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Review

Redox regulation of cytoskeletal dynamics during differentiation and de-differentiation☆

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ABSTRACT

Background: The cytoskeleton, unlike the bony vertebrate skeleton or the exoskeleton of invertebrates, is a highly dynamic meshwork of protein filaments that spans through the cytosol of eukaryotic cells. Especially actin filaments and microtubuli do not only provide structure and points of attachments, but they also shape cells, they are the basis for intracellular transport and distribution, all types of cell movement, and – through specific junctions and points of adhesion – join cells together to form tissues, organs, and organisms.
Scope of review: The fine tuned regulation of cytoskeletal dynamics is thus indispensible for cell differentiation and all developmental processes. Here, we discussed redox signalling mechanisms that control this dynamic remodeling. Foremost, we emphasised recent discoveries that demonstrated reversible thiol and methionyl switches in the regulation of actin dynamics.
Major conclusions: Thiol and methionyl switches play an essential role in the regulation of cytoskeletal dynamics.
General significance: The dynamic remodeling of the cytoskeleton is controlled by various redox switches. These mechanisms are indispensible during development and organogenesis and might contribute to numerous pathological conditions. This article is part of a Special Issue entitled Redox regulation of differentiation and de-differentiation.

1. Redox signalling

Cells constantly receive and process signals from their environment. The coordinated and specific response to these signals is the basis of essentially all cell functions. Errors, misinterpretations, or displacements in these signal transduction events are responsible for numerous diseases such as malignant or degenerative disorders. Signalling molecules are sensed by an extra- or intracellular receptor molecule; the activated receptor promotes the activation of transducer proteins, such as protein kinases, often through the conversion, production, release, or elimination of second messenger molecules such as calcium ions, cyclic adenosine monophosphate, or nitric oxide. Transducer proteins regulate further messenger molecules or act directly on effector molecules that trigger the biological response. These complex pathways and networks allow for the amplification, modulation, and adaptation of signal and response. In recent years, the reversible redox modifications of protein side chains emerged as a key mechanism that affects essentially all signalling pathways, in a rapid, compartmentalised, reversible, and highly specific manner [1–4]. Most notably, these post-translational redox modifications do not occur randomly, they need to be catalysed by specific enzymes [5].

1.1. Redox modifications of cysteinyl side chains

The major targets of redox signalling are cysteinyl side chains (Fig. 1). Two protein thiols can be oxidised to an intra- or intermolecular disulfide. Disulfides may also form with small molecular weight thiols, such as the most abundant cellular thiol compound, glutathione (GSH). This modification is known as S-glutathionylation [6]. S-nitrosylation of protein thiols can be induced, for instance, by metal catalysed reaction of endogenously produced nitric oxide with thiols, or by the subsequent transfer of S-nitroso groups to other thiols, i.e.

Abbreviations: ARP, actin-related protein; CDC42, cell division control protein 42; CRMP2, collapsin response mediator protein2; DPYL2, dihydropyrimidinase like protein 2; EAE, experimental autoimmune encephalomyelitis; GR, glutathione reductase; Grx, glutaredoxin; GSH, glutathione; GSSG, glutathione disulfide; Hif, hypoxia-inducible factor; MICAL, molecule interacting with CasL; MS, multiple sclerosis; Msr, methionine sulfoxide reductase; NDPK, nucleoside diphosphate kinase; NP1, neuropilin-1; OPC, ooligodendroglial progenitor cells; PlexA, class A plexin; Rac, RAS-related C3 botulinum toxin substrate; Rho, Ras homolog gene family member; Sema, semaphorin; SIRT1, sirtuin 1; Trx, thioredoxin, TrxR, thioredoxin reductase; VEGF-C, vascular endothelial growth factor-C; WASP, Wiskott–Aldrich syndrome protein; WAVE, WASP-family verprolin-homologous protein

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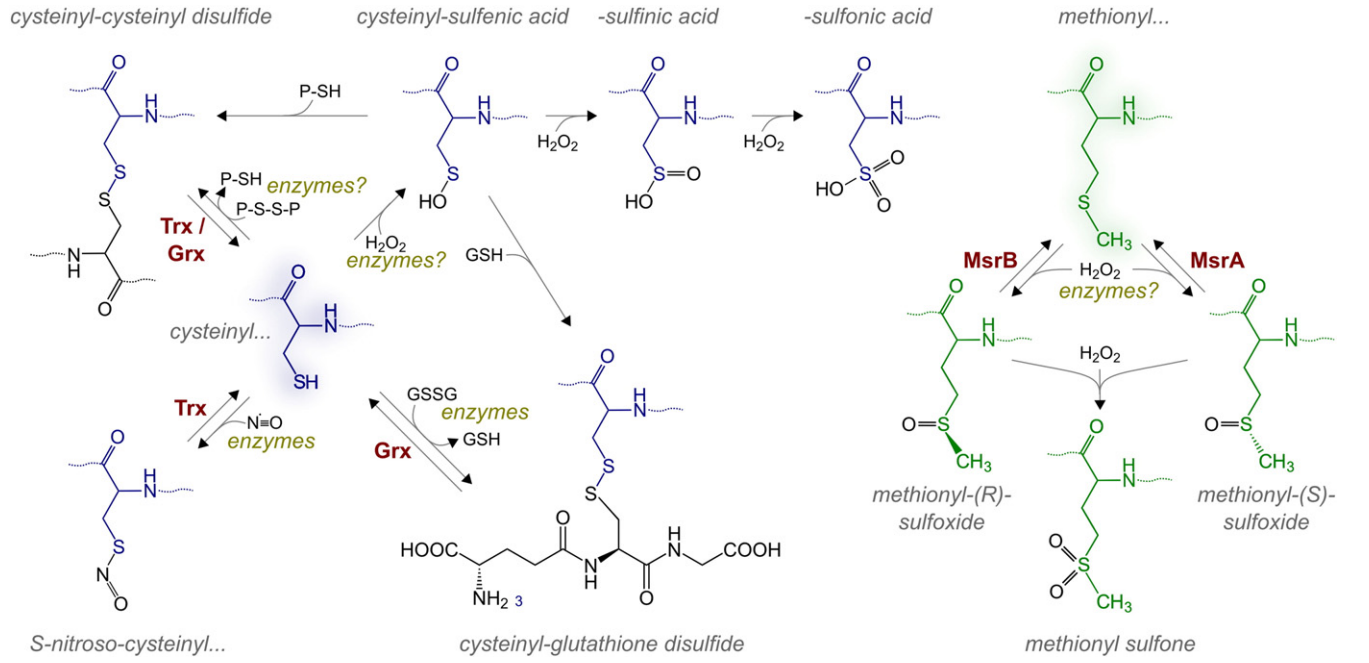

Fig. 1. Redox modifications of protein cysteinyl and methionyl residues. In the presence of another thiol (SH), the cysteinyl residue (left site, blue) can be modified to a protein (cysteinyl–cysteinyl) disulfide, that can be reduced by Trxs and Grxs, or cysteinyl–glutathione mixed disulfides. Protein cysteinyl residues can be oxidised to sulfenic acid (R-SOH) by peroxides or (at least in some cases) specific enzymes. In the presence of excessive peroxides this may be irreversibly 'over'-oxidised to sulfinic ($R\text{-}SO_2H$) and sulfonic acid ($R\text{-}SO_3H$). Cysteinyl–glutathione disulfides may also be formed through thiol–disulfide exchange reactions with glutathione disulfide or by specific enzymes, e.g. Grxs that also specifically catalyse the reduction of these disulfides. Nitric oxide (·NO) in general can only lead to the nitrosylation of cysteinyl residues through the catalysis during which one electron is transferred from the ·NO to a recipient, e.g. a metal cofactor. S-nitrosylation can be reversed by trans-nitrosylation to another protein thiol, e.g. to the active site of Trxs. Methionyl residues (right site) are oxidised stero-selective to R- or S-methionyl sulfoxides. These are specific substrates for methionine sulfoxide reductases (Msr) B and A, respectively. Further oxidation of methionyl sulfoxides results in methionyl sulfone, a step that has to be considered irreversible.

trans-nitrosylation [7,8]. Via the reaction with hydrogen peroxide or peroxy nitrite, cysteinyl thiols may be oxidised to sulfenic acids or further to sulfinic and sulfonic acids [9], the latter two have to be considered irreversible, although they do occur at specific target sites as well [10]. These modifications are specific for both the redox active compound, i.e. the second messenger, and the cysteinyl side chain of the transducer and effector proteins, respectively [11]. This specificity is determined by the molecular environment of the thiol group and the modifying enzymes potentially involved.

