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A systematic review of human antioxidant genes

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TABLE OF CONTENTS

1. ABSTRACT

The balance between production and clearance of reactive species is essential for cell survival. Antioxidant cellular systems evolved to maintain a redox homeostasis under different physiological and pathological conditions. Therefore, many authors aim at better understanding the mechanisms and functions of cellular antioxidant components and their relationships between each other and with more general cell functions. Nonetheless, the definition of an "antioxidant system" is a wide and sometimes relative concept, and there is no consensus regarding the necessary requisites for classifying a cell functional component into such category. Here, we suggest a list of human antioxidant genes comprehending all gene products fulfilling specific inclusion criteria, such as antioxidant enzymatic function, participation in redox reactions and other molecular interactions directly related to antioxidant activity. The criteria are discussed and the gene-protein-substrate associations between the components of the list are presented. In addition, at http://www.ufrgs.br/icbs/hag we provide a network-based model of human antioxidant genes, which can be used as reference tool to access several database resources (*e.g.*, RefSeq, Ensembl, HGNC and the NCBI Entrez database).

2. INTRODUCTION

Free radicals and related reactive species are ubiquitous molecules taking part in essential biological processes at the cellular level. Cells have mechanisms to maintain the production and clearance of reactive species in a homeostatic state, and abnormalities leading to the imbalance of this equilibrium may cause a condition termed "oxidative stress". Although the term "oxidative stress" is generally used to refer to biomolecular damage induced by both reactive oxygen (ROS) and reactive nitrogen (RNS) species, the term "nitrosative stress" has been used recently to separate oxidative damage from nitrosative damage (1). Here, for abbreviation, we will refer to both conditions under the general term "oxidative stress".

By definition, oxidative stress leads to the accumulation of damaged cell constituents, such as lipids, proteins, and DNA. Many types of ROS and RNS are readily diffusible and physiologically modulated to optimum levels at which they play important roles as signaling molecules. This is the case of H_2O_2 and nitric oxide, for instance. These molecules are important signaling factors in physiological processes such as cell division and vasoconstriction regulation; nonetheless, they

are also precursors of biologically relevant (and potentially toxic) reactive species such as hydroxyl radical and peroxynitrite (2). Basal production of ROS/RNS and related species arises from diverse physiological processes, such as phagocytosis and electron transport chain, among others. Variations in the regulation of these processes may increase ROS/RNS production, as in enhanced inflammatory response and uncoupled mitochondrial function.

To avoid the deleterious consequences of oxidative stress, cells developed various defense mechanisms that include detoxification, antioxidant enzymes, repair enzymes, and thiol-redox systems. Besides, they utilize secondary metabolites and exogenous compounds with antioxidant and/or ROS/RNS scavenging capacity. Cellular enzymatic and non-enzymatic antioxidant components are in general collectively referred to as the "antioxidant defense system" of the cells, and these components are interrelated in a complex network that maintains the homeostasis of ROS/RNS production and clearance [for detailed review, see ref. (3)]. Most enzymatic components of this antioxidant defense system are commonly known as "antioxidant enzymes" (*e.g.* catalase, superoxide dismutase, glutathione peroxidase). Many experimental works evaluate the activity and expression of such antioxidant enzymes in different physiological conditions as a parameter to assess oxidative stress in a given system. Moreover, antioxidant enzymatic activity and expression are studied in pathological processes such as atherosclerosis, hypertension, inflammation, Parkinson's and Alzheimer's diseases, type-2 diabetes and cancer, among others, as these conditions are all related to unbalanced ROS/RNS production and detoxification (4). Indeed, a relationship between deficiency of some antioxidant enzymes expression and increased incidence of some of these diseases has already been related, *e.g.* superoxide dismutase and catalase deficiency in some types of cancer (5,6).

Nonetheless, the definition of an enzymatic "antioxidant" system may be a relative concept, as many enzymes take part in reactions that directly or indirectly contribute to maintain the cellular redox homeostasis, however without interacting directly with reactive species or participating in the redox buffering. In the specialized literature, the term "antioxidant enzyme" is generally ascribed only to enzymes that work directly with potentially toxic reactive species as their primary substrates and convert them to less or non-toxic products (3).

In the present work, we compiled a list of human antioxidant genes based on the current human genome information available in public databases. In this list, we included two classes of genes: *i*) genes whose products are defined as "antioxidant enzymes", according to the definition mentioned above; and *ii*) genes whose products are not enzymes, but also deal directly with reactive species detoxification, such as some specific thiol-containing proteins. This compilation resulted in a comprehensive list of 63 human antioxidant genes, subclassified into three functional groups: peroxidases, superoxide dismutases, and thiol-redox proteins. This list is presented here with a description of classification criteria and procedures, together with a description of substrates and products of each gene product, besides their network interrelationships. We anticipate that the resulting antioxidant gene network will give insights on the systemic and tissue-specific properties of human antioxidant defenses.

