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Redox-signaling in innate immune memory: Similar mechanisms in animals/humans and plants

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ABSTRACT

Plants and animals/humans have evolved sophisticated innate immune systems to cope with microbial attack. Innate immunity implies the presence of membrane-located and intracellular receptors to recognize compounds released by damage or by invading pathogens. After detection the receptor molecules initiate intracellular defense signaling, resulting in cell death and/or production of defense molecules. Interestingly, the defense response includes also memory mechanisms, which allow the organisms to better cope with future microbial attacks. Redox mechanisms play an important role in defense signaling. In this review article, we compare the innate immune memory of animals/humans and plants and describe how reversible nitric oxide- and reactive oxygen species-dependent protein modifications enable the activation of defense signaling proteins and transcription factors and regulate the activity of chromatin modifying enzymes to establish innate immune memory. We hope to encourage efforts to characterize further molecular redox mechanisms of the innate immune memory, which might enable the development of new immunotherapies.

1. Innate immune memory in animals/humans and plants

Animals/humans and plants are continuously exposed to harmful biotic factors, for example infective virus particles or pathogenic bacteria and fungi. Especially plants as sessile organisms have to cope with the biotic environment at the place they are growing. But also animals/humans cannot easily escape from such pathogenic factors. On the one hand the outer surface of the organisms has direct contact to the environment, on the other hand biotic factors can enter the organisms via mouth/nose (animals/humans) and stomata (plants). In this way also internal organs/tissues are automatically exposed to harmful environmental factors (Fig. 1). So, especially at the borders to the environment effective defense mechanisms are required to respond to negative biotic factors.

Vertebrates are using two main immune systems – the non-specific broad coverage innate immune system on one side and the highly specific antigen-based adaptive immune system on the other side. The adaptive immune system has evolved only in vertebrates and is composed of specialized, systemic cells and processes to eliminate pathogenic microbes and viruses or infected cells. The invaders are recognized via specific antigen-antibody interaction. The adaptive immune system can provide long-term protection against specific pathogens.

The innate immune system is a conserved defense strategy which has evolved in nearly all higher organisms. It enables them to recognize and finally protect against pathogenic invaders. It is more generalized and provides rapid, but less specific protection against a wide range of pathogens.

Since plants do not possess a specific antigen-based adaptive immune system, their protection against biotic stress has to rely on their innate immune system. The associated immune mechanisms converge on phytohormone signaling pathways that drive resistance against different types of pathogens.

It was assumed for long time that the immune memory was a solely feature of the adaptive immune system. However, memory effects have been already described in the innate immune system of plants nearly 100 years ago [1]. In 1933 priming, at that time termed ‘sensitization’, was commonly accepted as predominant phenomenon in plant systemic immunity [2]. In the last two decades, molecular, genetic and epigenetic tools allowed a detailed characterization of the mechanisms behind this immune memory process [1,3–8]. Especially systemic acquired resistance (SAR), an inducible defense mechanism that enables long-lasting

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protection of the whole plant against a broad spectrum of microorganisms, has been investigated intensively [9–14]. Interestingly, such an innate immune memory occurs not only in plants, but also in animals/humans, where it is called "trained immunity". In general, when an organism has experiences biotic or abiotic stress, the signaling pathways and genes can become more sensitive or responsive to subsequent stimuli, allowing for a more rapid and effective response to future challenges (Fig. 2).

In plants and animals/humans, the innate immune response involves a complex network of signaling, including phosphorylation reactions and the alteration of nitric oxide (NO), reactive nitrogen species (RNS) and reactive oxygen species (ROS) production. Finally, the cells respond with genetic reprogramming and the synthesis of defense molecules. Additionally, cells undergo epigenetic changes in the training/priming phase, which have a key function in the memory process. In all of these processes, redox molecules as well as phosphorylation reactions have an important regulatory function via post-translationally modifying signaling proteins, enzymes of the methylation cycle, chromatin modifier or histone proteins (summarized in Refs. [15–19]). Moreover, they affect RNA-based mechanisms of chromatin regulation [16,18,20]. The general principle of innate immune mechanisms is depicted in Fig. 3.

2. Redox-signaling plays a pivotal role in innate immunity in animals/humans and plants

The evolution of photosynthetic active organisms ~2.5 billion years ago resulted in accumulation of oxygen and decrease of carbon dioxide. On one side essential for energy generation, the oxygen metabolism can on the other side produce reactive by-products that oxidize and damage all kinds of biological molecules. As a result of evolution, organisms are not only adapted to these toxic effects via developing anti-oxidative strategies or effective mechanisms to repair the oxidative damage, but are also using these reactive compounds as signaling molecules to regulate physiological processes, such as growth, development and stress response. Besides ROS, NO is another reactive molecule with biological effects. NO is a short-lived radical that regulates many physiological processes. It is well established that ROS and NO act as signaling molecules via transducing extracellular information to induce specific cellular response.