The key enzymes that catalyse post-translational redox modifications of protein thiol groups, for instance disulfide reduction, S-glutathionylation, and trans-nitrosylation, are part of the thioredoxin family of proteins, namely thioredoxins (Trxs) and glutaredoxins (Grxs) [12–15]. Isoforms of these proteins are ubiquitously expressed in all organisms, tissues, cells, and targeted to all subcellular compartments, including the extracellular space. The members of this protein family are characterised by a common structural motif of approximately 12 kDa, the thioredoxin fold, and the highly conserved dithiol active site motif, Cys-X-X-Cys, that facilitates thiol–disulfide exchange reactions (Fig. 2A). Both Trxs and dithiol Grxs utilise these two cysteinyl side chains for the reduction of protein disulfides in the so called dithiol mechanism (Fig. 2B). The N-terminal active site thiol easily deprotonates due to a low pK_a value, thus allowing a nucleophilic attack on one of the substrate's disulfide sulphur atoms. This reaction leads to the formation of a transient mixed disulfide intermediate between the Trx or Grx and the substrate (Fig. 2A and B, reactions 1 and 1a, respectively). In the second step the C-terminal active site thiol reduces the mixed disulfide, resulting in a reduced substrate and a disulfide in the active site of the Trx or Grx (Fig. 2, reaction 2). The protein disulfide in the active site of Trx is reduced by NADPH-dependent thioredoxin reductase (TrxR) [16]. Grx is reduced by two molecules of glutathione [17] that are kept reduced by NADPH-dependent glutathione reductase (GR) (Fig. 2A, reactions 3 and 4). Protein de-glutathionylation requires only the N-terminal active site cysteinyl residue and was thus named the monothiol reaction mechanism (Fig. 2B, reactions 1b and 4) [18–20]. The reaction sequence is initiated by a nucleophilic attack of the N-terminal active site thiolate on the sulphur atom of GSH in the glutathionylated protein. Thereby, the protein is reduced, and a mixed disulfide between glutathione and Grx is formed (Fig. 2B, reaction 1b), which is subsequently reduced by a second molecule of GSH yielding glutathione disulfide (GSSG) (Fig. 2B, reaction 4).

1.2. Methionine sulfoxidation

Methionine contains a thioether group that can be reversibly oxidised to methionine sulfoxide (Fig. 1). Similar to the variety of thiol redox modifications, reversible methionine oxidation is now being recognised as a redox signalling mechanism [21]. The methionyl thioether group can be oxidised to a mixture of two diastereomers, methionine-S-sulfoxide and methionine-R-sulfoxide. Methionine-S-sulfoxide is stereospecifically reduced by methionine sulfoxide reductase (Msr) A, the reduction of methionine-R-sulfoxide is specifically catalysed by MsrB. In general, the reaction mechanism of MsrA requires three cysteinyl residues in its catalytic centre, MsrB's activity requires two cysteinyl residues [22].

Human MsrA is expressed in various isoforms, encoded by a single gene, that are localised in different cellular compartments, i.e. mitochondria, cytosol, and nucleus [23–25]. The first catalytic sulfenic cysteinyl residue of MsrA reacts with methionine-S-sulfoxide leading to a sulfenic acid intermediate (Fig. 2C, reaction 1a or 1b). This is reduced by the second cysteinyl residue leading to a disulfide with the catalytic cysteinyl residue (Fig. 2C, reaction 2). This disulfide is attacked by the third cysteinyl residue leading to a disulfide between the second and third cysteinyl residues (Fig. 2C, reaction 8). This disulfide is a substrate for Trxs or Grxs that regenerates the fully reduced enzymes (Fig. 2C, reactions 9 and 10) [22,26]. Most mammalian genomes possess three MsrB genes. MsrB1 is characterised by one selenocysteinyl residue in its active site instead of the sulfenic catalytic cysteinyl residue and

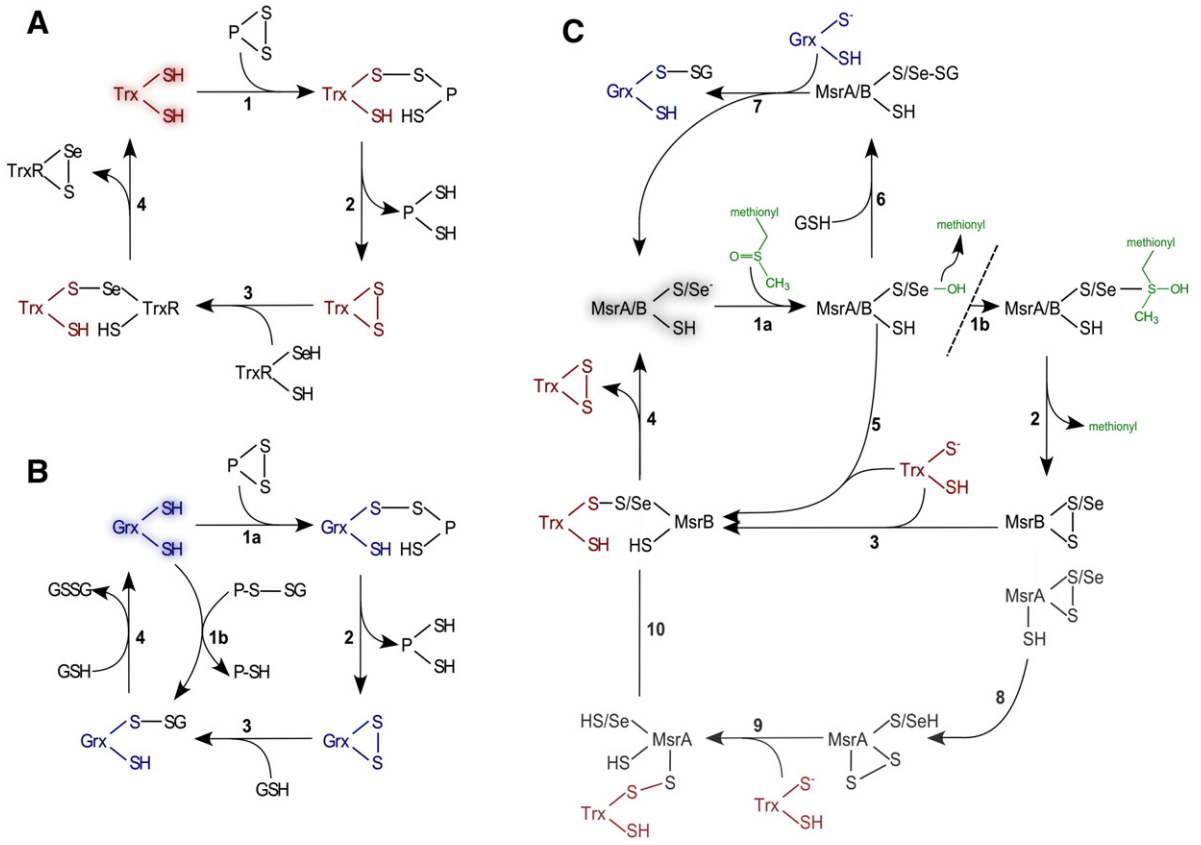

Fig. 2. Reaction mechanisms of thioredoxins, glutaredoxins, and methionine sulfoxide reductases. (A) Trxs (red) reduce protein disulfides in the dithiol mechanism using both active site thiols (SH). The N-terminal active site cysteinyl residue forms a covalent mixed disulfide intermediate with the oxidised substrate protein (A 1), which is reduced in the second step by the C-terminal active site cysteinyl residue, releasing the reduced protein (A 2). The disulfide in the active site of oxidised Trx is reduced by NADPH-dependent TrxR in a similar reaction sequence (A 3 and 4). (B) Grxs (blue) also reduce protein disulfides, similar to Trxs, but their active site disulfide is reduced by two molecules of glutathione (GSH) (B 1–4). In addition, Grxs reduce protein–cysteinyl–glutathione mixed disulfides in the so called monothiol mechanism (B 5–4), that only depends on the N-terminal active site cysteinyl residue. This thiolate attacks the GSH moiety and forms a GSH-mixed disulfide intermediate itself (B 5), that is subsequently reduced by another GSH molecule (B 4). (C) The catalytic active site sulfenic cysteinyl residue of MsrAs and Bs (black/grey) react with methionine-R/S-sulfoxide yielding a sulfenic acid intermediate (C 1a) or a methionyl-bound intermediate (C 1b). Both are attacked by the second cysteinyl residue leading to the formation of a disulfide with the catalytic cysteinyl residue (C 2). In case of the MsrBs, this disulfide is attacked by a third cysteinyl residue leading to a disulfide between the second and third cysteinyl residues (C 8). In either case, the disulfide in the active sites of the MsrA and MsrB is a substrate for Trxs or Grxs (C 3–4 or 8–10). Alternatively, the sulfenic/selenenic intermediate may react with GSH yielding a glutathione-mixed disulfide (C 6), that is reduced by Grxs (C 7).