3. SEARCHING FOR POTENTIAL ANTIOXIDANT GENES

3.1. Databases and data selection

To search for potential antioxidant related genes, we conducted a systematic review using Gene Ontology database (http://www.geneontology.org/) in September 2007. Search criteria included subject-heading terms for gene products associated with oxygen and reactive oxygen species (GO:0006800 and its children). The results were manually curated in order to identify additional relevant published studies enrolling these genes in antioxidant defense. To retrieve functional associated genes we used STRING database (http://string.embl.de/) (7), which provides bioinformatics tools in order to construct functional associated gene networks. Genes were eligible for inclusion if they were identified following the standard nomenclature for human genes in HGNC database (http://www.genenames.org/) (8).

3.2. Defining antioxidant genes and criteria of inclusion

It is consensually difficult to define clearly and concisely what is an antioxidant. Many compounds do not present an evident antioxidant role in physiological situations, but perform an important function when a system is subjected to oxidative stress. This is the case of endogenous compounds such as uric acid, albumin, and bilirubin, for instance. Besides, other enzymatic and non-enzymatic compounds may greatly influence the redox status of cells by playing a primary role in the metabolism of substances that may be relevant to the metabolism of free radicals, such as iron or copper ions. This is the case of proteins such as transferrins and metallothioneins. Considering this wide definition of antioxidants, we established the following criteria for the construction of the human antioxidants genes list:

1. Inclusion of genes whose products are widely accepted as being primarily antioxidant enzymes. These are enzymes that catalytically remove reactive species, converting them into less or non-toxic products, and do not present any known function other than reactive species cleaning.

2. Inclusion of genes whose products may not be antioxidant enzymes, but are also recognized as having a primary antioxidant function. These are proteins that serve as co-substrates or co-factors in redox reactions carried by antioxidant enzymes, or show specific interactions with such enzymes, being indispensable to their function. Genes whose proteins are described as having a role in non-enzymatic cleaning of reactive species were also in this category.

3. Inclusion of genes whose products are recognized as having a primary role in other physiologic processes, but are known to physically interact with reactive species, also converting them into less or non-toxic products, through redox reactions carried by functional groups. Proteins that were first described as having a different function but were later recognized as playing a major role in reactive species cleaning by direct involvement in redox-reactions were included in this group.

4. Inclusion of genes whose products were described to maintain exclusive, specific interactions with the gene products described above, being essential for the antioxidant function of such proteins.

By following these criteria, we attempted to comprehend only the genes whose products actively participate in the clearance of reactive species by physically interacting with such species, along with their exclusive chaperones and co-factors; this excluded diverse proteins that are considered important in the maintenance of the cellular redox homeostasis, as mentioned earlier. Nonetheless, our aim was to focus on gene products that are solely antioxidants. Genes being described as isoforms/isogenes of primary antioxidant genes were also included.

4. THE HUMAN ANTIOXIDANT GENES LIST

The list of human antioxidant genes obtained by following the database search and inclusion criteria described above is shown in Table 1. This list is also available at http://www.ufrgs.br/icbs/hag. A functional analysis of these genes subdivides them into three groups: superoxide dismutases (4 genes), peroxidases (17 genes), and thiol-redox proteins (42 genes).

4.1. Superoxide Dismutases

Superoxide dismutases (SODs) were the first enzymes recognized as having an important antioxidant role, and they are widely accepted as an enzyme family with specific function. These enzymes dismutate two molecules of superoxide radical into H_2O_2 and O_2, and the remaining H_2O_2 is generally further metabolized by catalase or glutathione peroxidase. Here we included the three genes encoding different SODs in humans: *SOD1* (encoding the cytosolic/nuclear Cu/Zn-superoxide dismutase), *SOD2* (encoding the mitochondrial Mn-superoxide dismutase) and *SOD3* (which encodes the so-called extracellular superoxide dismutase). Besides, we included in this group of genes the copper chaperone for SOD (*CCS*) gene, which encodes a copper-delivering protein essential for the function of *SOD1* (9). This protein may be not be functionally classified as antioxidant, but it has a specific role in delivering copper to SOD1, being essential for its activation. Therefore, the modulation of this gene is directly related to the modulation of the enzymatic function of SOD1, and due to the exclusive nature of this interaction, we decided to include *CCS* in the list as a member of the SODs group.

