# Q QUÍMICA, BIOQUÍMICA E SINALIZAÇÃO: O CAMINHO NFE2L2/AP-1

# CHEMISTRY, BIOCHEMISTRY AND SIGNALING: THE NFE2L2/AP-1 PATHWAY

# ХИМИЯ, БИОХИМИЯ И СИГНАЛИЗАЦИЯ КАСКАДОВ NFE2L2/AP-1

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## RESUMO

Mais de 5% das proteínas codificadoras dos genes de humanos são controladas pelo sistema NFE2L2/AP-1. É responsável pelas reações celulares às EROs, xenobióticos, compostos altamente reativos de diferentes naturezas, fornece resistência a drogas e muitas outras funções - funções intracelulares, extracelulares, microambientais. A impressionante variedade de funções dessas cascatas levanta questões sobre como elas fornecem à célula reações bastante específicas. Esta revisão enfoca o conhecimento atual nessa área. Atualmente, as funções do NFE2L2/AP-1 já são utilizadas no desenvolvimento de novas abordagens em diagnósticos médicos, farmacêuticos e terapêuticos. O preenchimento dos pontos brancos existentes em interactoma NFE2L2/AP-1 avançará significativamente as áreas de pesquisa associadas e abrirá novas perspectivas para a tecnologia médica.

**Palavras-chave**: *NFE2L2, AP-1, Interatômica, sinalização intracelular.*

## ABSTRACT

In humans, the NFE2L2/AP-1 pathway controls more than 5% of the protein-coding genes. This pathway is responsible for cellular reactions towards ROS, xenobiotics, highly reactive substances of various nature, drug resistance and a plethora of other intracellular, intercellular and microenvironment functions. The great diversity of the pathway functions is astonishing and raises questions of how the pathway operates to provide the cell with specific enough reactions. The present review focuses on current knowledge in the field. Today, the pathway functioning is already used in developing novel pharmaceutics and diagnostics approaches, in therapy follow-up. Filling the existing blanc spots of the NFE2L2/AP-1 interactome would significantly advance the related fields and open new horizons in medical technologies.

**Keywords:** *NFE2L2, AP-1, interactomics, signaling*

## АННОТАЦИЯ

У человека более 5% кодирующих белки генов контролируются системой NFE2L2/AP-1. Она отвечает за клеточные реакции на АФК, ксенобиотики, высокореактивные соединения различной природы, обеспечивает лекарственную устойчивость и множество других функций – внутриклеточных, межклеточных, функций микроокружения. Поразительно широкое разнообразие функций этих каскадов вызывает вопросы о том, каким образом они обеспечивают клетку достаточно специфическими

реакциями. В данном обзоре основное внимание уделяется современным знаниям в этой области. Сегодня функции NFE2L2/AP-1 уже используются при разработке новых подходов в медицинской диагностике, фармацевтике и терапии. Заполнение имеющихся белых пятен в интерактоме NFE2L2/AP-1 значительно продвинет вперед связанные с ним научные области и откроет новые перспективы для медицинских технологий.

**Ключевые слова:** *NFE2L2, AP-1, интерактомика, внутриклеточная сигнализация.*

## INTRODUCTION

In the human cell and in the surrounding microenvironments, a plethora of biochemical processes inevitably leads to the generation of reactive oxygen and nitrogen species (ROS and RNS, respectively) – detrimental for DNA, RNA, lipids and proteins structure and function. To name a few:

- in mitochondria, ROS are generated at complexes I and III and by MAOA, MAOB, OGDH, GPD1, GPD2, p66 SHC1 enzymes (Hung and Burton, 2008; Starkov, 2008);
- in endoplasmic reticulum (ER), ROS are generated by a membrane-bound family of cytochromes P450; CYB5A, CYB5B enzymes; microsomal monooxygenase electron transport chain; folding mediator proteins P4HB, ERO1L and ERO1LB (Bondy and Naderi, 1994; Tu and Weissman, 2004; Gross *et al.*, 2006). ER stress leads to significant ROS production as well (Zeeshan *et al.*, 2016);
- peroxisomes name speaks for itself: the organelle is rich in ROS/RNS-producing enzymes: beta-oxidation enzymes, D- and L-amino acid, polyamine, alpha hydroxy acid oxygenases, DAO, ACOX1, ACOX2, PAOX, HAO1, HAO2, XDH enzymes, nitric oxide synthase NOS2 (Engerson *et al.*, 1987; Ijlst *et al.*, 2000; Hung and Burton, 2008; Van Veldhoven, 2010; Burton *et al.*, 2011);
- lysosomal sources of ROS have also been described in detail – those are mostly a part of the mTOR pathway (Kubota *et al.*, 2010; Hamacher-Brady *et al.*, 2011);
- cytosolic ROS generators are also numerous, including AOC2, NOS3, arachidonate lipoxygenases Alox, and Post proteins (Kukreja *et al.*, 1986; Roy *et al.*, 1994);
- even the most vulnerable to ROS components of the cell – membranes – are enriched with ROS/RNS sources, such as AOC2 isoform 1, AOC3, NOXes (including DUOXes), NOS1 and NOS3 (O'Donnell, 1996; Nüsse, 2011);
- remarkably, the nucleus contains ROS producing proteins as well – e.g. ALOX5, ALOX5AP, SMOX, LOXL2 (Woods *et al.*, 1993; Barker *et al.*, 2011; Cho *et al.*, 2011);
- extracellular (and intercellular) also play into the equation of ROS/RNS generation. Such sources are, for example, ABP1, XDH (also found in peroxisomes), LOXL2, NOXes (membrane-bound enzymes) and NOSes (NO is able to cover significant distances) (Rodriguez *et al.*, 2010; Schietke *et al.*, 2010; Barker *et al.*, 2011;).

Listed were solely protein sources of reactive species. However, a great deal of small molecules and ions participates in ROS production – via auto-oxidation, enzymes-dependent and enzyme-independent redox cycling, and chain reactions (Griffiths *et al.*, 2014; Wagner, 2015).

All this principally inevitable ROS/RNS production in humans is evolutionally coupled with unexpendable signaling function (Alberts *et al.*, 2007).

The cell, accordingly, should have a wide network of factors supervising ROS production rate. A key position among the signaling pathways controlling this network belongs to the NFE2L2/AP-1 pathway. In the present review, we will focus on this pathway and revise its functioning step by step – from the level of immediate antioxidant effectors and to the epigenomic regulation and yet back to the metabolomic bottom.

## EFFECTOR PROTEINS

The NFE2L2/AP-1 effector proteins serve to prevent excessive ROS propagation or generation in the first place.

The primary reactive oxygen species – the superoxide anion – is scavenged by two NFE2L2/AP-1 target enzymes – SOD1 and NQO1. Just as two other Sod enzymes, SOD1 reduces superoxide to produce hydrogen peroxide. The intracellular SOD2 and SOD3 enzymes have never been explicitly proven to be

targets of the pathway discussed, despite claims elsewhere. Along with SOD1, the NFE2L2/AP-1 pathway does contain a protein capable of intracellular superoxide reduction – this is NQO1 (Dinkova-Kostova and Talalay, 2010).

Although this is not at all the protein's primary function, NQO1 still appears to be central in superoxide scavenging mechanisms of the pathway (Ross *et al.*, 2000). The protein primarily serves to prevent redox-cycling of organic compounds (e.g. quinones, including the widely used in food industry redox-cycler tBHQ, estrogens, tocopherol quinone, etc.) – and redox-cycling reactions are a prominent source of ROS (Ross *et al.*, 2000; Jaiswal, 2000; Kim *et al.*, 2010).