The general principle of redox-signaling is highly conserved within different kingdoms and is primarily based on redox-dependent modification of proteins. Metal nitrosylation corresponds to the direct binding of NO to transition metals of metalloproteins resulting in a metal–nitrosyl complexes. In mammals, examples for this type of modification are the binding of NO to the iron of the heme center in cytochrome *c* oxidase and soluble guanylate cyclase. In both enzymes, NO binding results in conformational changes, leading to inactivation of cytochrome oxidase and activation of soluble guanylate cyclase [21,22]. The oxidation of distinct amino acids of proteins can result in altered protein function/activity and if the modification is reversible, it represents an optimal biochemical regulatory mechanism. The most important redox-sensitive amino acid is cysteine (Cys), but also other amino acids, e. g. tyrosine, tryptophan, methionine, or histidine, can be oxidized. During redox signaling, NO or ROS are oxidizing the thiolate anion of cysteine residues reversibly to a S-nitrosothiol (Cys-SNO) or the sulfenic form (Cys–SOH), respectively [23–25]. The reversible, covalent modification of cysteine thiols by NO is termed *S*-nitrosation. Additionally, oxidation of Cys thiol groups can result in formation of disulfide bridges that can be reduced again to thiols via the action of distinct reductases or just in presence of strong reducing agents. This kind of post-translational modification is also an important redox-signaling mechanism and is conserved in all living organisms. However, depended on the concentration and exposure time, ROS can have deleterious effects on proteins, e. g. formation of irreversible sulfinic (Cys–SO_2H) and sulfonic acids (Cys–SO_3H), or carbonyl groups [26,27]. Moreover, superoxide can react with NO resulting in peroxynitrite, a very potent oxidant that nitrates proteins, lipids, nucleic acids and metabolites [28]. Hence, ROS and NO homeostasis is in general very important for optimal performance of an organism.

In plants, rapid generation and accumulation of ROS and RNS, termed as "oxidative burst", is one of the earliest responses to pathogen detection. S-Nitrosothiols regulate different immune signaling pathways [29] and there are several immunity-related targets of S-nitrosation identified [30]. For instance, NO-dependent regulation of salicylic acid binding protein 3 [31], zinc finger protein SRG1 and SRG3 [32,33], botrytis-induced kinase 1 (BIK1) [34] and NADPH oxidase RBOHD [35] is crucial for effective defense response. Interestingly, there is a direct interaction between NO-signaling and ROS production. Pathogen

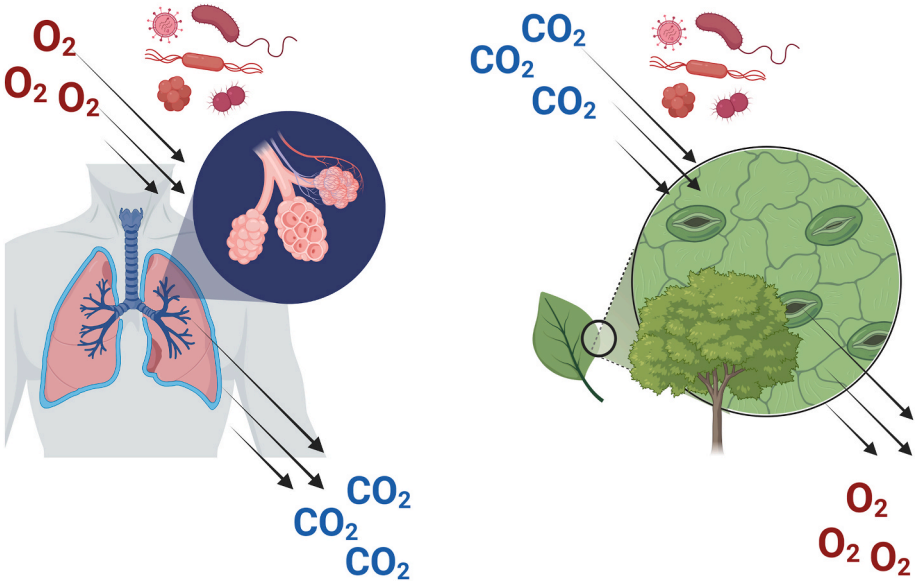


Fig. 1. Lung and leaf have direct contact to the environment and are critical entering gates for undesirable biotic factors. The primarily function of the lung and leaves is gas exchange, meaning uptake of oxygen (animals/humans) or carbon dioxide (plants) and release of carbon dioxide (animals/humans) or oxygen (plants). The gases are taken via mouth/nose (animals/humans) or stomata (plants). In this way also biotic environmental factors are taken up and get in direct contact with internal organs and tissues. Created in https://BioRender.com.

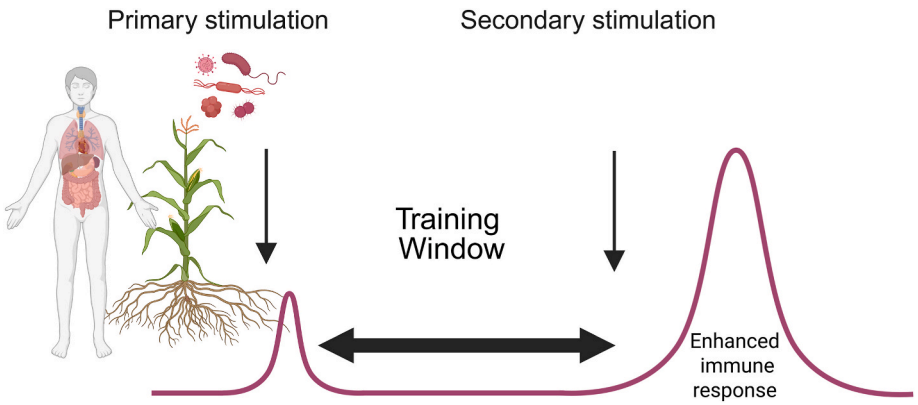


Fig. 2. Innate immune memory in plants and animals/humans. A first stimulus is inducing the priming or training process in plants and animals/humans, respectively. This physiological state allows a more rapid and robust response to very low levels of a (second) stimulus. Created in https://BioRender.com.