4.2. Peroxidases

This group comprises a wide, heterogeneous group of genes encoding different proteins with a common characteristic: they function as hydroperoxides and detoxify organic peroxides. However, some peroxidases are directly involved in the production of highly toxic molecules, generally by using hydroperoxides as substrates for generating specific reactive species with microbicidal action. This is the case of myeloperoxidase, which catalyzes the following reaction:

$$H_2O_2 + Cl^- \rightarrow HOCl + OH^-$$

The HOCl produced by myeloperoxidase is very important for the process of bacterial killing by phagocytes. Nonetheless, HOCl is highly reactive and may cause severe damages to biomolecules either directly or by its decomposition into chlorine. HOCl is, therefore, a powerful oxidant and triggers cell death in diverse situations. Increased myeloperoxidase function has been implicated in the pathogenesis of Alzheimer's disease and cardiovascular diseases. Lactoperoxidase plays a similar role in breast milk and saliva.

Although the products of myeloperoxidase and lactoperoxidase catalysis reactions are pro-oxidant molecules, in most textbooks these enzymes are historically grouped along with other peroxidases presenting a well-established antioxidant function, such as glutathione peroxidase. This is probably due to their common peroxidatic mechanism of enzymatic function. Here, we will follow these same criteria and include both myeloperoxidase and lactoperoxidase in the human antioxidant genes list by their mechanistic similarity with other peroxidases, but further analysis in the future may review this classification.

4.3. Thiol-redox proteins

This is perhaps the group most susceptible to changes in future revisions of the human antioxidant gene list. The reason is the growing number of proteins being lately recognized as having a major role in reactive species cleaning through thiol-redox reactions mediated by their thiol-containing side chains. These genes were grouped together due their common multi-step mechanism of reactive species cleaning: 1) oxidation of cysteine residues forming protein disulfides; and 2) reduction of these disulfides by specific proteins (such as glutaredoxins or thioredoxin reductase) using specific co-factors (reduced glutathione, thioredoxin, or NADPH). Although all cysteine-containing proteins are subjected to oxidation of their thiol groups when cells are submitted to oxidative stress, some proteins are considered more important in the function of "thiol-redox buffering" due to their elevated number of reactive cysteines. This is the case of some metallothioneins included here, which are rich in cysteine residues and act as scavengers of several reactive species, besides their more established role in the aggregation of metal ions (11). Recently, however, it has been suggested that the elevated number of reactive cysteines is not the only factor for classifying a protein as having a thiol-redox function, as several factors are involved in the

