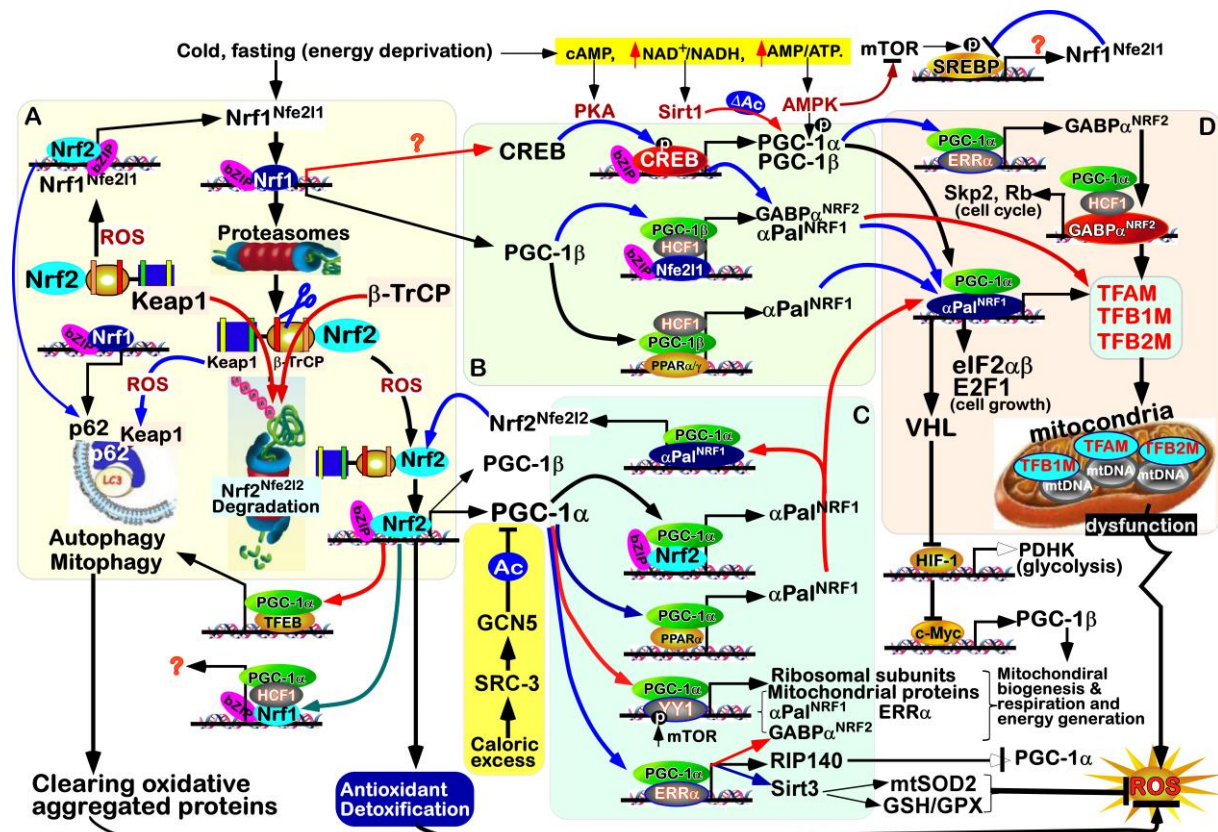
Supplemental FIGURE S9 ● A proposed model for a better understanding of α Pal^{NRF1} acting as a major nuclear respiratory factor, which making multiple cross-talks from the nucleus (and endoplasmic reticulum) to mitochondria, through several distinct signaling to target gene regulatory networks.



Supplemental FIGURE S10 ● Transcriptomic analysis of tetracycline-inducible HEK293 cells expressing each of indicated CNC-bZIP factors. Of note, Nrf1 and TCF11 have similar target gene regulatory roles, that are completely distinctive or even oppositely from those regulated by Nrf2 (but almost resembles TCF11^{ΔN}).



Supplemental FIGURE S11 ● Metabolome analysis of distinctions between Nrf1α/TCF11 and Nrf2.



Supplemental FIGURE S12 ● A proposed model to provide an understanding of differentiated yet integrated roles of Nrf1^{Nfe2l1}, Nrf2^{Nfe2l2} and αPal^{NRF1} in coordinately mediating multi-hierarchical molecular-cellular signaling to target gene regulatory networks in order to tightly govern cellular (redox and energy metabolism) homeostasis, as well as mitochondrial homeostasis, under the strict quality control.

The following work had been suspected of being fraudulent, adapted from PubPeer
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Nrf1 is targeted to the endoplasmic reticulum membrane by an N-terminal transmembrane domain. Inhibition of nuclear translocation and transacting function

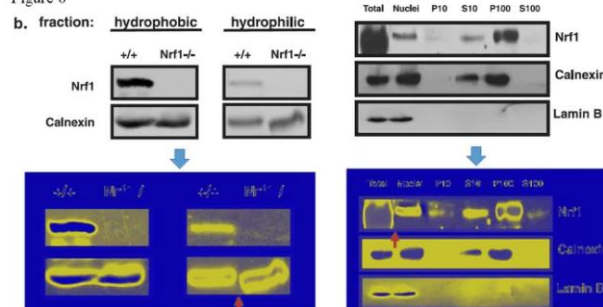
Journal of Biological Chemistry (2006) - 1 Comment
pubmed: 16687406 doi: 10.1074/jbc.m602802200 issn: 0021-9258 issn: 1083-351x

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#1 *Tropaeolum emarginatum* commented June 2020

Figure 6



There are multiple undeclared splicing sites in the immunoblots in Figure 6B and C.

Supplemental FIGURE S13 ● In the past near 20 years, this group has almost no more continuing studies except for this misleading publication having been suspected by the PubPeer, which was wrongly designed for the tagged protein, resulting in a misfolded topology of Nrf1 across the membranes, as accompanied by several misleading interpretations. For example, i) Tunicamycin (TU)-leading decreases in molecular weights of Nrf1 were misunderstood to be proteolytically processed in a fashion similar to that of ATF6; ii) Nrf1 was viewed to be repressed directly by Keap1 in another fashion similar to that of Nrf2. This is attributed to the routine CO-IP assayed in the total lysates with broken membranes, leading to a false positive interaction of Keap1 with Nrf1. All these have been later experimented to be wrong. Correctly, TU enables to block the N-linked glycosylation of Nrf1 inasmuch as to yield a non-glycosylated form, but not be processed by TU-induced proteases through a similar mechanism accounting for the proteolytic processing of ATF6 or SREBP. In fact, the Neh2-like domain of Nrf1 is positioned in the ER lumen and only when it is retro-translocated out of the ER, it can gain access to the cytosolic Keap1. Thus, in total cell lysates with broken membranes, Nrf1 is easy to interact with Keap1 upon lacking the membrane barrier. In addition, there should also exist another subtle 'grey' story being hidden behind this publication, which has been not uncovered heretofore to anyone except for the authors.

REFERENCES

182. Lloyd D, Aon MA, Cortassa S (2001). Why homeodynamics, not homeostasis? *ScientificWorldJournal* 1: 133-145. doi: 10.1100/tsw.2001.20