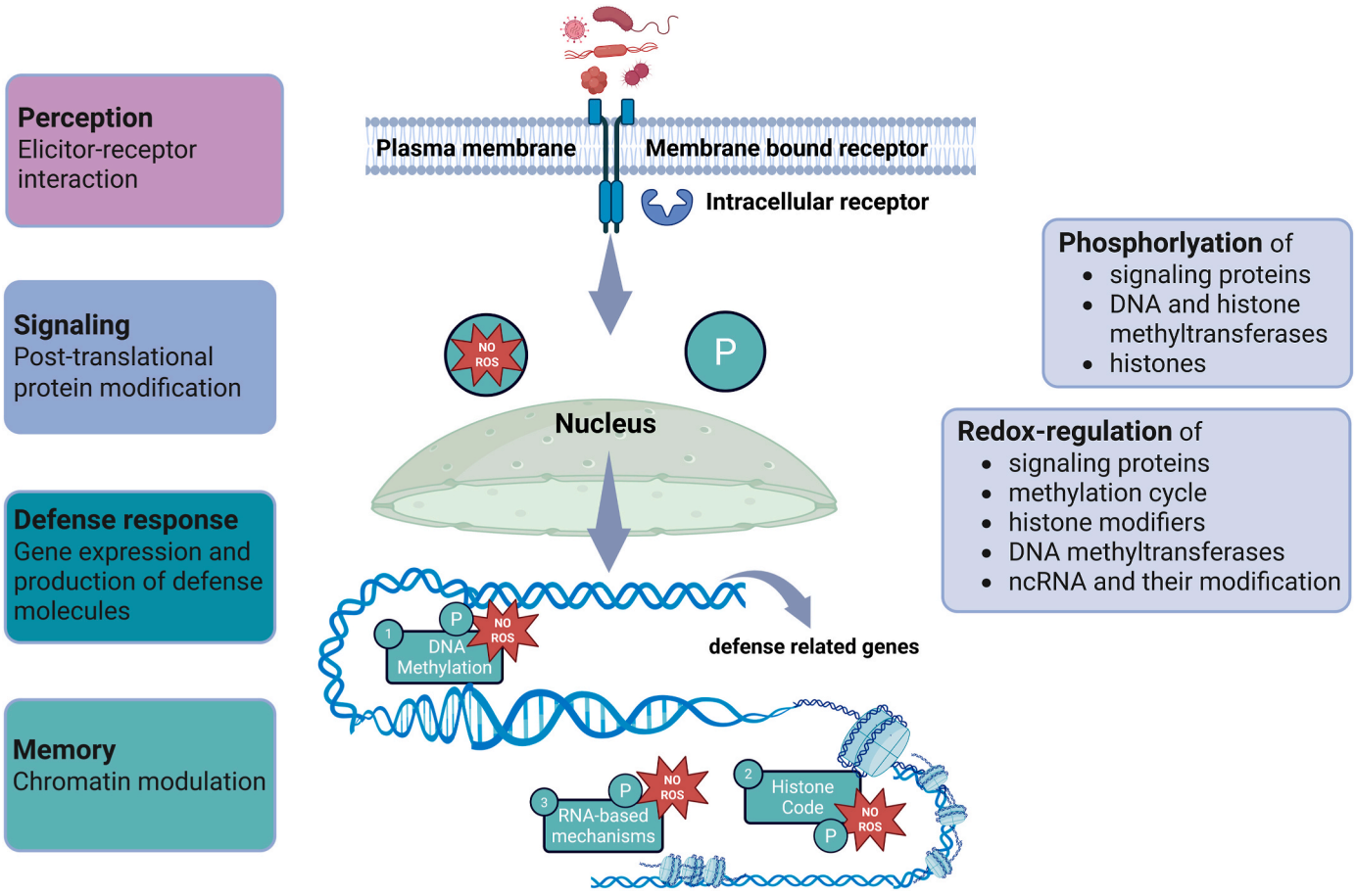


Fig. 3. The principle of innate immune mechanisms is evolutionary conserved in plants and animals/humans. Pathogen perception is achieved via specific membrane-bound or intracellular receptor proteins. Signaling makes use of redox and phosphorylation reactions (post-translational modifications). Main targets of these modifications are summarized in boxes on the right. Finally expression of defense-related genes and production of defense molecules are regulated in this way. Moreover, stress memory is induced via chromatin modulation to enable a faster and stronger response to future infections. Chromatin structure and accessibility is affect by methylation of C5 position of cytosine [1], modification of lysine, arginine, serine, threonine and tyrosine residues of histone tails [2] and the interaction with non-coding RNA [3]. Created in https://BioRender.com.

recognition triggers the nitrosative burst, leading to S-nitrosation of BIK1 and its activation, including BIK1 phosphorylation. Phosphorylated BIK1 interacts with RBOHD promoting oxidative burst and associated defense response [34]. Interestingly, in plants abiotic stress reactions are interfering with biotic stress response [36,37]. For instance, cold is activating nucleotide-binding leucine-rich repeat receptors, ROS production, MAP kinases and NPR1, resulting in expression of defense genes.