Table 1. Human antioxidant genes

Gene Group[1]	Gene Symbol[2]	Gene Name[2]	Chromosome	RefSeq ID	Entrez ID
Peroxidases	*CAT*	catalase	11p13	NM_001752	847
Peroxidases	*CP*	ceruloplasmin (ferroxidase)	3q23-q25	NM_000096	1356
Peroxidases	*GPX1*	glutathione peroxidase 1	3p21.3	NM_000581	2876
Peroxidases	*GPX2*	glutathione peroxidase 2 (gastrointestinal)	14q24.1	NM_002083	2877
Peroxidases	*GPX3*	glutathione peroxidase 3 (plasma)	5q23	NM_002084	2878
Peroxidases	*GPX4*	glutathione peroxidase 4 (phospholipid hydroperoxidase)	19p13.3	NM_002085	2879
Peroxidases	*GPX5*	glutathione peroxidase 5 (epididymal androgen-related protein)	6p22.1	NM_001509	2880
Peroxidases	*GPX6*	glutathione peroxidase 6 (olfactory)	6p22.1	NM_182701	257202
Peroxidases	*GPX7*	glutathione peroxidase 7	1p32	NM_015696	2882
Peroxidases	*LPO*	lactoperoxidase	17q23.1	NM_006151	4025
Peroxidases	*MPO*	myeloperoxidase	17q21.3-q23	NM_000250	4353
Peroxidases	*PRDX1*	peroxiredoxin 1	1p34.1	NM_181697	5052
Peroxidases	*PRDX2*	peroxiredoxin 2	19p13.2	NM_181737	7001
Peroxidases	*PRDX3*	peroxiredoxin 3	10q25-q26	NM_006793	10935
Peroxidases	*PRDX4*	peroxiredoxin 4	X	NM_006406	10549
Peroxidases	*PRDX5*	peroxiredoxin 5	11q13	NM_181651	25824
Peroxidases	*PRDX6*	peroxiredoxin 6	1q24.1	NM_004905	9588
Sup. dismutases	*CCS*	copper chaperone for superoxide dismutase	11	NM_005125	9973
Sup. dismutases	*SOD1*	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	21q22.11	NM_000454	6647
Sup. dismutases	*SOD2*	superoxide dismutase 2, mitochondrial	6q25	NM_000636	6648
Sup. dismutases	*SOD3*	superoxide dismutase 3, extracellular	4pter-q21	NM_003102	6649
Thiol redox	*GLRX*	glutaredoxin (thioltransferase)	5q14	NM_002064	2745
Thiol redox	*GLRX2*	glutaredoxin 2	1p31.2-q31.3	NM_016066	51022
Thiol redox	*GLRX3*	glutaredoxin 3	10q26	NM_006541	10539
Thiol redox	*GLRX5*	glutaredoxin 5	14q32.2	NM_016417	51218
Thiol redox	*GSR*	glutathione reductase	8p21.1	NM_000637	2936
Thiol redox	*MSRA*	methionine sulfoxide reductase A	8p23.1	NM_012331	4482
Thiol redox	*MT1A*	metallothionein 1A	16q13	NM_005946	4489
Thiol redox	*MT1B*	metallothionein 1B	16q13	NM_005947	4490
Thiol redox	*MT1E*	metallothionein 1E	16q13	NM_175617	4493
Thiol redox	*MT1F*	metallothionein 1F	16q13	NM_005949	4494
Thiol redox	*MT1G*	metallothionein 1G	16q13	NM_005950	4495
Thiol redox	*MT1H*	metallothionein 1H	16q13	NM_005951	4496
Thiol redox	*MT1M*	metallothionein 1M	16q13	NM_176870	4499
Thiol redox	*MT1X*	metallothionein 1X	16q13	NM_005952	4501
Thiol redox	*MT2A*	metallothionein 2A	16q13	NM_005953	4502
Thiol redox	*NXNL1*	nucleoredoxin-like 1	19p13.12	NM_138454	115861
Thiol redox	*PDIA6*	protein disulfide isomerase family A, member 6	2p25.1	NM_005742	10130
Thiol redox	*SEPP1*	selenoprotein P, plasma, 1	5q31	NM_005410	6414
Thiol redox	*SRXN1*	sulfiredoxin 1 homolog (S. cerevisiae)	20p13	NM_080725	140809
Thiol redox	*TXN*	thioredoxin	9q31	NM_003329	7295
Thiol redox	*TXN2*	thioredoxin 2	22q13.1	NM_012473	25828
Thiol redox	*TXNDC1*	thioredoxin domain containing 1	14q22.1	NM_030755	81542
Thiol redox	*TXNDC10*	thioredoxin domain containing 10	18q22	NM_019022	54495
Thiol redox	*TXNDC11*	thioredoxin domain containing 11	16p13.13	NM_015914	51061
Thiol redox	*TXNDC12*	thioredoxin domain containing 12 (endoplasmic reticulum)	1p32.3	NM_015913	51060
Thiol redox	*TXNDC13*	thioredoxin domain containing 13	20p12	NM_021156	56255
Thiol redox	*TXNDC14*	thioredoxin domain containing 14	11cen-q22.3	NM_015959	51075
Thiol redox	*TXNDC17*	thioredoxin domain containing 17	17p13.2	NM_032731	84817
Thiol redox	*TXNDC2*	thioredoxin domain-containing 2 (spermatozoa)	18p11.31-p11.2	XM_942162	84203
Thiol redox	*TXNDC3*	thioredoxin domain containing 3 (spermatozoa)	7p15.2	NM_016616	51314
Thiol redox	*TXNDC4*	thioredoxin domain containing 4 (endoplasmic reticulum)	9q22.33	XM_088476	23071
Thiol redox	*TXNDC5*	thioredoxin domain containing 5	6p24.3	NM_030810	81567
Thiol redox	*TXNDC6*	thioredoxin domain containing 6	3q22.3	NM_178130	347736
Thiol redox	*TXNDC8*	thioredoxin domain containing 8 (spermatozoa)	9q31.3	NM_001003936	255220
Thiol redox	*TXNDC9*	thioredoxin domain containing 9	2q11.2	NM_005783	10190
Thiol redox	*TXNIP*	thioredoxin interacting protein	1q11	NM_006472	10628
Thiol redox	*TXNL1*	thioredoxin-like 1	18q21.1-18q21.32	NM_004786	9352
Thiol redox	*TXNL4A*	thioredoxin-like 4A	18q23	NM_006701	10907
Thiol redox	*TXNL4B*	thioredoxin-like 4B	16q22.2	NM_017853	54957
Thiol redox	*TXNRD1*	thioredoxin reductase 1	12q23-q24.1	NM_003330	7296
Thiol redox	*TXNRD2*	thioredoxin reductase 2	22q11.21	NM_006440	10587
Thiol redox	*TXNRD3*	thioredoxin reductase 3	3p13-q13.33	XM_051264	114112

[1]Gene groups defined according to specific inclusions criteria, such as antioxidant enzymatic function, participation in redox reactions and other molecular interactions directly related to antioxidant activity. [2]Gene names and symbols follow the official nomenclature of HGNC (8).

susceptibility of a given cysteine to different oxidant conditions (3). This may lead to the inclusion of new genes in future revisions of the human antioxidant genes list.

