ANTIOXIDANTS & REDOX SIGNALING
Volume 12, Number 1, 2010

DOI: 10.1089/ars.2009.2785

CORRECTION

Corrigendum for Pedone E, Limauro D, and Bartolucci S. The Machinery for Oxidative Protein Folding in Thermophiles. *Antioxid Redox Signal* 10:157–169, 2008

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We, the authors of the above-mentioned article, write this in response to a charge of plagiarism brought forth against our article (75). We accept that, without having cited the source, specific sentences and paragraphs of the review introduction, were reproduced unchanged (Table 1a) or were left similar (Table 1b) to content from previous published articles, including Gruber CW, Cemazar M, Heras B, Martin JL, and Craik DJ. *Trends Biochem Sci* 31: 455–464, 2006 (28), and our own previous publication D'Ambrosio K, Pedone E, Langella E, De Simone G, Rossi M, Pedone C, and Bartolucci S. *J Mol Biol* 362: 743–752, 2006 (16). However, we would like to defend that this represents a small portion of the overall text and that the reproduction represents supporting text and does not compromise the originality of our review article. In Table 2, we itemize the main points that support the originality of our review article. This is the first review that reports a detailed overview of the oxidative folding from thermophiles, focusing on the particular proteins protagonists of this event in these microorganisms. These proteins play a leading role in the adaptation to drastic life conditions, and surely our group has had a key role in the discovery and structural and functional characterization of this class of proteins. Our review focuses on a completely different main topic compared with other articles, and in addition, the review structure and organization are innovative. Our laboratory has extensive track record (3–5, 14–18, 29–32, 49, 51–54, 65–75, 79, 81, 82) in the discovery and structural–functional characterization of protein disulfide oxidoreductases from thermophilic microorganisms, which is documented by a 15-year long list of publications. In this review we reported our knowledge in the said field.

In recognition of the fact that we indeed reproduced content without having cited the source, as reported above in Table 1a and 1b, we extend our apologies to the respective authors and journals as cited in Tables 1a and 1b. We also take this opportunity to provide appropriate credit to the source material we used in our article. We regret that we did not cite the authors and the necessary references for the text we used in our article. We are thankful for this opportunity to report and mend our honest error.

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Table 1a. (Text reported verbatim)

Reproduced content	*Page and line in the original publication*	*Page and line in publication (Ref. 75)*	*Reference of the original publication*
Although TRX-like redox proteins or redox active domains share no overall sequence homology, they all contain a CXXC catalytic motif, which is located at the N terminus of the first helix in the consensus TRX fold (21), and a *cis*-Pro loop, which precedes the $\beta3\beta4\alpha3$ motif.	Page 458 Line 18b	Page 157 Line 14a	28. Gruber CW, Cemazar M, Heras B, Martin JL, Craik DJ. Protein disulfide isomerase: the structure of oxidative folding. *Trends Biochem Sci* 31: 455–464, 2006.
The nature of the amino acids between these two cysteines varies widely among the different enzymes.	Page 230 Line 18	Page 157 Line 3b	12. Carvalho AP, Fernandes PA, Ramos MJ. Similarities and differences in the thioredoxin superfamily. *Prog Biophys Mol Biol* 91: 229–248, 2006.
THE BACTERIAL MACHINERY FOR OXIDATIVE PROTEIN FOLDING	Page 455 line 12b	Page 157 Line 9b	28. Gruber CW, Cemazar M, Heras B, Martin JL, Craik DJ. Protein disulfide isomerase: The structure of oxidative folding. *Trends Biochem Sci* 31: 455–464, 2006.
DsbA introduces disulfide bonds into newly translocated proteins by donating its active-site disulfide bond. The active form of DsbA is restored by the inner-membrane protein DsbB, which uses the oxidizing power of the electron transport system (7). Under aerobic conditions, electrons are passed from DsbB via ubiquinone and the cytochrome bo and bd oxidase to molecular oxygen. Under anaerobic conditions, DsbB uses menaquinone as an intermediate electron acceptor from which electrons are transferred to either fumarate reductase or nitrate reductase (4–6). The disulfide oxidation step catalyzed by DsbA is rapid and nonspecific and, in proteins with multiple thiols, can result in the formation of nonnative disulfide bonds. In this pathway, the isomerase DsbC must be kept reduced in the oxidative environment of the periplasm, a requirement that is mediated by the membrane protein DsbD.			
In gram-negative bacteria, disulfide bond formation is assisted by proteins of the Dsb family, which are either located in extracytoplasmic compartments or secreted into the medium. Recent genetic studies suggested that Dsb homologue systems are also found in gram-positive bacteria (45, 82). In Bacillus subtilis, two putative extracytoplasmic proteins (DdbA and DdbD), which are homologues of Trxs, and two putative membrane proteins (DdbB and DdbC), which show sequence homology to E. coli DsbB, have been identified. Genetic evidence indicates at least three genes encoding proteins that play a role in disulfide-bond formation. Moreover, the identification of DsbA and DsbB homologues by BLAST searches in the protein databases of both gram-positive bacteria and the previously mentioned B. subtilis supports the assumption that gram-positive bacteria may comprise oxidative pathways similar to those of gram negative bacteria.	Page 743 line 5b	Page 157 line 11b Page 58 line 17a	16. D'Ambrosio K, Pedone E, Langella E, De Simone G, Rossi M, Pedone C, Bartolucci S. A novel member of the protein disulfide oxidoreductase family from Aeropyrum pernix K1: Structure, function and electrostatics. *J Mol Biol* 362: 743–752, 2006.

