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# The Expanding List of Redox-Sensing Transcription Factors in Mammalian Cells

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## Editorial

Mammalian cells do not survive in the absence of redox reactions; oxidation and reduction predominate in the swamp of metabolic biochemical reactions inside the cell. In a situation which is less stoichiometric, subtle alterations of the redox status in the intracellular environment also have significant impacts on cell biology. Changes in the intracellular redox status can be assessed by quantifying the reduction potentials of various intracellular redox couples [1]. However, in practice, the motto "redox environment" used by cell biologists usually means the relative abundance of reactive oxygen species (ROS) inside or in proximity of a cell. More than three decades ago people have observed that mammalian cells can actively produce ROS, and utilize these molecules to regulate cell functions [2]. Then it has been discovered that in prokaryotes, some transcription factors switch on and off their DNA binding activity by directly sensing the presence of pro oxidant ROS molecules such as superoxide and hydrogen peroxide, which regulate gene expressions [3]. This phenomenon was also observed in mammalian cells [4]. The term "redox signaling" was coined to describe the process that cells use ROS (including nitric oxide) molecules to carry out intracellular or intercellular communications [5]. The principal molecular mechanism of the redox sensing property of proteins relies on redox modifications of thiol moieties (generally those associated with key cysteine residues) by ROS (oxidation) or nitric oxide (S-nitrosylation) [6]. When discussing redox regulation, we should distinguish whether the relevant signaling proteins are direct redox sensors (i.e., their functions are modulated by redox modification of the proteins per se), or alternatively the activity of the signaling protein is indirectly affected by ROS via other redox sensors. The second issue that needs to be considered is whether the target protein is responsive to intracellularly produced ROS molecules (e.g., from NADPH oxidase or mitochondria, which may be regarded as genuine cellular signal messengers), or can only be activated or inhibited by exogenously applied ROS (mimicking a situation of severe oxidative stress).

The prototype of mammalian transcription factor with redox sensing functions is probably AP-1 (a heterodimer of c-Fos and c-Jun proteins), in which a highly conserved cysteine residue in the DNA-binding domains of both Fos and Jun is sensitive to redox regulation [4]. Oxidation of this cysteine inhibits the DNA binding activity of AP-1, which can be alleviated by thiol antioxidants. Later on, people have identified that mammalian heat shock factor 1 (HSF1) is another transcription factor that can directly sense redox changes. It has been shown that hydrogen peroxide stimulates HSF1 assembly into a homotrimer, which is dependent on two cysteine residues within the HSF1 DNA-binding domain; these cysteines are engaged in formation of redox-sensitive disulfide bonds [7]. HSF1 mutants in which either or both of the cysteines are mutated are defective in ROS-induced trimerization and DNA binding. A very recent study has shown that the Ets transcription factors Etv1, Etv4, and Etv5 can form homodimers via a disulfide-linkage, which exhibit decreased DNA binding affinities as compared to the monomers, indicating a redox-dependent regulatory mechanism that may control the activity of these Ets transcription factors [8]. These Etv proteins are tightly involved in oncogenesis, hence the possible redox-mediated dimerization of these transcription factors may provide a link between the Etv proteins to the responses of cancer cells to their microenvironment. However, the notion that the functions of Etv1/4/5 are subject to redox regulation is predicted by structural analyses, the relevance of this process remains to be confirmed in vivo. Another newly identified redox-sensing transcription factor is Rev-erbβ, a heme-binding nuclear hormone receptor [9]. A thiol-disulfide redox switch in the Rev-erbβ molecule appears to control the interaction between heme and the ligand-binding domain, with the reduced form exhibiting an affinity which is 5-fold higher than that of the oxidized form [9]. Moreover, Okamoto et al. have demonstrated that the muscle-specific transcription factor myocyte enhancer factor 2 (MEF2) can undergo NO-induced nitrosylation, which disrupts MEF2-DNA binding and the transcriptional activity [10]. Specifically, MEF2 dimerization creates a pocket that facilitates S-nitrosylation of an evolutionally conserved cysteine residue in the DNA binding domain. This redox switch inhibits neurogenesis and neuronal survival, and it is suggested that this may be an important molecular mechanism to explain the effects of NO in neurodegenerative diseases [10].