In addition to organic compounds, iron ions are prone to redox-cycling and thus represent a threat to the human cells and organism as a whole. In this case, four NFE2L2/AP-1 pathway proteins take an action. First of all, the two of the three human ferritins securing iron ions, FTL and FTH1, are controlled by NFE2L2 and/or AP-1 (discussed later) (Iwasaki *et al.*, 2007; Kim *et al.*, 2010). To date, there is no evidence that FTMT is an NFE2L2/AP-1 target. The third NFE2L2/AP-1-dependent protein participating in iron ions handling is HMOX1. In the first step of heme degradation, HMOX1 metabolizes it to biliverdin (Gozzelino *et al.*, 2010) allowing for controlled ferrous ion release that is to be further captured by iron-storing proteins. The fourth factor controlling iron metabolism in the NFE2L2/AP-1 pathway is an ion channel SLC40A1 (Maher and Yamamoto, 2010).

In various reactions, be it the described above superoxide reduction or direct processes, hydrogen peroxide is formed. Despite not being a radical, this relatively stable ROS is still an oxidizing agent itself and, more importantly, decomposes to form hydroxyl radical (the fastest reacting ROS typically present in the cell) or peroxyl radical. Thus, hydrogen peroxide concentrations in the cell should be tightly controlled. On the other hand, hydrogen peroxide has been evolutionally coupled to signaling, even at the level of the PI3K/Akt pathway and intercellular communication (Zhang *et al.*, 2010; Martinez-Outschoorn *et al.*, 2011). Consequently, hydrogen peroxide cannot be completely scavenged in the cell in order to preserve normal signaling. As the result, the cell evolved a stand-by protection represented by proteins that serve to prevent oxidative damage emanating from hydrogen peroxide presence and metabolism. In part, these proteins serve to reduce hydrogen peroxide. Other proteins react with oxidized molecules and prevent oxidative damage spread.

An often seen in literature misconception of the regulation of catalase by NFE2L2 appears to have no solid ground to date. In fact, catalase has been proven to be controlled by other pathways – coupled with peroxisomes and mitochondrial functioning and biogenesis (Valle *et al.*, 2005). Thus, the first-line defense of the cell from hydrogen peroxide controlled by the NFE2L2/AP-1 pathway is glutathione peroxidases, glutathione-S-transferases, and associated proteins and thioredoxin-domain containing factors and associated proteins.

Some evidence suggests glutathione peroxidase GPX1 be an NFE2L2 target (Yang *et al.*, 2015). GPX2 is a proven NFE2L2 target (Sykiotis and Bohmann, 2010). GPX3-GPX7 have not been reported to directly depend on the NFE2L2/AP-1 pathway. Of 22 humans glutathione-S-transferases, three are known NFE2L2 targets – these are GSTA1, GSTA4, and GSTP1 (Borde-Chiché *et al.*, 2001; Dickinson *et al.*, 2003; Sun *et al.*, 2011). The two latter proteins are also AP-1 targets (Borde-Chiché *et al.*, 2001; Dickinson *et al.*, 2003).

Both families rely on glutathione pool of the cell. The key glutathione synthesis proteins GCLC and GCLM are both targets of the both NFE2L2 and AP-1 (also discussed below) (Moinova and Mulcahy, 1998; Marrot *et al.*, 2008). In mice, direct observations led to a conclusion that NFE2L2 controls glutathione reductase GSR (Harvey *et al.*, 2009; Kato *et al.*, 2010), and indirect evidence suggest that this holds true in humans as well.

Thioredoxins are another prominent cytoplasmic, mitochondrial and nuclear agents. Unlike the peptide glutathione, thioredoxins 1 and 2 (TXN and TXN2) and 24 related molecules are all proteins. The major cellular thioredoxin is TXN, and its closest homolog TXN2 is a mitochondria-restricted protein. The extent of function substitution of the thioredoxins is still mostly unknown, but all these 24 proteins do exert specific redox effects.

Among these 26 proteins, only TXN is a known NFE2L2/AP-1 target (Yu et al., 2011), and moreover, it is also a regulator of the pathway (discussed below). TXN2, in turn, is regulated along with catalase (Valle *et al.*, 2005; Olmos *et al.*, 2009). Nevertheless, TXN is the key protein of the thioredoxin-domain containing proteins, and this is mostly due to it's regulatory, not purely chemical or biochemical, functions.