exhibits the highest activity; MsrB2 and 3 contain cysteinyl residues only and are catalytically less efficient [27,28]. Reaction of MsrB with methionine-R-sulfoxide results in a sulfenic or selenenic acid intermediate, that is reduced by the second cysteinyl residue to a disulfide or selenosulfide bond (Fig. 2C, reactions 1 and 2). This disulfide is directly reduced by Trxs, regenerating the reduced active form of MsrB (Fig. 2C, reaction 3) [27,22]. Alternatively, the sulfenic/selenenic intermediate might be directly or via a glutathione-mixed disulfide reduced by Trxs or Grxs, respectively (Fig. 2C, reactions 6 and 7) [26].

While previously an unspecific oxidation of methionyl residues, for instance by hydrogen peroxide, leading to an inactivation of protein function was the prevalent concept, kinetic constrains and the discovery of enzymes that specifically catalyse methionine oxidation (see Sections 2.1 and 2.3) suggest a fine tuned, enzymatically catalysed activation and inactivation of protein functions by methionine sulfoxide formation [21].

1.3. Redox modifications of non-sulphur containing amino acid side chains

Various redox modifications of non-sulphur containing amino acid side chains have been reported. These have to be considered irreversible, however, they may serve as signals that are recognised by specific receptor molecules, or they may compromise distinct signalling pathways.

Aromatic and heterocyclic amino acid side chains, for instance, are highly susceptible to a broad range of modifications, e.g. mono- and dihydroxy derivatives, dityrosine, and various others [29,30], often by reaction with the most reactive oxygen species, the hydroxy radical. Tyrosine residues are susceptible to reaction with reactive nitrogen species, such as peroxynitrite and nitrogen dioxide, that may react with tyrosyl residues, leading to 3-nitrotyrosine [31–33], a reaction that, at least in some cases, may also require catalysis [34].

One of the most common oxidative modifications of proteins is the unspecific generation of carbonyl groups, termed protein carbonylation. It is so common that it has been widely analysed as a biomarker of "oxidative stress", aging, and various pathologies [29,30,35]. Protein carbonyl modifications are predominantly the product of hydroxy radicals that are metal-dependent generated in the Fenton reaction from hydrogen peroxide. Despite of the rather unspecific nature of this reaction, it could even be signal regulated. As an example, the endothelin-1-mediated carbonylation and subsequent degradation of annexin A1 was shown to promote cell growth of smooth muscle cells [36]. Due to their high reactivity, any given hydroxy radical likely abstracts the first hydrogen atom of a biomolecule it hits. Hence, they also abstract α-hydrogen atoms of peptide-bonded amino acids. This reaction leaves a carbon-centered radical that reacts further and ultimately leads to the cleavage of the peptide bond, another irreversible oxidative protein modification [37,38].

Prolyl and lysyl hydroxylases are enzymes that catalyse the introduction of hydroxyl groups into prolyl and lysyl amino acid side chains using molecular oxygen and α-ketoglutarate as substrates. These modifications are required for the quaternary structures of matrix proteins

such as collagen and elastin. In the case of the hypoxia-inducible factors (Hifs), this enzymatically catalysed modification is also used for sensing and signalling the presence of molecular oxygen. In the presence of oxygen, the α-subunits of the Hif proteins are hydroxylated at two specific prolyl residues targeting them for degradation. During hypoxia, when the proteins cannot be hydroxylated and degraded, Hifs act as transcription factors promoting the transcription of several specific genes [39–41].

2. Redox signalling in actin dynamics and cell movements

Actin filaments are assumably the most dynamic cytoskeletal structures. The dynamics of filamentous actin is controlled by numerous actin-binding proteins that stabilise filaments, promote elongation, severing, or nucleation of new or daughter-filaments [42]. Cell movements are controlled by numerous signalling pathways, including phosphorylation cascades, calcium signalling, and phospholipid signalling. These signals allow the spatio-temporal control of actin dynamics in specific regions of the cytosol, for instance the lamellipodia at the leading edge of the moving cell. One of the nucleation factors of filamentous actin is the ARP (actin-related protein) 2/3 complex. It is active at the leading edge of motile cells and in neuronal growth cones, where it initiates branches on the sides of existing filaments. The growing filaments produce force that induces membrane protrusion, for an overview see [43]. The unbound ARP2/3 complex is inactive in the nucleation of new daughter-filaments and requires an activation step facilitated by nucleation promoting factors. These factors belong to the Wiskott–Aldrich syndrome protein (WASP) and WASP-family verprolin-homologous protein (WAVE) families of proteins [44,45]. The WASP/WAVE complexes are recruited to the membrane and activated by the action of the Ras (rat sarcoma) family GTPases Rho (Ras homolog gene family, member), Rac (Ras-related C3 botulinum toxin substrate), and CDC42 (cell division control protein 42) in response to various signalling pathways [46]. These small GTPases are probably the key signal integrators and mediators controlling the coordinated dynamic changes that move cells.

2.1. Redox modifications and regulation of actin

B.F. Straub (1914–1996) is credited for the discovery of actin in 1942 [47,48], however, most likely actin was isolated for the first time by W. D. Halliburton (1860–1931) in 1887 [49]. Interestingly, Straub was affiliated in the laboratory of A. Szent-Györgyi working also on aspects related to redox regulation. Szent-Györgyi (1893–1986) was awarded with the Nobel Prize in Physiology and Medicine in 1937 for his discovery and general findings of vitamin C. Actin is one of the most abundant eukaryotic proteins and is present as monomeric, globular (G)-actin or as filamentous (F)-actin. The latter forms microfilaments, an essential part of the cytoskeleton in all eukaryotic cells, and is thereby essential for apoptosis, cell division, cellular adhesion, cell polarity, connectivity, and migration.

Actin is susceptible to a number of post-translational modifications including for instance acetylation, phosphorylation, methylation, and thiol redox modifications [50]. More or less all cysteinyl residues (except for a single cysteine in α-actin) and almost half of the methionyl residues are susceptible to redox modifications (Fig. 3A). Cysteines 10 (only in α-actin), 217, 257, and 374 can be reversibly S-glutathionylated [51–53]; cysteines 217, 257, 285, and 374 can be S-nitrosylated [54–56]; cysteines 217, 257, 272 (only in β-actin), 285, and 374 can be oxidised to sulfenic, sulfinic, and sulfonic acids [57–59]. Methionines 44, 47, 178 (only in α-actin), 190, 227, 269, 325, and 355 can be oxidised to sulfoxides, whereas methionine 82 can be further oxidised to the sulfone [60,59,61]. These redox modified sulphur containing amino acids are distributed all over the primary structure of the actins (Fig. 3B). In addition, histidyl (40, 87, 173), as well as tryptophyl residues (79, 86, 340, 356) can be irreversibly oxidised [62,59,63].

Most of the redox modifications have been connected to conformational changes (e.g. oxidation of Cys272, Fig. 3C, D) affecting polymerisation/de-polymerisation as well as the interaction with binding partners. The majority of oxidative post-translational modifications lead to a generally decreased polymerisation rate of G-actin and depolymerisation of F-actin, effects which have been already observed by Straub using an oxidising agent [64]. Intra- and intermolecular disulfide formation enhances the flexibility of the actin network [65]. Actin S-nitrosylated at Cys374, glutathionylated at Cys374, or (sulf)oxidised at Cys374 and methionyl residues 44, 47, or 355 showed a moderate inhibition of polymerisation of G-actin and stability of F-actin [66,54,67,60]. In contrast, sulfoxidation of methionyl residues 178 and 190 completely inhibits polymerisation and induces rapid disassembly of F-actin [60] indicating specific effects of different redox modifications. Some reports speculate that S-glutathionylation might protect actin sulfhydryl groups against irreversible oxidation during conditions of "oxidative stress" and preserve microfilament organisation [68,52].