In animals/mammals, ROS and RNS fulfil important regulatory functions in the activation and performance of defense-related cells, such as neutrophils, T-cells, B-cells, macrophages, dendritic cells and natural killer cells. During immune-inflammatory responses the redox changes are arranged via many different factors, such as mitogen-activated protein kinases, the phosphatidylinositol 3-kinase/protein

kinase B signaling pathway, nuclear factor kappa beta (NF-κB), HIF1α, the mechanistic target of rapamycin, and others [38]. Moreover, intracellular and extracellular levels of ROS/RNS are important for performance and survival of individual immune cells. Important sources of ROS production in innate immune response are, similar as in plants, NADPH oxidases (primarily NOX2 and NOX4) [39–41].

In macrophages, alteration of the redox state is crucial for controlling many vital cellular functions, such as transcription, differentiation and inflammatory response [42–44]. NO, especially produced from inducible nitric oxide synthase (iNOS) has also important roles in immune regulation, inflammation and microbial invasion [45]. Together with ROS, NO can have toxic effects on invading bacteria and virus to prevent infection. This includes for example S-nitrosation of vital pathogen enzymes. Antiviral effects of NO has been demonstrated against RNA and DNA viruses via affecting virus replication [46–48]. However, there are also examples that viral activities can impair host NO production [49]. Besides that, NO seems to be involved in regulating epithelial ciliary beating, which is a first physical barrier to prevent pathogens reaching the inside of the lung [50].

Moreover, NO regulates the activity of several inflammatory mediators on the posttranslational level. NF-κB has a pivotal function in the inflammatory response of the airway epithelium. Dependent on the time of exposure and the NO level, the "activity" of NF-κB increases or decreases. After iNOS induction, elevated NO increases activation of NF-κB via cGMP-dependent and independent pathways. To avoid prolonged NF-κB activation and consequently inflammation, NO inhibits NF-κB "activity" via a feedback mechanism [51]. Moreover, a dual redox regulation of NF-κB via H_2O_2 has been described [52]. Interestingly, NO increases interleukin 8 (IL-8) expression in airway epithelial cells highlighting the importance of NO in the initiation of an inflammatory response in the airway epithelium [53]. In sum, redox-associated mechanisms modulate a large number of immune response pathways and an imbalance of the redox system can result in a decreased or increased immune response.

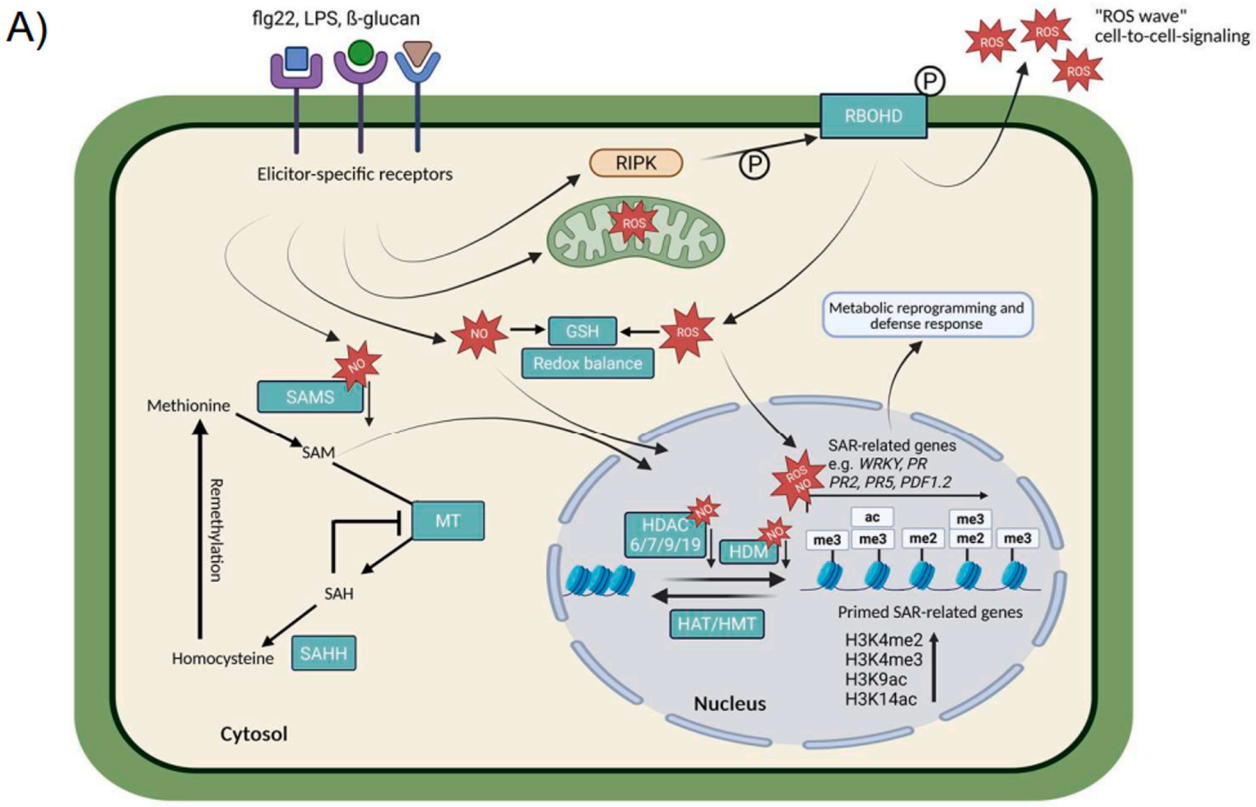
3. Redox-signaling in innate immune memory