THE EUKARYOTIC MACHINERY FOR OXIDATIVE PROTEIN FOLDING In eukaryotes, protein folding, modification and quality control occur mainly in the ER (9). Whereas different compartments in plants, such as the cytosol, mitochondria and chloroplasts, have their own protein folding machinery, the ER is unique in that it produces proteins for other compartments of the cell. Newly synthesized polypeptide chains destined for the secretory pathway are translocated into the ER with the aid of signal recognition particles and receptors (10). Various folding factors that are resident in the ER recognize nascent proteins; these folding factors include chaperones from the heat shock protein family, peptidylprolyl cistrans isomerases, protein folding catalysts from the PDI family, Ero family and Erv family, and many lectins and glycoprotein-modifying enzymes (10). On the basis of findings in yeast (11), it is estimated that approximately one-third of all eukaryotic proteins pass through the ER on their way to maturity, including all cell-surface and secretory proteins and proteins located in compartments along the exocytic or endocytic pathways (10). The ER is also one of the few compartments in the eukaryotic cell where proteins can acquire disulfide bonds (the mitochondria is another). PDI catalyzes the oxidation and shuffling of disulfides in substrate proteins. In turn, PDI is oxidized by the ER oxidoreductin proteins Ero1-La and Ero1-Lb in mammalian cells (12, 13), AERO1 and AERO2 in plants (14), and Ero1p (15–17) or the ER oxidase Erv2p (18–20) in yeast. ER oxidoreductins couple disulfide bond formation to reduction of molecular oxygen with the help of a bound flavin adenine dinucleotide cofactor. This cascade, which involves a series of protein–protein interactions, leads to the formation of native disulfides in substrate proteins (3, 16, 17).	Page 455 Line 16b Page 456 Line 15a	Page 157 Line 17b- Page 158 Line 1a Page 158 Line 30a	28. Gruber CW, Cemazar M, Heras B, Martin JL, Craik DJ. Protein disulfide isomerase: the structure of oxidative folding. *Trends Biochem Sci* 31: 455–464, 2006.
Notably, proteins from this family were not observed in certain key organisms, such as M. jannaschi, Methanococcus kandleri and Archaeoglobus fulgidus.	Page 4173 Line 3b	Page 162 Line 32a	45. Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. *FEBS J* 273: 4170–4185, 2006.
Numerous problems related to protein disulfide oxidoreductases in hyperthermophiles remain unsolved to date, but can probably successfully be studied by genetic and in vivo approaches.	Page 4181 Line 46b	Page 166 Line 43b	45. Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. *FEBS J* 273: 4170–4185, 2006.