As mentioned above, actin dynamics depend on the interaction with many actin-binding proteins. The best known interaction of actin is the formation of the actomyosin S1 ATPase complex together with myosin which is essential for muscle contractility. Already 1947, Bailey and Perry noted that the thiol state of actin does not affect actomyosin formation [69]. Although post-translational redox modifications of actin, especially S-glutathionylation, do not alter the binding efficiency of myosin, ATPase activity of actomyosin and thereby muscle functionality were significantly deceased via inhibition of disassembly of the inactive ADP-bound complex [70,71]. Fiaschi et al. demonstrated the involvement of Cys374 glutathionylation in this process by the expression of a Cys374Arg mutant, however, here actin S-glutathionylation seems to promote the disassembly of this complex [72]. The binding efficiency to tropomyosin, another interaction partner important for muscle contractility, is decreased upon actin S-glutathionylation [73]. Actin harboring a Cys374Ser mutation lacks its binding ability to profilin, a protein important for polymerisation of actin monomers, indicating that thiol redox modifications regulate the formation of the actin–profilin complex [74].

Several reports connect redox modifications of actin with a variety of diseases (see also Section 4). Elevated levels of carbonylated actin have been observed in ischemia–reperfusion [75] and diabetes mellitus [76] among other pathological conditions [77]; S-nitrosylated actin accumulates in the spinal cord of inflammatory pain model mice [78]; in fibroblasts isolated from Friedreich's ataxia patients glutathionylated actin is connected to an abnormal pattern of actin filaments [79] and failed actin de-glutathionylation attenuates neutrophil recruitment to sites of inflammation [80].

However, actin is not only redox regulated under pathological conditions or treatments inducing "oxidative stress". Redox-regulated actin dynamics are also important in physiological conditions, e.g. axonal outgrowth. Therefore, redox modifications of actin need to be regulated by specific enzymes (see Section 1). Grxs 1 and 2 are able to deglutathionylate actin in vitro and in vivo increasing the polymerisation rate of G-actin and thus affecting cellular migration [67,81–83,53]. The Trx system enhances actin polymerisation via reduction of oxidised cysteinyl residues [58,84]. Surprisingly, not the active site cysteines, but Cys62 of Trx1 is essential for regulation of actin polymerisation [84]. Thiol–disulfide exchange between actin Cys374 and protein disulfide isomerase regulates cell migration [85]. De-nitrosylation of actin is facilitated by TrxR, which is linked to actin filaments via the focal adhesion kinase [86]. Methionine R-sulfoxide reductases – SelR in *Drosophila*, MsrB1 and 2 in mammals – specifically reduce Met44- and Met47-R-sulfoxides [87,88], modifications introduced by direct interaction between actin and the flavo-mono-oxygenase molecule interacting with CasL (MICAL) [89,87]. In mammals two of the three MICAL isoforms, 1 and 2, oxidise actin [87,90]. The antagonistic effect of Msr and MICAL on the oxidation state of actin methionine and thereby on F-actin (de)-polymerisation was demonstrated by transgenic flies. Overexpression of SelR resembled MICAL mutant actin phenotypes,

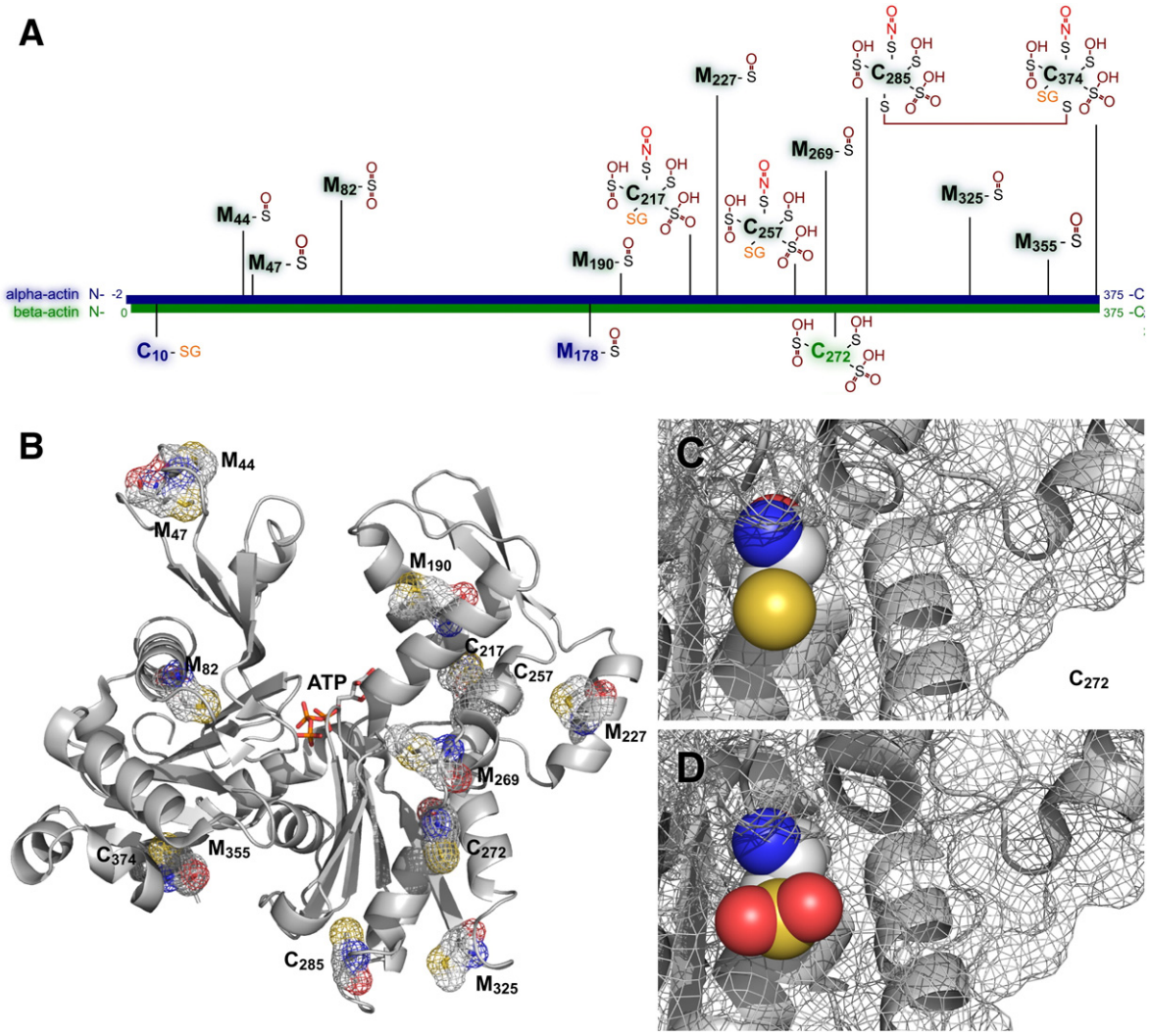

Fig. 3. Post-translational redox modifications of actin. (A) Schematic representation of the cysteinyl and methionyl residues of alpha- (blue) or beta-actin (green) that are susceptible to S-glutathionylation (orange/–SG), S-nitrosylation (red/–NO), and oxidation (dark red/disulfide: S–S, sulfenic acid: –SOH, sulfinic acid: $-SO_2H$, sulfonic acid: $-SO_3H$, sulfoxide: –SO, sulfone: $-SO_2$). (B) Structure of human beta-actin (PDB entry: 2BTF, [198]) in cartoon representation with all redox susceptible cysteinyl and methionyl residues in stick and mesh surface representation. ATP is highlighted in its central binding pocket. (D) Cysteinyl residue 272 in its reduced form (PDB entry: 2BTF), and (E) in the sulfinic form (PDB entry: 2OAN, [58]).

whereas SelR mutants phenocopied MICAL overexpression phenotypes [88]. MICAL links actin dynamics to semaphorin 3A signalling, which is important for axonal outgrowth and guidance (see Section 2.3).

Actin dynamics are also indirectly modulated by redox regulation via redox modification of binding proteins. As described above, redox modulation of actin is not interfering with myosin binding. In contrast, oxidised myosin does not react with actin [69]. Moreover, myosin cysteins are susceptible to S-glutathionylation modulating its ATPase activity [91]. Cofilin controls stability of F-actin and, depending on its oxidation state, actin dynamics are impaired [92].