As a biochemical reactant, thioredoxin

(which is not an enzyme) is used to reduce oxidized peroxiredoxins, in line with sestrin 2 (SESN2) and sulfiredoxin 1 (SRXN1) proteins. The only exception here is PRDX6, which is a thioredoxin-independent enzyme. Notably, the both SESN2 and SRXN1 are NFE2L2 and/or AP-1 targets (Soriano et al.,2009; Shin et al., 2012), just as PRDX3, PRDX5, and PRDX6.

Upon peroxiredoxins regeneration, oxidized TXN and TXN2 should be recycled. This is accomplished by three known thioredoxin reductases (Txnrd) and probably by a gene sharing genomic locus with TXNRD3. Among these proteins, TXNRD1 is an NFE2L2 target (Reichard *et al.*, 2007). Interestingly, this is a cytoplasmic and nuclear protein, i.e. it is capable of reducing TXN in all its characteristic compartments, thus rendering the pathway self-sufficient. Mitochondrial protein TXNRD2 is controlled along with TXN2 (Valle *et al.*, 2005).

There is also a cellular biochemical pathway of glutaredoxins-dependent TXN reduction (Du *et al.*, 2012). To date, no known Glrx have been demonstrated to be NFE2L2/AP-1-dependent. This topic requires attention, since the missing link may only be due to Glrx regulation being poorly studied.

Most of the discussed protective proteins not only scavenge ROS but also repair or remedy the ROS-derived damage. There is yet another large group of proteins serving to ameliorate chemical impacts on the cell. These are several protein families.

For instance, four aldo-keto reductases Akr (AKR1B1, AKR1C1, AKR1B10, AKR1C2) are known NFE2L2 targets, with the latter two being also AP-1 targets (Lou *et al.*, 2006; Nishinaka *et al.*, 2011; Jung *et al.*, 2013).

Two carbonyl reductases (CBR1, CBR3) are NFE2L2-regulated factors as well (Cheng *et al.*, 2012; Miura *et al.*, 2013).

On a higher level, the NFE2L2/AP-1 pathway controls the recycling of cellular and internalized agents. It is extremely likely, that in humans, the pathway regulates expression of seven of 55 major 26S proteasomal proteins – as it has been experimentally shown to be true in mice (Kwak *et al.*, 2003). Interestingly, another 26S protein PSMD14 functionally interacts with the TXNL1 thioredoxin-like protein (Andersen *et al.*, 2009).

Not only proteasomal function is dependent on NFE2L2/AP-1. It is an experimentally proven fact that NFE2L2 controls SQSTM1 protein expression – so the pathway contributes to autophagy (Taguchi *et al.*, 2012). Moreover, SQSTM1 function appears to be SESN2-dependent (Bae *et al.*, 2013), and, as mentioned earlier, the latter is an NFE2L2 target as well.

As it was mentioned above, the NFE2L2/AP-1 pathway, in fact, controls pump proteins as well. Critically important proteins in this sense are the multidrug resistance proteins (MRP). Astonishingly, the major MRPs ABCB1 (MDR1), ABCG2 (BCRP), ABCC2 (MRP2) and ABCC3 (MRP3) are all NFE2L2 targets (Jeong *et al.*, 2015). This is a prominent cellular protection mechanism conferred by the NFE2L2/AP-1 pathway, since xenobiotics may effectively be effluxed from the cell before even taking any damaging effects.

It should be admitted that the NFE2L2/AP-1 pathway controls pro-oxidant proteins along with anti-oxidant ones.

## ROS GENERATORS OF THE PATHWAY

NFE2L2 and AP-1 significantly differ in pro-oxidants they control, quite unlike the situation with the antioxidants.