Table 1b. (Similar Sentences)

Sentences in the original (Bold) and in ref. 75 (italics)	*In bold page and line in the original publication*	*In Italics page and line in publication ref. 75*
Disulfide bonds are required for the stability and function of a large number of proteins. Recently, the results from genome analysis have suggested an important role for disulfide bonds concerning the structural stabilitazion of intracellular proteins from hyperthermophilic Archaea and Bacteria *Disulfide bonds are required for the stability and function of many protein.* *Recently the results from genome analysis suggested an important role for disulfide bonds in the structural stabilitazion of intracellular proteins from thermophiles.*	**Ref. 45** Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. FEBS J 273(18):4170–4185, 2006. **Page 4170/Line 1**	*Page 157 Line 1 abstract Line 5 abstract*
A large number of enzymes which catalyze protein disulfide formation belong to a set of thiol-disulfide oxidoreductases found in all living organisms. *A large number of thiol-disulfide oxidoreductases, belonging to the thioredoxin superfamily, catalyze protein disulfide bond formation in all living cells, from bacteria to humans*	**Ref. 45** Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. FEBS J 273(18):4170–4185, 2006. **Page 4171 Line 29**	*Page 157 Line 1 abstract*
In the endoplasmic reticulum of eukaryotes, disulfide formation is catalyzed by protein disulfide isomerase (PDI); by contrast, prokaryotes produce a family of disulfide bond (Dsb) proteins, which together achieve an equivalent outcome in the bacterial periplasm. *The protein disulfide isomerase (PDI) is the eukaryotic factor that catalyzes oxidative protein folding in the endoplasmic reticulum; by contrast, in prokaryotes, a family of disulfide bond (Dsb) proteins have an equivalent outcome in the bacterial periplasm.*	**Ref. 28** Gruber CW, Cemazar M, Heras B, Martin JL, Craik DJ. Protein disulfide isomerase: the structure of oxidative folding. Trends Biochem Sci. 31(8):455–464, 2006. **Page 455 Line 6**	*Page 157 Line 3 abstract*
A specific protein, known as protein disulfide oxidoreductase (PDO) is recognized as a potential key player in intracellular disulfide-shuffling in hyperthermophiles. *A specific protein disulfide oxidoreductase (PDO) has a key role in intracellular disulfide shuffling in thermophiles.*	**Ref. 45** Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. FEBS J 273(18):4170–4185, 2006. **Page 4170 Line 6**	*Page 157 Line 6 abstract*
The reduced form is regenerated by the flavoenzyme thioredoxin reductase which in turn is kept reduced by NADPH (1). *The reduced form is regenerated by the flavoenzyme thioredoxin/glutathione reductases, respectively, which in turn are kept reduced by NADPH (39).*	**Ref. 86** Ritz D, Pate H, Doan B, Zheng M, Åslund F, Storz G, Beckwith J. Thioredoxin 2 is involved in the Oxidative Stress Response in Escherichia coli J. Biol. Chem. 275: 2505–2512, 2000. **Page 2505 Line 27**	*Page 158 Line 84*
Therefore, its precise correlation with richness in disulfides can be considered as strong evidence for a true relationship to this cellular property. *Therefore, its precise correlation with richness in protein intracellular disulfides can be considered as strong evidence for a true relation to this cellular property.*	**Ref. 45** Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. FEBS J 273(18):4170–4185, 2006. **Page 4173 Line 8b**	*Page 162 Line 35*
How would the phenotype of archaeal cells react upon a knock-out of a PDO gene? What are the pathways and the regulation mechanisms for protein disulfide formation in Archaea? What is the global redox potential in archaeal cells? *How would the phenotype of a thermophilic microorganism react on a knockout of a PDO gene?* *What are the pathways and the regulation mechanisms for PDO dependent protein disulfide formation in thermophilic microorganisms? What is the global redox potential in these cells?*	**Ref. 45** Ladenstein R, Ren B. Protein disulfides and protein disulfide oxidoreductases in hyperthermophiles. FEBS J 273(18):4170–4185, 2006. **Page 4181 Line 50b**	*Page 167 Line 1*

Footnote: a and b labels, next to the lines numbers in the 2nd and 3rd columns, are referred to the left and right column in the manuscript.