Cytosolic Trx1 also functions in the regulation of nuclear proteins, e.g. transcription factors such as NF-κB. Recently, Go et al. demonstrated that cadmium treatment that also induces the oxidation of Cys39 and 139 of β-actin [93], stimulates the nuclear translocation of Trx1 and p65 of NF-κB. This translocation depended on actin polymerisation [94], suggesting that actin polymerisation itself contributes to specific redox signalling.

2.2. Redox regulation of cofilin activity

Cofilins are small (15–20 kDa), abundant proteins of the actin-binding protein family, found in all eukaryotic species. They bind to monomeric as well as filamentous actin and control cytoskeletal dynamics mostly by actin de-polymerisation, but can also induce the dissociation of phosphate from ADP-Pi filaments and exhibit to a lower extent actin-filament severing activity, thereby promoting actin polymerisation. The activity of cofilins is regulated by phosphorylation, phosphoinositides, pH and interactions with other proteins [95]. Post-translational phosphorylation of the conserved N-terminal serine (Ser3), regulated by LIM and TESK kinases and slingshot and chronophin phosphatases (for an overview see [96]), was shown to act as a switch of cofilin function. De-phosphorylated cofilin can bind to actin and functions in actin de-polymerisation, whereas phosphorylated cofilin cannot bind to actin and therefore promotes actin polymerisation [97]. Cofilin activity can be regulated via reactive oxygen species through redox-sensitive proteins and signalling cascades, including the activities of RhoA [98], PKD1 [99], and 14-3-3 zeta [100]. Moreover, redox regulation of specific cysteine residues of cofilin is emerging as another form of post-translational regulation, also assuring rapid and spatial control of protein function and cytoskeleton action towards distinct stimuli [92]. The human, non-muscle isoform cofilin-1 contains four cysteine residues at the positions 39, 80, 139 and 147; with 39 and 80 being located inside the protein and 139 and 147 being located on the surface of the protein [101]. The muscle-specific isoform, cofilin-2, only contains the two conserved Cys39 and Cys80 (Fig. 4).

In vitro studies showed that cofilin-1 exists in different redox states and that treatment with hydrogen peroxide leads to the formation of an intramolecular disulfide between the conserved Cys39 and Cys80 residues, inducing a conformational change that prevents phosphorylation by LIM kinase and thereby actin polymerisation, even though actin binding is not altered. Treating unstimulated and stimulated T cells with 50 μM of hydrogen peroxide also led to de-phosphorylation of cofilin and increased levels of F-actin independent of Ras, MEK and PI3K activity. It is worth mentioning that concentrations of 1–10 μM H_2O_2 did not affect the phosphorylation state of cofilin. H_2O_2 endogenously produced by activated granulocytes led to reduced levels of phosphorylated cofilin in unstimulated T cells, which could be prevented by the addition of catalase [102]. 30 min incubation with 500 μM H_2O_2 also induced the de-phosphorylation of cofilin in vascular smooth muscle [103]. Taurine chloramine, the main oxidant produced by activated neutrophils, oxidised all four Cys residues of cofilin-1 in B-lymphoma and COS cells and induced the formation of two intramolecular disulfides, presumably Cys39–Cys80 and Cys139–Cys147. The authors stated that Cys39 can generally also form a disulfide bridge with Cys139, however Cys80 only crosslinks with Cys39. Interestingly, the oxidation of all four Cys residues, as well as the de-phosphorylation at Ser3, was necessary for cofilin to lose its affinity for actin, translocate from the cytosol into mitochondria and induce apoptosis by opening the permeability transition pore and cytochrome c release [104,105].

Moreover, all four Cys residues seem to be crucial for the disulfide isomerisation process during protein folding (self-chaperoning). Following protein expression cofilin-1 contains at least one disulfide bridge in vivo, possibly involving Cys39 and Cys80, that is susceptible to reduction [106]. The authors furthermore claimed, that the surfaces Cys139 and Cys147 are most likely essential for protein oligomerization, a process that has been described for cofilin-1 before [107–109]. Mutating these Cys residues to Ala renders the protein more stable than the WT and prevents oligomerization and protein aggregation [106]. A different study indicated Cys39 and Cys147 to be involved in the formation of intermolecular disulfides and oligomers that constitute different redox states of the protein with distinct biological functions. Using in vivo disulfide cross-linking experiments and gel filtration, the different fractions were analysed. While the main, monomeric form exhibited severing activity, the dimeric and oligomeric forms exhibited actin bundling activity [107]. Interestingly, only the monomeric cofilin was phosphorylated, whereas the dimeric and oligomeric forms were not phosphorylated. The authors postulated that de-/phosphorylation influences the equilibrium of monomer/oligomer cofilin and thereby regulates actin dynamics [109].

It was shown that cofilin self-association was significantly increased by PIP_2, which is known to inhibit the binding of cofilin towards actin and thereby de-polymerisation activity [107]. Schulte and coworkers showed that reduction of WT cofilin and Cys/Ser mutants with dithiothreitol did not change the actin binding or de-polymerisation activity, but counteracted the inhibitory effect of PIP_2 on cofilin function. This redox regulatory mechanism modulates cofilin function in a spatial way, because the cofilin–PIP_2 complex is anchored in the plasma membrane. Upon specific stimuli, including a so far unknown cellular reductase, the reduction of cofilin prevents the inhibition by PIP_2, resulting in