Redox signaling seems to be a key process in "training" of the immune system in both plants and animals (Fig. 4). In plants, exposure to biotic stressors leads to production of NO and ROS, which can subsequently modulate and activate cellular pathways regulating the defense response (Fig. 4A). In this context, NO and ROS can also function as second messengers in priming plants for future stress conditions. For example, extracellular polysaccharides of *Bacillus cereus* AR156 are priming plant defense by inducing the accumulation of H_2O_2 followed by activation of peroxidases and superoxide dismutases, primarily via SA and MAPK signaling pathways [54]. Pyocyanin, produced by *Pseudomonas aeruginosa* 7NSK2, increases H_2O_2 levels both in the treated leaves as well as in distal leaves resulting in resistance to blast disease (*Magnaporthe grisea*) but not sheath blight (*Rhizoctonia solani*). Interestingly, applying the antioxidant sodium ascorbate together with pyocyanin alleviates the opposite effect, suggesting that ROS can act in different directions in priming against different diseases [55].

In Arabidopsis, SAR-related ROS is produced by chloroplasts, mitochondria or by plasma membrane-localized NADPH oxidase "respiratory burst oxidase homolog D" (RBOHD) [6]. In SAR, a newly identified receptor-like cytoplasmic kinases, "RPM1-induced protein kinase" (RIPK), was proposed to regulate ROS production [56]. RIPK phosphorylates the N-terminal part of RBOHD. Consequently, mutation of RIPK results in reduced ROS accumulation and impaired SAR in response to pipecolic acid and SA [56], suggesting that this kinase might be acting specifically in SAR as positive regulator of RBOHD-mediated ROS production. Recently, H_2O_2 has been identified as mobile signal that activates the transcription factor "CCA1 hicking expedition" via sulfenylation of a cysteine residue in systemic tissues [57]. In addition, redox signaling via ROS and NO can directly activate defense-related genes and lead to the synthesis of phytohormones, such as salicylic acid, that on one side help to enhance the immune response and on the other side act as essential initiator of local and systemic priming of the defense system [58]. Interestingly, the production of antioxidants, such as glutathione (GSH), play a key role in redox-signaling in innate immune memory, predominantly via keeping the optimal "oxidative-reductive balance" [59,60]. This has been demonstrated for example by buthionine sulfoximine-dependent inhibition of GSH biosynthesis, which resulted in elevated ROS accumulation, accelerated oxidative damage and finally in compromised SAR [59]. Moreover, analysis of knock-out mutants of γ-glutamylcysteine synthetase (cad2-1, pad2-1), an enzyme of the GSH biosynthesis pathway, further demonstrated that GSH is required for SA signaling and the activation of defense response [60–62]. In this context the function of thiol reductases, such as glutaredoxin and thioredoxin (TRX) also needs to be mentioned. These enzymes catalyze the reduction of oxidized cysteine residues to enable RNS and ROS signaling and to preserve the activity of antioxidant enzymes in innate immune memory [6,63,64]. E. g. S-nitrosylation of NPR1 at Cys156 facilitates its disulphide-linked oligomerization, thereby impeding NPR1-induced gene activation [65]. Both, TRX-h5-dependent disulphide reduction as well as TRX-h5-dependent denitrosylation of NPR1, result in its nuclear transloction, where NPR1 is involved in activation of defense genes [65–67]. Similarly, mammalian NF-κB transcription factor function in the respiratory epithelium is inhibited by site-specific S-nitrosylation. In response to cytokine stimulation, NF-κB is denitrosylated by thioredoxin 1 enabling its transcriptional activity [68].

Like in plants, GSH metabolism also contributes to the establishment of innate immune memory in animals/humans [69,70]. Inhibition of β-glucan induced GSH biosynthesis with buthionine sulfoximine resulted in decreased IL-6 accumulation after LPS re-stimulation. However, the detailed regulatory role of GSH in induction of immune training is not known. It's important to highlight that the function of redox signaling in innate immune memory is complex and context-dependent. ROS/NO-dependent signaling plays also a key function in the activation of the immune response in animals/humans [38,71–73] (Fig. 4B). Here too, exposure to pathogens results in the accumulation of NO and ROS, which subsequently activate immune cells as well as transcription factors that are regulating immune gene expression. Moreover, NO and ROS function as second messengers in amplifying the immune response and training of cells for future infections, although the target proteins and their redox-sensitive cysteine residues are still not completely characterized for these processes [43,74–78]. Remarkably, β-glucan or Bacillus Calmette-Guérin-induced elevated ROS levels have been observed even after a 5-day resting period and pretreatment with the ROS scavenger N-acetyl cysteine significantly reduces TNFα production compared to cells treated with β-glucan alone [69]. Although these results demonstrate a participation of ROS in establishing innate immune memory, the exact ROS-dependent molecular mechanisms still needs to be investigated in detail.