Sensing redox changes by a binding partner/regulator of a transcription factor is also an important fashion of redox-dependent transcriptional regulation in cell biology. For example, the redox-sensitive multifunctional protein APE1/Ref-1 is thought to be a critical redox-dependent regulator of multiple transcription factors, including AP-1, nuclear factor κB, p53, activating transcription factor/cAMP-response element–binding protein (ATF/CREB), and hypoxia-inducible factor-1α [11]. Generally, ROS-induced oxidation of these transcription factors reduces the DNA-binding activity, while Ref-1 appears to be able to reduce the transcription factors thereby stimulating their transcriptional activities [11]. However, in this scenario, the effects of Rel-1 are rather nonspecific, and people would reluctant to consider these processes as particular signaling pathways. Probably the best example of specific regulation of transcription factor function via a redox-sensing auxiliary partner is the Keap1-Nrf2 system. Keap1 is a cysteine-rich protein; three of these cysteines (151, 273 and 288) are thought to be critical for redox-dependent conformational changes of Keap1 [11,12]. Keap1 binds to Nrf2, leading to ubiquitylation and rapid degradation of the Nrf2 protein, while redox modification of Keap1 dissociates Nrf2 from the complex, allowing Nrf2 to translocate and accumulate in the nucleus, driving the

expression of multiple cytoprotective enzymes including NAD(P)H quinone oxidoreductase 1, heme oxygenase 1, glutamate-cysteine ligase and glutathione S transferase [12]. Keap1 is responsive to general oxidative stress stimuli as well as intracellular ROS production from NADPH oxidase [13]. Recently, Smith et al. have provided evidence suggesting that a cysteine-based redox-sensitive switch may exist in the non-receptor tyrosine kinase JAK2, and may regulate JAK2 catalytic activity [14]. JAK2 is the upstream kinase responsible for phosphorylation and activation of the transcription factor STAT following stimulation by multiple cytokines; activation of STAT proteins regulates cell proliferation, survival and myeloid development. It has been demonstrated that two cysteine residues (866 and 917) may act together as a redox-sensitive switch, allowing catalytic activity of JAK2 to be directly regulated by the redox state of the cell; consistently, the activity of a JAK2 mutant in which these two cysteines are replaced by alanine is redox insensitive [14]. Interestingly, another study has shown that STAT3 can also be regulated by redox changes via a different mechanism, involving the thiol peroxidase peroxiredoxin-2 [15]. Peroxiredoxin-2 is one of the most hydrogen peroxide-reactive proteins in the cell, which can form disulfide exchange intermediates with STAT3 and catalyze the formation of disulfide-linked STAT3 oligomers with reduced transcriptional activity. The oxidation of STAT3 is reversible and can be reduced by the thioredoxin system [15]. These results suggest that peroxidase-based redox relays may be a common mechanism in mammalian cells, which can explain the specificity and efficiency of intracellular hydrogen peroxide-mediated signaling. It is intriguing to know whether this redox mechanism is also used by other transcription factors.

The list of transcription factors with direct or indirect redox sensing properties is expanding. In addition to transcription factors, redox sensing proteins belonging to different categories including protein kinases, phosphatases, ion channels and structural proteins are also emerging [16-19]. It is poorly understood why cells contain so many redox sensing proteins. Two plausible explanations are proposed. First, from a viewpoint of evolution, this may highlight the scope of impacts of oxidative stress on mammalian cells. To combat the deleterious effects exerted by oxidative stress, cells need a signaling network, rather than a few isolated pathways, to orchestrate the complex biological activities required to maintain intracellular homeostasis. Secondly, redox signaling on the whole may represent a unified intracellular alarm system for cellular stress response, which integrates and amplifies signals from different kinds of pathways, and primes cells into a relatively stress-resistant status, providing pre-emptive protections against further cellular challenges [20]. Obviously, more studies are required to make a clear picture in this aspect.

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