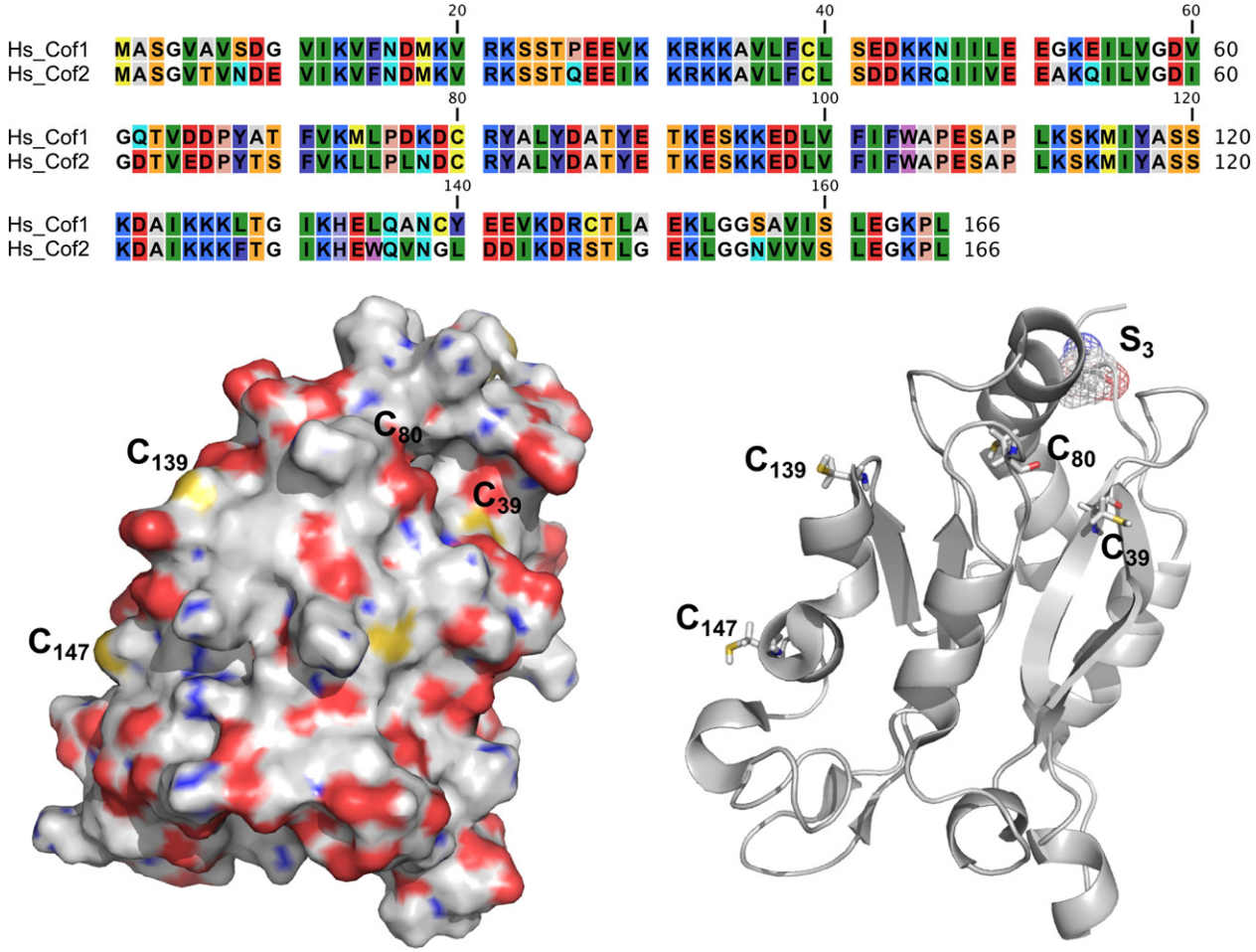

Fig. 4. Primary and tertiary structure of human cofilin. Upper panel: Alignment of the primary structures of human cofilin 1 and 2. Below: tertiary structure of human cofilin 1 (PDB entry: 1Q8G, [101]) with all four cysteins highlighted. Left site: surface representation coloured by the nature of the atoms (grey, carbon; blue, nitrogen; red, oxygen; yellow, sulphur). Right site: cartoon representation with the cysteinyl residues in stick representation. The regulatory seryl residue 3 is shown in stick representation with mesh surface.

increased actin dynamics, e.g. in the immune synapse of untransformed T cells [106]. The Cys39–Cys147 intermolecular disulfide was confirmed in vivo and was shown to be important for the cofilin–actin rod formation in neurons [108].

Besides the formation of disulfides, single Cys modifications were described for cofilin. The thiol group of Cys139 can be oxidised to sulfenic, sulfinic or sulfonic acid [102]. In addition, cofilin and other cytoskeletal proteins including actin, myosin, profilin, tropomyosin, and vimentin were shown to be glutathionylated in PBMCs treated with either 1 mM diamide or 1 mM hydrogen peroxide for 5 min. So far, no physiological function for the S-glutathionylation of cofilin has been demonstrated, however it might be a protective mechanism against irreversible over-oxidation or a regulatory function inhibiting actin polymerisation [110].

2.3. Semaphorin signalling, CRMP2, and MICALs

Semaphorins (Semas) are secreted and membrane-bound signalling proteins that control cellular differentiation and organogenesis such as axonal guidance during neuronal differentiation [111]. Semaphorins are grouped into eight major classes, each of these classes contains many subgroups and each of these subgroups various individual proteins [112]. Class 3 Sema's are secreted signalling molecules. In the kidney, for instance, Sema3A modulates ureteric bud branching, vascular patterning, and podocyte-endothelial crosstalk [113]. In neuronal development, Sema3A induces the collapse of axonal growth cones, thereby controlling axon guidance [114]. Moreover, Sema3A controls migration of developing thymocytes within the thymic lobules [115] and adult T-cell polarisation and migration [116]. Higher expression levels of a Sema3A mutant in smooth muscle cell segments lacking ganglion cells of patients suffering from Hirschsprung's disease indicate a correlation with this disease [117]. The Sema3A receptor is a heterodimeric transmembrane protein build up from neuropilin-1 (NP1) and a class A plexin (PlexA) (see Fig. 5). NP1 was characterised as the high-affinity ligand binding partner, and PlexA as the part transducing the signal into the cell [114]. Receptor binding of Sema3A to NP1 and PlexA leads to the inactivation of RhoA and therefore diminishes stress fibre formation by promoting F-actin de-polymerisation, e.g. through cofilin activation (Fig. 5) [118]. Prolonged inflammatory stress (e.g. IL-1β) as well as hypoxia induce Sema3A expression and secretion in neuronal cells and therefore prevent vascular regeneration. The role of Sema3A during development is elucidated by high mortality rates and confounding neuronal deficits in transgenic mice [119]. Galectin-1, an endogenous glycan-binding protein, promotes functional recovery of spinal lesions by binding to the NP1/PlexA4 receptor and therefore interfering with inhibitory signals triggered by Sema3A binding to NP1/PlexA4 [120]. In response to Sema3A signalling, Rac1 function changes from promoting actin polymerisation associated with axon growth to driving endocytosis of the plasma membrane, leading to growth cone collapse [121]. Lacking a defined signalling domain, NP1 still has a specific function in this signalling pathway presumably via its C-terminal domain and interaction with intracellular binding partners. NP1 appears to be essential for neuronal and cardiovascular development [122].

Collapsin response mediator protein 2 or dihydropyrimidinase like protein 2 (CRMP2/DPYL2) is a mediator of the semaphorin signalling cascade. The protein is subject to various post-translational modifications, including alternative splicing and phosphorylation by other mediators of Sema signalling, namely CdK5 and GSK3β, [123,124]. CRMP2 is essential for mediating the repulsive effect of Sema3A on axons [125], but the molecular interactions of CRMP2 are not well defined. CRMP2 binds tubulin-heterodimers and promotes microtubuli assembly during neuronal differentiation, axonal outgrowth and branching [126], however, the function of the protein controls the dynamics of the actin cytoskeleton in a dramatic way as well, e.g. [127,128], see also (Fig. 5). CRMP2 forms homo-tetramers as well as hetero-tetramers with other CRMPs, quaternary structures that were suggested to be important in regulating CRMP2 function as well [129]. Recently, also redox modifications of CRMP2 were reported that are essential for at least some of the protein functions. CRMP2 can form an intermolecular disulfide through two Cys504 residues in the tetrameric complex [130,131]. This disulfide may be a target for Trx. In fact, Morinaka et al. reported a mixed

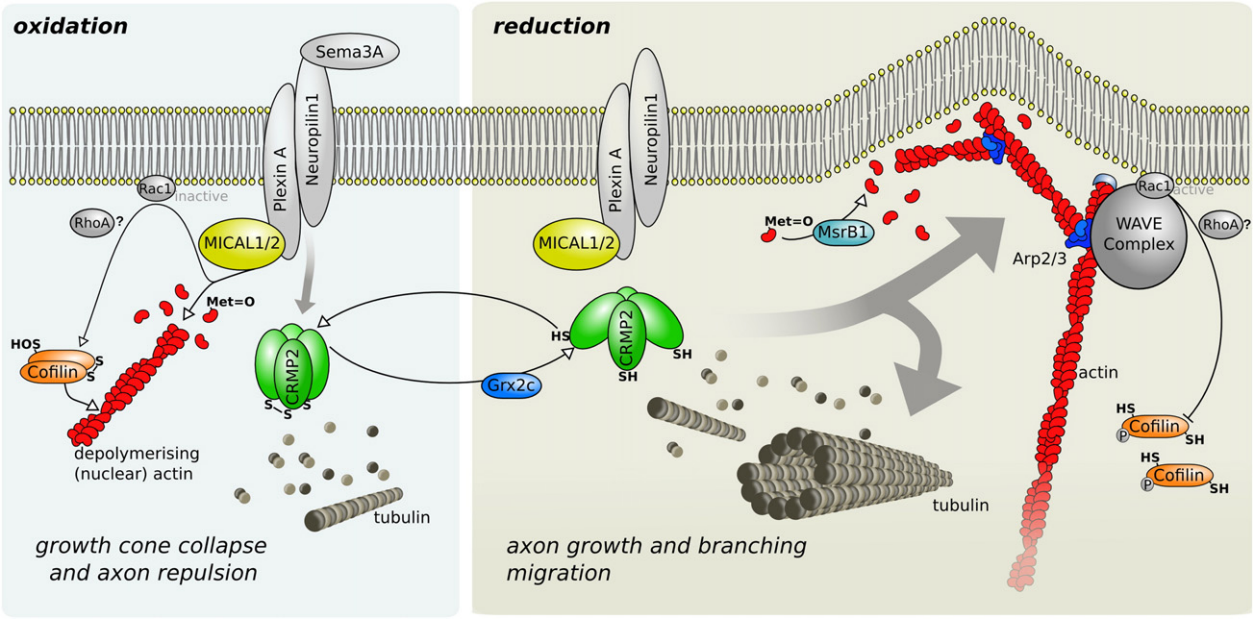

Fig. 5. Redox switches in semaphorin signalling, cofilin, and actin dynamics. Sema3A binding to NP1 activates PlexA and the semaphorin signalling cascade. Activated PlexA interacts with MICAL1/2 that then leads to actin de-polymerisation, through cofilin activation or the proposed sulfoxidation of methionyl residues of β-actin. CRMP2 is another mediator of the Sema3A signalling cascade that induces growth cone collapse and axon repulsion (left side: 'oxidation'). Without ligand binding, MICALs are not activated by the NP1/PlexA receptor. The reduction of CRMP2 by cytosolic Grx2 leads to a conformational change of the homo-tetramer. This conformational change causes (directly or indirectly) the polymerisation of actin and tubulin. MsrB1 is able to reduce the sulfoxides of methionyl residues of β-actin, allowing polymerisation. The WAVE complex is activated close to the membrane by active Rac1 and binds Arp2/3 which leads to actin polymerisation and branching. Activated Rac1 also leads to the phosphorylation and therefore inactivation of cofilin. The absence of Sema3A and the resulting changes of the cytoskeletal dynamics lead to axon outgrowth and branching as well as enabling active migration (right side: 'reduction').