For example, NOX1, a superoxide-generating NADPH-oxidase complex component, is an AP-1 target, and the known regulatory AP-1 components (discussed below) are ATF1 and JUNB (Cevik *et al.*, 2008), i.e. this is a non-canonical AP-1 variant-dependent transcription regulation. In contrast, NFE2L2 controls a related NOX4 via a canonical pathway (Pendyala *et al.*, 2011). Even more, interestingly, NFE2L3 (the second closest and the most evolutionally recent NFE2L2 homolog) has the same effect on the target (Pepe *et al.*, 2010) – a situation yet never observed in antioxidants control (Chowdhury *et al.*, 2017). Another key component of the NADPH-oxidase complex, CYBA, is an AP-1 target (Manea *et al.*, 2008).

AP-1 also controls at least one detoxication phase I factor – CYP17A1 (Sirianni *et al.*, 2010) – a member of a prominent family of proteins generating ROS by-products.

## NFE2L2 AND AP-1 PROTEINS FUNCTIONING AND CROSS-TALK: DECISION MAKING:

In addition to the factors mentioned above, the even the NFE2L2 sub-pathway controls at least about a thousand more proteins and RNAs (Malhotra et al., 2010). In many instances, these targets are not at all related to anti-oxidant nor even pro-oxidant systems of the cell (Humbert *et*

*al*., 2003; Manea *et al*., 2008; Samuel *et al*., 2008; Zolotukhin *et al*., 2018).

Thus, an important question is, how do NFE2L2 and AP-1 fit into cellular context with so many target genes, only a small fraction of which code for immediate antioxidants and detoxifying enzymes? It is the more challenging since key proteasomal (Kwak *et al*., 2003), autophagic (Taguchi et al., 2012), general signaling (Ho *et al*., 2010; Erttmann *et al*., 2011), and, furthermore, cell proliferation, cell cycle and survival regulation factors (Malhotra *et al*., 2010) are NFE2L2 or AP-1 targets.

Apparently, the finely tuned cellular functions controlled by the NFE2L2/AP-1 pathway are only possible by the actually great number of transcription factors participating in regulation. While NFE2L2 only has two more closest homologs (NFE2L1 and NFE2L3) capable of binding with its binding site, AP-1 is represented by a couple of dozens of proteins. The major AP-1 constituents are JUN, JUNB, JUND proteins (these can form Jun-only homodimers or heterodimers), FOS, FOSB, FOSL1, FOSL2 proteins (these can only form heterodimers) and ATF proteins (can form various heterodimers) (Gozdecka and Breitwieser, 2012; Srivastava *et al*., 2013; Juilland *et al*., 2016). Moreover, AP-1 proteins are capable of forming oligomers with different and even non-related proteins (Mo *et al*., 2001). So how does the regulatory system work?

NFE2L2, along with NFE2L1, NFE2L3, and AP-1 proteins (including ATF proteins) are all basic leucin zipper (bZip) transcription factors of similar structure (Novotny *et al*., 1998; Sykiotis and Bohmann, 2010; Babu *et al*., 2013). Functional roles and regulation of the Nfe2l- and AP-1-proteins significantly overlap (Xanthoudakis *et al*., 1992; Venugopal and Jaiswal, 1998; Kim *et al*., 2003; Iwasaki *et al*., 2006), and, what's even more, these two groups of proteins regulate each other at several levels, including transcription control (Zolotukhin *et al*., 2018). It should be noted that NFE2L2 binding site ARE and AP-1 binding site TRE often overlap with AP-1 being embedded into ARE (Reichard and Petersen, 2004; Zolotukhin *et al*., 2013). Specifically, ARE, the antioxidant response element, has a core sequence of RTGACWHAGCA (minor frequencies are not shown), while TRE, the TPA response element, has a sequence of TKAMWSA. Thus, elements containing RTGACWCAGCA are entirely double ARE/TRE elements (Zolotukhin *et al*., 2013). Due to this fact, AP-1 and NFE2L2 and its homologs readily positively interact or compete, substitute for each other upon transcription factor expression disturbances, etc.