Interestingly, in oxLDL-induced trained immunity in human monocytes, mTOR regulates cytosolic and mitochondrial ROS production [79]. Furthermore, ROS production has been observed in monocytes in case of training with Bacillus Calmette-Guérin and oxLDL [80]. Pre-treatment of laying and broiler hen monocytes with a combination of β-glucan microparticulates and IL-4 resulted in enhanced expression of IL-1β, HIF1α and iNOS after re-stimulation with LPS [75]. In contrast, enhanced NO production and CD40 expression was only observed in layers [76]. Moreover, scavenging of ß-glucan-induced ROS accumulation reduced the amount of released IL-6 and IL-8 in A549 lung epithelial cells, suggesting a regulatory function of ROS in initiating innate immune memory [78]. In response to injury, intracellular accumulation of H_2O_2 in hemocytes is required for induction of the cytokine upd-3 in adult *Drosophila*. Interestingly, at the site of a sterile injury, hemocyte activation and production of ROS resulted in innate immune training and protection against subsequent infection [77]. Moreover, ROS



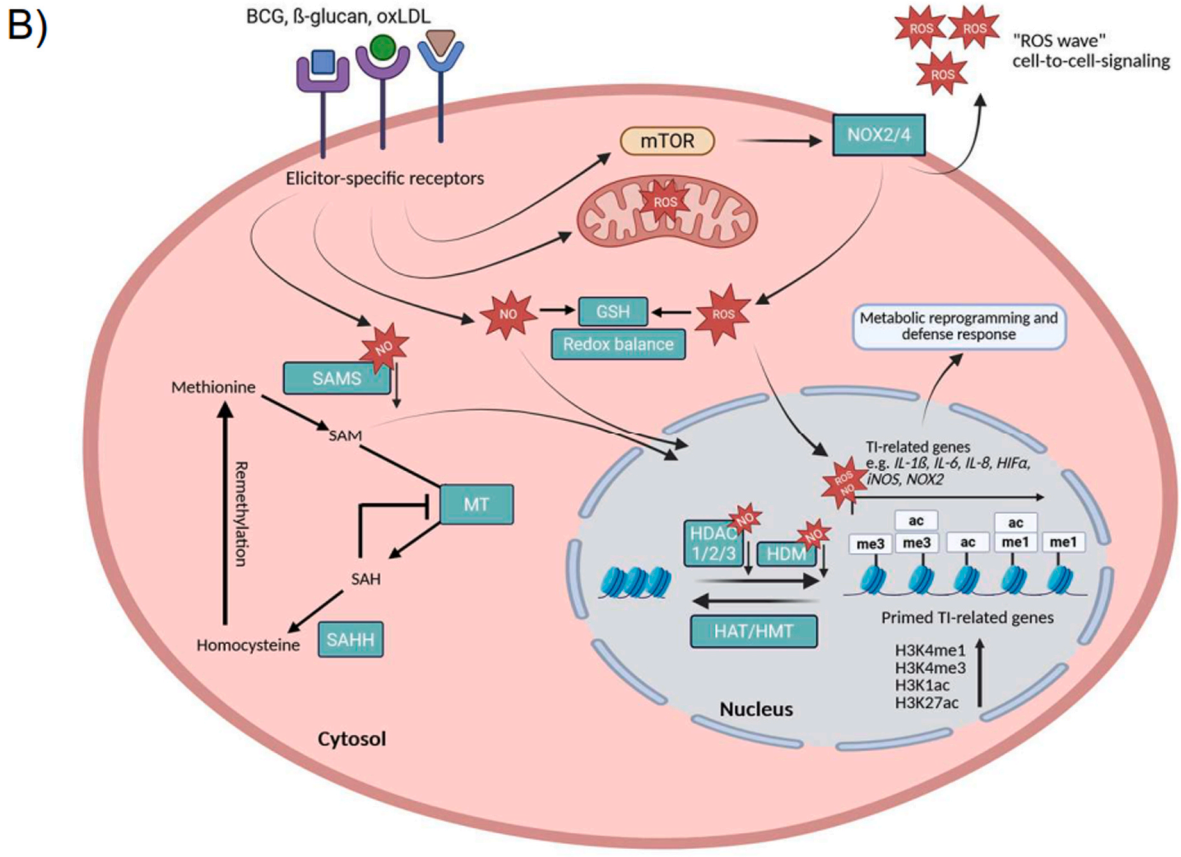


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Fig. 4. Simplified model showing functions of ROS/NO in innate immune memory in plants (A) and animals/humans (B). Elicitors are detected via elicitor-specific receptor molecules. In plants, this interaction is activating RIPK, which is phosphorylating NADPH oxidase RBOHD resulting in ROS production. Similar in animals, elicitor-receptor interaction activates mTOR, which is inducing ROS production via NOX2/4. Moreover, elicitor-receptor interaction leads to mitochondrial ROS production as well as NO production. To keep the redox balance, in both systems biosynthesis of glutathione is required for establishing innate immune memory. Moreover, thiol reductases are reducing oxidative thiol modifications to facilitate RNS and ROS signaling and to preserve the activity of antioxidant enzymes. Produced NO inhibits nuclear histone deacetylases and histone demethylases resulting in loosen chromatin structure at SAR/TI-related genes. Redox-sensitive plant histone deacetylases are 6, 7, 9, and 19, whereas histone deacetylase 1, 2, and 3 are redox-sensitive animal histone deacetylases. In both systems, H3K4 methylation and H3K14 acetylation is increased resulting in accessible chromatin structure reflecting gene priming. Additionally, NO regulates the supply of the methyl group donor S-adenosylmethionine via inhibition of S-adenosylmethionine synthetase. Moreover, ROS and NO can directly activate transcription factors responsible for expression of SAR/TI-related genes. Extracellular ROS is inducing "ROS waves", which are spreading throughout cell colonies, tissues, or even organisms as part of systemic innate immune memory. SAMS: S-adenosylmethionine synthetase, SAH: S-adenosylhomocysteine, MT: methyltransferase, HDAC: histone deacetylase, HDM: histone demethylase, HAT: histone acetyltransferase, HMT: histone methyltransferase, GSH: glutathione, NOX: NADPH oxidase, RBOH: respiratory burst oxidase homolog D, me: methyl group, ac: acetyl group. Created in https://BioRender.com.

production activates the transcription factor HIF1α, which is involved in metabolic reprogramming during innate immune memory [81–83]. While NO and ROS can be beneficial in training/priming the innate immune response, excessive NO and ROS production can lead to cellular damage and the development of chronic inflammatory diseases (maladaptive trained immunity).