disulfide of Cys504 with Trx that shall stimulates CRMP2 phosphorylation through GSK3β [130]. This mechanism, however, is unlikely, since the transient mixed disulfide of Trx with its substrate cannot be stable enough to serve as signal. The rate limiting step of the reaction is the nucleophilic attack that leads to the transient mixed disulfide, the second step takes place instantly, see [13,15] for in depth discussions. Cytosolic vertebrate-specific Grx2c is essential for embryonic brain development [128] and is specifically induced in many cancer cells [132]. We identified CRMP2 as redox regulated target of Grx2c [133] and demonstrated that this regulation is required for normal axonal outgrowth [128,131]. We identified a specific and reversible intermolecular thiol–disulfide switch in homo-tetrameric CRMP2 that determines two conformations of the complex and is efficiently reduced by Grx2c in vivo and in vitro [131]. Cysteine residues in CRMP2 are not modified by S-nitrosylation in vivo in experimental autoimmune encephalomyelitis (EAE), a murine model for multiple sclerosis (MS), even though S-nitrosylation could be induced in vitro by incubation with NO donors [134].

MICALs are another family of transducer/effector proteins of the Sema3A–PlexA signalling cascade, directly interact with PlexA. As CRMP2, MICALs are required for axon repulsion and guidance [135]. Noteworthy, MICALs were also reported to interact with CRMP2 [136]. MICAL1 interacts with PlexA1 and A3 of the semaphorin receptor (Fig. 5), MICAL2 with PlexA4 but neither directly interact with B, C or D class plexins [135]. MICALs and other FAD-dependent monooxygenases catalyse the NADPH-dependent oxygenation of nucleophilic nitrogen, sulphur, selenium, or phosphorus atoms. The reduced flavin ($FADH_2$) reacts with molecular oxygen yielding peroxyflavin. One of these oxygen molecules is transferred to a nucleophilic substrate. Peroxyflavin may also dissociate and lead to the production of H_2O_2 [137]. MICALs supposedly act through the local production of H_2O_2 in response to receptor activation [138,139], however, also the direct sulfoxidation of amino acid side chains, for instance a methionyl residue in β-actin, has been suggested [89], see also Fig. 5. Recently, the control of actin assembly by MICAL1/2 and MsrB1 was suggested via site-specific stereo-selective methionine oxidation and reduction. This regulatory redox couple may be important in macrophages during cellular activation [87]. In addition, the redox-dependent de-polymerisation of nuclear actin is induced by MICAL2, which therefore also influences gene transcription of certain targets [140].

3. Redox regulation of microtubuli dynamics

Microtubuli are polymers of small globular proteins, mostly α- and β-tubulin family members. α/β-Tubulin heterodimers assemble, generally with the help of numerous chaperones and scaffolds, into polarised microtubuli of variable length that often reach from the microtubuli organisation centre/centrosome somewhere near the nucleus to the periphery of the cells. This railway network enables both transport and organisation of cellular contents such as organelles and vesicles. The dynamics of microtubuli are controlled by β-tubulin's intrinsic GTPase activity as well as numerous tubulin-binding proteins, for recent summaries see, for instance, [141–144]. Dynamics of microtubuli are, among many other functions, essential for chromosome alignment and segregation during mitosis [145,146] and the formation of dendritic spines and axons during neuronal differentiation [147,148]. Human α-tubulins contain twelve conserved cysteinyl and eight conserved methionyl residues; human β-tubulin's seven conserved cysteinyl and 17 conserved methionyl residues. Even between these two subfamilies that make up the majority of microtubuli, three cysteinyl and four methionyl residues were conserved during evolution.

Protein disulfides i.e. intermolecular disulfides between the α- and β-tubulin subunits could be induced in porcine brain extracts by peroxynitrite, likely through a sulfenic intermediate. In vitro, these disulfides were a substrate for Grxs, similar to cysteinyl–glutathione disulfides formed under the same conditions [149], or the Trx system [150]. The reduction of the disulfide bonds restored tubulin polymerisation activity that was lost following peroxynitrite addition [151,149]. Both α- and β-tubulin isoforms were identified as potential protein disulfide substrates of the cytosolic Grx2c [133], whose crucial functions during development have been demonstrated before [128,131,152,53].

S-glutathionylation of tubulin family proteins has been demonstrated in response to peroxynitrite treatment [149] and treatment with the antimitotic agent 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylcarbonylamino)phenyl carbamoylsulfanyl]propionic acid, leading to the de-polymerisation of microtubuli [153]. Interleukin 22 treatment of vascular smooth muscle cells leads to the activation of the NADPH oxidase and, specifically to the S-glutathionylation of α-tubulin [154]. In Friedreich's ataxia, an iron overload disorder, microtubuli abnormalities co-localised with an increase in overall protein S-glutathionylation in the affected areas [155].

S-nitrosylation of both α- and β-tubulin cysteinyl residues were identified by proteomic techniques in the hippocampus, substantia nigra and cortex of Alzheimer's disease patients [156], during the differentiation of spermatogenic cells [157], and in EAE [134]. The treatment of cultured vertebrate neurons with nitric oxide led to the collapse of axonal growth cones, and thus axon retraction, along with the reconfiguration of axonal microtubuli. The microtubule-associated protein MAP1B was identified as being regulated by S-nitrosylation leading to enhanced interactions with microtubuli and the inhibition of neuronal differentiation [158].

4. Disturbed redox-regulated migration under pathological conditions — therapeutic implications

Cytoskeletal dynamics, especially cell migration, is the underlying scaffold of fundamental biological processes. During embryonic development migration of different cell types is essential for the precise and accurate development of the organism. Formation of all organs, bones, and other tissues depends on the appearance of specialised cells at defined places at certain time points. In adults, the regulation of migratory processes is essential for regeneration, tissue repair and inflammatory immune response. Altered migration contributes to cancer metastasis as well as age related disorders like atherosclerosis. This chapter focuses on redox-regulated mechanisms modifying cell migration of differentiating and de-differentiating cells under pathological and age-related conditions.

Surprisingly little is known about redox regulation of cytoskeletal rearrangements and migration during embryonic development. The cytosolic isoform of Grx2, Grx2c [132,159], has been identified as essential for vertebrate development. Regulation of reversible thiol redox modifications of sirtuin 1 (SIRT1) [152], actin [53], and CRMP2 [128,131] (see Section 2.3) controls axon formation, vessel outgrowth as well as migration of cardiac neural crest cells and thereby formation of both the cardiovascular system and the brain.

Due to its tightly regulated and restricted regeneration potential, the central nervous system is a well-studied and therefore suitable model to investigate the role of migratory defects in failed regeneration. Here, impaired regeneration is a common pitfall in the chronic phase of degenerative disorders, e.g. succeeding a stroke, or in Alzheimer's disease, or MS [160–162]. In chronic MS, de-myelination by oligodendroglial cell death and disturbed re-myelination lead to lesion areas and subsequently to neuronal cell loss responsible for neurological dysfunctions [163]. Re-myelination is thought to ameliorate disease symptoms and to delay progression. Recent findings highlight the importance of altered migration capacities of oligodendroglial progenitor cells (OPCs) into de-myelinated lesion areas as the major cause for disturbed myelin regeneration [164]. Changes in the chemotactic milieu in chronic lesion areas inhibit OPC migration and subsequently their differentiation into myelinating mature oligodendrocytes and have the potential to reduce protective effects of drugs like IFN-β [165]. Among others, semaphorin guidance molecules are responsible for these effects

[165–167], see also Section 2.3. In addition, Bizzozero et al. demonstrated increased S-nitrosylation and carbonylation of cytoskeletal proteins, e.g. α/β-tubulin and β-actin in diseased animals of EAE [134,168], the animal model for MS. Among others, these findings manifest the importance of a functioning redox regulated OPC migration in MS disease progression [169]. Beyond MS, migration of progenitor cells is of importance for several other diseases comprising neuro-inflammation and their regeneration capacity like traumatic brain injury, stroke and other oligo- and neurodegenerative diseases [170,171].