There is yet another level of regulation of Nfe2l-proteins specificity. TRE may be embedded into ARE, and ARE itself is a derivative of another transcription factor binding site – MARE. MARE is a Maf-proteins binding site. And Nfe2l-factors, being bZip proteins, can only function when in a dimer. Due to ARE evolution pathway from MARE, Nfe2l-proteins retained the Maf-co-dimerization ability of the Nfe2l-subfamily primal protein – NFE2 (p45) (Kim *et al*., 2003). In humans, there are six Maf-proteins: MAF, MAFA, MAFB MAFF, MAFG, MAFK. Accordingly, this great diversity and orders of magnitude greater diversity of the hetero- and homodimers provide the cell with the subtle mechanisms of tuning of the NFE2L2/AP-1 pathway. The more important in this sense is the fact that NFE2L2 does form heterodimers with AP-1 components (Tsuji *et al*., 2005; Iwasaki *et al*., 2006; Iwasaki *et al*., 2007).

Furthermore, transcription factor binding sites ARE and TRE differ not only in their internal structure but in numbers, direction, and location. There are genes containing clustered binding sites (in this case, specific intra-pathway transcription suppressors can bind these sites (Reichard *et al*., 2007), clustered binding sites with a different direction of the sites, and various ARE/TRE combinations (Li and Jaiswal, 1992; Ishikawa *et al*., 2005). Similarly, the target genes differ in their transcripts dependence on these binding sites (Belanova *et al*., 2017).

All this together implies that binding of the transcription factors dimers or oligomers to the regulatory sites is a powerful tool to diversify cellular reactions towards stimuli of different nature and power. There are yet three more levels regulating the stimulatory outcome in the nucleus. First of all, the Nfe2l-factors are prone to cell signaling background-dependent fragmentation, yielding active positive or negative regulatory polypeptides, with the most prominent being NFE2L1 p65 (Chepelev *et al*., 2011) and tNFE2l2 (Sykiotis and Bohmann, 2010). Secondly, there is a great deal of epigenome regulation cross-talk between the NFE2L2/AP-1 and other pathways, with the exemplary case of the NF-kappaB pathway causing NFE2L2 loci suppression via histone code modification (Yu *et al*., 2011). The intra-pathway regulators, such as KEAP1 which binds and inactivates NFE2L2 in both cytoplasm and the nucleus, are themselves subject to epigenetic regulation (Guo *et al*., 2012). Thirdly, the pathway components, such as

KEAP1 and TXN, are highly important variables in the outcome of transcription factors binding activation (Brandes *et al*., 2009).

And lastly, all the NFE2L2/AP-1 transcription factors are indirectly or even directly controlled by higher-order cellular kinases. In turn, cellular hydrogen peroxide levels regulate the expression of these transcription factors and activation of the kinases – CAMKII, PKA, PKB (Akt), PKG, MAPKs, ERK to name a few, and 14-3-3 proteins functions. Apparently, this cross-talk represents an enormous feedback loop spanning from small molecules of metabolome to the top levels of cell regulators and epigenomic machinery (Blanc and Pandey, 2003; Burgoyne *et al*., 2013; Zhang *et al*., 2013; Jeon *et al*., 2016). From our previous analyses, we know that feedback and feed-forward circuits are key to the pathway functioning (Zolotukhin and Belanova, 2016), and they all have been introduced into the human oxidative status interactome map (Zolotukhin *et al*., 2013).

## CONCLUSIONS:

Considering its functions, the NFE2L2/AP-1 pathway is central to numerous fields of medicine (especially, cancer), pharmacology and biosensor technologies. It has extremely intricate multi-layered mechanisms of functioning, but the great effort over the years all over the world made it possible to map the pathway with a good resolution. Today, the pathway functioning is already used in developing novel pharmaceutics and diagnostics approaches, in therapy follow-up. Filling the existing blanc spots of the NFE2L2/AP-1 interactome would significantly advance the related fields and open new horizons in medical technologies.

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