Interestingly, the function of ROS as long distance signaling molecules might be important for establishing systemic innate immune memory in animals/humans and plants. The principle of systemic ROS signaling is based on cell-to-cell signaling [84–87]. Extracellular NADPH oxidase-produced ROS is detected by neighboring cells and initiates extracellular ROS production in these cells, which is again detected by neighboring cells. This results finally in so called "ROS waves", which are spreading throughout cell colonies, tissues, or even organisms [87]. In Arabidopsis, leucine-rich-repeat receptor-like kinase "H_2O_2-induced Ca^{2+} increases 1" (HPCA1) functions as H_2O_2 receptor, which is initiating the amplification and propagation of this extracellular ROS signaling [88]. Overall, redox signaling seems to be a key process in trained immunity and understanding the mechanisms of redox signaling in innate immune memory may enable to engineering new therapeutics/compounds to strengthen human, animal or plant immunity.

4. Redox-regulation of epigenetic processes in innate immune memory

Epigenetic modifications play a crucial role in innate immune memory. Such modifications involve a range of different molecular mechanisms, such as DNA methylation, histone modifications, as well as the synthesis of non-coding RNA molecules. Their primarily function is the regulation of the accessibility of the DNA for regulatory proteins and transcription factors. This includes on one side the compactness of the chromatin structure and on the other side the ability of DNA-binding proteins to interact with the DNA. Epigenetic modifications can be inherited through cell division and can be influenced by environmental factors.

In plants, alteration of the chromatin structure is important for regulating gene expression in response to biotic stress and the involvement of chromatin modifications in immune priming was also described [89]. In SAR, transcriptional memory is associated with sustained changes in histone modifications, such as H3K4me2, H3K4me3, H3K9ac, H4K5ac, H4K8ac, and H4K12ac [90,91]. In animals/humans, chromatin modifications also function as important regulators of immune responses and immune memory. There are multiple epigenetic marks associated with trained immunity. For example, an enhanced level of H3K4me3, a mark observed at the promoter regions of actively transcribed genes, an enhanced level of H3K4me1, typically found at distal enhancers, as well as an enhanced level of H3K27ac, which marks active enhancers and promotor regions, have been observed after stimulation of human monocytes/macrophages with β-glucan or BCG [92,93]. Additionally, an enhanced level of the activating mark H3K14ac has been observed in many stimuli-induced immune training conditions [94], whereas the level of the repressive histone mark H3K9me2 decreased [95].

Interestingly, the level of some of these marks is altered by ROS/RNS. In mammals, NO regulates histone and DNA methylation in different ways (reviewed in Refs. [96–98]). On one side, NO affects the transcription of DNA and histone methyltransferases as well as demethylases. For instance, the expression of H3K9-histone methyltransferases is differentially regulated by NO in human cells. In response to NO treatment, the expression of both H3K9-tri-methylases, SETDB2 and SUV39H2, is increased, while that of the H3K9-di-methylase G9a is decreased [96,99]. Moreover, application of the RNS and ROS generating compound RRX-001 reduced the expression of mammalian DNA methyltransferases (DNMTs) resulting in decreased global DNA methylation levels [100]. In contrast, the expression of DNMTs is not changed after treatment of mammalian cells with the NO donor SNAP [101].

On the other side, DNA and histone methylation can be regulated via the supply of the predominant methyl-group donor S-adenosylmethionine (SAM). In both animals and plants, the availability of SAM is controlled via redox mechanisms. The activity of S-adenosylmethionine synthetase, for instance, is inhibited by S-nitrosylation of a cysteine residue nearby its substrate binding site [102,103]. But there is also evidence that other enzymes of the SAM metabolism, such as methionine synthase, S-adenosylhomocysteine hydrolase or betaine homocysteine methyltransferase, are targets for redox modifications [104–106].