In Alzheimer's as well as Parkinson's disease redox based cytoskeletal modifications were found to play a major role in axonal de- and regeneration [172,173]. Elevated carbonylation of β-actin as well as cysteine oxidation of microtubule-associated proteins directly influence both degeneration rates and the regeneration capacity of axonal loss [35,174]. Carbonylation of β-tubulin, however, was not enhanced in Alzheimer's disease brain extracts [173]. Moreover, migratory processes play an essential role in the origin of age-related diseases aside from the CNS, for instance atherosclerosis [175] and impaired wound healing. There are several cell types known to have an altered migration potential upon aging for example dermal fibroblasts, endothelial cells, smooth muscle cells and CD4 T cells [176–179]. Age-related impaired migration in dermal fibroblasts is based on disorganized β-actin and a decreased function of collagen-binding protein integrin α1β2, for instance [180]. The structure of β-actin depends on redox regulation of Cys374 during integrin-mediated cell adhesion [72], pointing towards a considerable role of specific redox switches in cytoskeletal dynamics upon aging. Furthermore, beneficial effects of hypoxia on wound healing via increased TGFβ1-mediated migration of dermal fibroblast are lost during aging [177]. The relaying signalling pathway was sshown to generally depend on the amount of free thiols even though the exact type and site of redox modification remain elusive [181,182].

Cancer cell spreading is connected to pathological cell migration. Metastasis is linked to expression of both SIRT1 [183,184] and cellular nucleoside diphosphate kinase (NDPK) [185]. SIRT1 was found to be highly expressed in brain metastatic tissue of non-small cell lung cancers [186]. Both SIRT1 and NDPK activities are regulated by redox modification of a single cysteine. NDPK loses its ability to suppress tumor metastasis depending on the redox state of Cys109 which is reduced by the Trx system [187], whereas SIRT1 activity is modulated via Grx2(c)-dependent reversible S-glutathionylation of Cys204 [152]. NDPK as well as SIRT1 regulate the activation of the transcription factor FOXO-1 and thereby the release of vascular endothelial growth factor-C (VEGF-C). Subsequently, an enhanced release of VEGF-C positively regulates cell migration and metastasis [188]. These findings connect redox-modulated pathways with cancer cell migration and might represent a possible target in cancer therapy.

In summary, redox regulated migration is essential not only during embryonic development but also under pathological conditions and in age-related diseases, affecting the fate of differentiating and de-differentiating cells (Fig. 6). Within this section, we presented some examples of specific thiol redox switches in proteins forming or controlling the cytoskeleton that play a defined role in the onset and progression of distinct diseases. To our knowledge, at present only two pharmacological substances are being evaluated that potentially affect the redox control of cytoskeletal dynamics in these pathologies. First, U-83836E which attenuates cytoskeletal damage after traumatic brain injury via scavenging lipid peroxyl radicals [189]. Second, nitroxyl (HNO) or rather HNO donors. HNO can react as both nucleophile and electrophile depending on the nature of its interaction partner and targets predominantly iron heme proteins and protein thiols [190]. Although known for quite a long time, just recently HNO emerged as a potential pharmacological agent not only in cardiovascular diseases but also in cancer [191]. By specifically inducing disulfides between actin Cys257 and tropomyosin Cys190 as well as Cys81 and Cys37 in myosin light and heavy chain, HNO increases cardiac contractility [192].

Microtubule dynamics (see Section 3) are essential for cell division and microtubule-targeting drugs have been used in anti-cancer treatment for almost 50 years. These drugs either destabilise or stabilise microtubules subsequently leading to inhibition of mitosis and cancer cell proliferation. Moreover, the targeting of microtubule dynamics may become of importance in neurodegenerative diseases [193,194]. All these drugs bind to tubulin within the microtubule structure. In contrast, pharmacological inhibitors of actin assembly and nucleation are so far not implemented in the clinics, however, some may be used to combat cancer development and metastasis in the future [195]. CRMP2 has a strong influence on both microtubule and actin filament dynamics (see Section 2.3). CRMP2 is inhibited by the compound lacosamide, also known as the anti-epileptic drug VIMPAT. The mode of action of the drug is not understood on a molecular level, but it was suggested that lacosamide-mediated inactivation of CRMP2 leads to inhibition of the aberrant neurite outgrowth during epilepsy [196]. Moreover, CRMP2 is also considered as a promising target in several other neurological diseases including Alzheimer's disease [197].

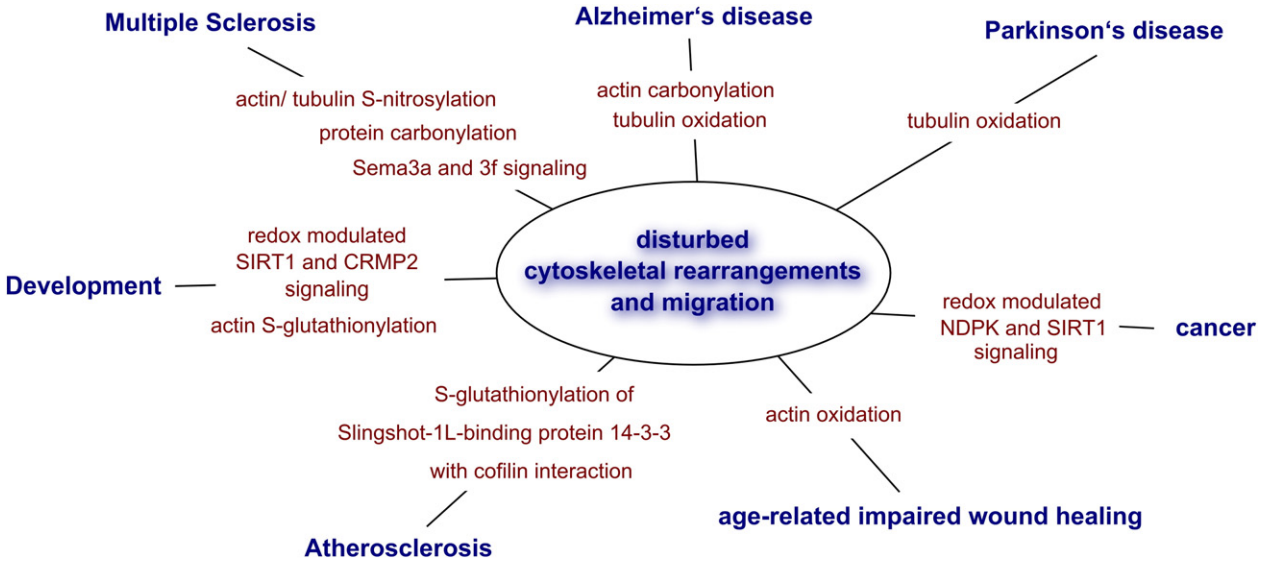

Fig. 6. Disturbed redox regulation of cytoskeletal rearrangements connected to selected physiological and pathophysiological conditions. CRMP2: collapsin response mediator protein 2, NDPK: nucleoside diphosphate kinase, Sema: semaphorin, SIRT1: sirtuin1.

The understanding and modulation of the particular redox mechanisms and signalling pathways mentioned above, might lead to the development of new therapeutic strategies which are urgently needed in diseases connected to failed migration/cytoskeletal rearrangements, e.g. metastatic cancer and neurological disorders such as MS or spinal cord injury.

5. Conclusion

The dynamic remodeling of the cytoskeleton can be spatio-temporally controlled by various redox signalling mechanisms, as exemplified in the thiol/disulfide switch in CRMP2 and the methionyl/methionyl sulfoxide switches in β-actin (Fig. 5). These mechanisms are indispensible during development and organogenesis, and they might also contribute to numerous pathological conditions. We currently witness a shift in paradigms. The redox switches that control these cellular functions might not be the result of random modifications by unspecified oxidants. More and more appear to be controlled by specific enzymes that specifically catalyse the oxidation and reduction of these distinct redox modifications in a manner similar to the kinases and phosphatases in phosphorylation signalling.

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