Table 2. Topic (Column 1) and Point made (Column 2) with Reference to Original Citation (Column 3) that are Completely INDEPENDENT of the Sentences in Table 1a and 1b

Topic	*Point made*	*References*
THIOL DISULFIDE OXIDOREDUCTASE Page 157	An introduction of the different members of the oxidoreductases superfamily and their common functional features as deduced on the basis of the structural data present in the literature are shown.	**19, 42–43, 56–57**
THIOREDOXIN/GLUTAREDOXIN, UBIQUITARIOUS REDUCTANTS	General information on the two well characterized systems: Trx and Grx. The paragraph highlights their peculiar structural and functional aspects.	**1, 7, 22, 25–26, 33–34, 47, 58–59, 77, 88**
THE CHIMERIC PATHWAY FOR OXIDATIVE PROTEIN FOLDING IN THERMOPHILES	A detailed description of the three ancestral Trx/Grx from methanogenes is presented. The features of these proteins from *Methanobacterium thermoautotrophicum* and *Methanococcus jannaschii* are reported.	
The ancestral Trx and Grx from methanogenes Page 158–160	It has been highlighted the archaic nature of these proteins correlating structure and function.	
Trx/Grx from thermophilic microorganisms Page 160–162	This paragraph presents the first overview on Trx/Grx from thermophilic source. In particular our studies conducted on the determinants of the thermostability of Trx fold are illustrated. It is the first time that in a review it is possible to find all the most recent studies performed on thermophilic Trxs. Figure 1 is original. The experiments described in Fig. 1 are reported in ref. 68 and they are presented as a new arrangement. Figure 2 is completely original performed to search for common determinants among different Trx sequences. Table 1 is original. The experiments described in this table are reported in ref. 71 and they are presented as a new arrangement.	**3, 5, 9, 37, 47–48, 61, 65–69, 73, 74, 80, 87, 91, 101**
• **Disulfide-bonded proteins in thermophile: PDO, a primary catalyst of disulfide bond formation in thermophiles** • **PfPDO** • **AaPDO** • **ApPDO** • **SsPDO** • **Conclusions on the PDO family** Page 162–165	We have reported our pioneristic studies on this new protein disulphide oxidoreductase (PDO), playing a key role in the adaptation to the elevated temperatures of thermophilic microorganisms (Archaea and Bacteria) as reported in the cited literature. It is the first time that all the results on PDOs are reported together. Our group has had a well defined role in these studies as proved by the numerous publications. Figure 4 is completely original. It compares the activities of different PDOs described in our papers (ref. 18-74-76).	**4, 6, 11, 14–16, 20–21, 26, 32, 36, 44, 46, 50, 55, 64, 71–74, 76, 81–83, 89, 92, 94, 96, 99**
TR/PDO system and its involvement in the redox homeostasis Page 165–166	Overview of different Thioredoxin Reductases (TR). An analysis of the systems TR/Trx (*Aeropyrum pernix*) and TR/PDO (*Sulfolobus solfataricus* and *Pyrococcus horikoshii*) is presented. The involvement of TR/PDO in the detoxification system of the peroxides through the peroxiredoxins is suggested. Figure 5 is completely original.	**2, 8, 10, 13, 23, 24, 27, 35, 37–41, 52, 60, 62–63, 78, 84–85, 90, 93, 95, 97–98, 100, 102**

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Date of first submission to ARS Central, July 20, 2009; date of final revised submission, August 17, 2009; date of acceptance, August 17, 2009.