Moreover, NO directly affects the enzymatic activities of chromatin-modifying enzymes. For example, application of NO to a nuclear extracts, increased the activity of DNMTs [101]. Similarly, *Helicobacter pylori* induced endogenous NO production correlated with increased DNMT activity and resulted in increased DNA methylation [107]. Furthermore, several studies have demonstrated that HMTs activities are also redox-sensitive [108,109]. For instance, the NO donor DETA-NO globally increases H3K9me2, H3K9me3, and H3K36me3 levels in macrophages. This could be due to the NO-dependent inhibition of non-heme iron dioxygenases such as JmjC domain-containing histone demethylases and TET DNA-demethylases. Here, NO and the catalytic non-heme iron of the enzymes is forming a nitrosyl–iron complex [99,110]. In sum, redox reactions are important mechanisms to regulate the activity of chromatin-modifying enzymes, enabling alteration of histone modification patterns and DNA methylation levels in mammalians and might play a key role in stress memory.

In plants, the activity of chromatin-modifiers responsible for histone (de)acetylation and (de)methylation and DNA (de)methylation seems to be also controlled by ROS and/or NO [106]. There is evidence that cysteine residues of plant HDAC6 are a target for NO [111]. Moreover, H3K9 and H3K14 acetylation is enhanced in genes involved in plant defense response after treatment with NO [112], which could be also part of the priming and memory process.

Interestingly, plants and animals/humans share a group of conserved histone deacetylases [16]. The comparison of the amino acid sequences of 18 Arabidopsis HDACs and 18 *Homo sapiens* HDACs revealed, that HsHDAC1, HsHDAC2, HsHDAC3 share 43,9–55,9 % sequence identity with AtHDAC6, AtHDAC7, AtHDAC9, and AtHDAC19. Within the

catalytic domain the identity is up to 70 %. Human HDAC2 is S-nitrosated at Cys262 and Cys274, both are located close to the substrate biding site [113,114]. These cysteine residues are also conserved in HDAC6, HDAC9 and HDAC19 of many plant species [115] and there is already evidence that these cysteine residues are a target for NO in plants as well [111,116,117]. In AtHDAC7 only the cysteine residue corresponding to Cys262 of HsHDA2 is conserved. Interestingly, the physiological function of AtHDAC6, AtHDAC9, and AtHDAC19 is related to stress response [111,118,119] and also the function of mammalian HDAC1, HDAC2, and HDAC3 is described in context of stress and immune response [120,121]. Important similarities in redox signaling in plant and animal/human innate immune memory are summarized in Fig. 4.

5. Conclusion

Animals/humans and plants share sophisticated mechanisms for sensing and responding to invading pathogens and particles. They include receptor proteins and cellular signaling enzymes and similar modifications of the chromatin structure. Enhanced levels of H3K4me3 marks in defense gene promoters enable a faster and more effective response to future challenges. Redox molecules, such as ROS and NO are key players in regulating stress response, adaptation as well as immune memory and many redox-dependent mechanisms are conserved in animals/humans and plants. The increasing knowledge about these mechanism in innate immune memory might offer promising tools to improve human/animal health as well as sustainable agriculture. Actually, there are already several redox-based priming approaches described and discussed. In plants, different “redox-priming” strategies have be followed in the past, e. g. treatment with redox-active compounds (e. g. H_2O_2, sodium nitroprisside, S-nitrosoglutathione, hydrogensulphide, GSH, ascorbate) to induce/prime redox-sensitive genes or genes of the anti-oxidative system (summarized in Refs. [122–124]) to finally improve stress response or enhance growth and development. For example, redox priming of *Zygophyllum simplex* seeds with H_2O_2 or NO donor sodium nitroprusside improves seed germination and seedling growth under high salinity conditions [125]. Moreover, application of H_2O_2 reduced negative drought effects and improved yield in quinoa [126]. But also expression of pathogen-related defense genes can be induced by spraying a NO donor solution (S-nitrosoglutathione) on the leaf surface [60]. However, since NO donors are often quite unstable when directly applied to the plant surface (light-sensitivity), nanoparticles have be used to encapsulate NO donors resulting in a higher stability and a slower NO release [127]. Encapsulation of redox-active compounds might by also a promising approach to enable a controlled, tissue- or organ-specific redox-priming in humans/animals. This is of special importance, since an uncontrolled use of such redox compounds could unbalance intracellular redox-signaling resulting in contradictory or harmful effects due to unwanted activation of redox-sensitive transcription factors.

Although therapies with anti-oxidative compounds have demonstrated potential in conditions primarily driven by oxidative stress, their effectiveness in diseases with complex and multifactorial causes is still debated. A more nuanced understanding of the functions of redox-sensitive proteins and their redox-modified cysteine residues in trained immunity is essential for developing targeted treatments that aim to modulate specific redox-signaling pathways. Moreover, a targeted activation/inhibition of the “ROS wave” might allow to modulating the spreading of the redox response. In general, small molecule compounds that selectively target specific redox-sensitive processes have already shown encouraging preclinical results and might enter the way into clinical trials. In sum, such redox-based approaches can be promising tools for developing new immunotherapies to promote trained immunity on one side and to treat excessive or defective trained immunity on the other side.

CRediT authorship contribution statement

Christian Lindermayr: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Ali Önder Yildirim:** Writing – review & editing.

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Declaration of competing interest

None.

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Data availability

No data was used for the research described in the article.

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