5. HUMAN ANTIOXIDANT RELATED GENE/PROTEIN/SUBSTRATE ASSOCIATION NETWORK

When analyzing the redox reactions carried by the proteins coded by the genes selected for the antioxidant genes list, it became evident that a significant number of genes was related by their substrates and products. Some gene products share the same substrates; other gene products metabolize enzymatic products of others, while still other gene products do both. This observation led us to hypothesize that the human antioxidant genes of the present list could operate as a functional network containing protein-protein, substrate-proteins, product-proteins, and substrate-product interactions. Therefore, we tried to examine these interactions by using tools of systems biology. The underlying principle to construct the network model of antioxidant genes is simple, but nontrivial, and is founded in a metabolic context, that is, all genes with primary antioxidant function are considered together with their substrate/product reactions to construct the network interactions. Therefore, the criteria to construct the network follow two major steps.

In the first step, we established the protein-protein interactions associating antioxidant genes. This process was supervised using database STRING (7) with input options "databases", "experiments", and 70% confidence level (12). Each gene was identified in the database according to both HUGO ID (8) and Ensembl Peptide ID (13) (see www.ufrgs.br/icbs/hag). Alternatively, the amino acid sequence of a given protein was supplied to identify the corresponding entry. The results of the search were saved in data files "tab-delimited text fields" describing edge relationships and then handled in Medusa software (14) (an optimized software for accessing protein interaction data from STRING database).

Next, the protein data were crossed with substrates in order to integrate the network. For this purpose, we considered the substrates annotated for each gene product in KEGG database (15) (http://www.genome.jp/kegg/). The complete file matching entry IDs, data interactions and substrates are available at www.ufrgs.br/icbs/hag. The graph resulting from our network construction is depicted in Figure 1 and reveals topological properties related to their grouping classification criteria, as expected. First, a cluster of genes is formed by the groups of thiol-redox proteins and peroxidases linked by molecules containing oxidized (R-S-S-R) and reduced (R-SH) thiol groups as substrates/products. It is also possible to observe that the group of SODs is linked to the group of peroxidases through associations with hydrogen peroxide and oxygen, as expected. The four members of the SODs group formed a separate nucleus of association, evidencing the functional separation of SODs in relation to other antioxidant genes and the functional specificity of this group. The graph may also suggest a functional redundancy in the group of thiol-redox proteins, as the association between the genes of this group is almost exclusively due to their recurrent association of individual genes with common substrates and products (reduced sulfides and oxidized disulfides).

The group of peroxidases also presents a separate subgroup of genes encoding proteins that do not work with thiol groups; therefore, they are not related to thiol-redox proteins by substrate interactions, – and these are lactoperoxidase, myeloperoxidase, catalase, and ceruloplasmin. These four proteins present some peculiarities in relation to the other members of the peroxidases group: first, lactoperoxidase and myeloperoxidase present a strong pro-oxidant function, related to their microbicidal function, as commented earlier. Ceruloplasmin was included in the list due to its recently reported peroxidatic activity at some specific situations, but there is no consensus on the primary function of this protein (16). Catalase, on the other hand, is very well known for its role in H_2O_2 decomposition in cells, especially in peroxisomes. Catalase is not functionally considered a peroxidase, as it does not use H_2O_2 to oxidize another substrate, which defines the peroxidatic function. In this sense, catalase is considered by most textbooks as a separate class of enzyme, although represented by only one gene in humans. However, catalase may also catalyze peroxidase-type reactions, taking part in the peroxidation of exogenous metals (17). Therefore, we included this gene in the list as a peroxidase.

It is important to note that the construction of the network model following the criteria listed earlier evidenced functional differences not only between genes from different groups, but also among members of the same group, as observed in the peroxidases group. It is possible that, in the future, these network associations will also be part of the criteria used to include, review, and classify genes for the human antioxidant genes list.

6. POSSIBLE APPLICATIONS AND PERSPECTIVES

Classifying genes is far from a simple task. In general, gene products can overlap several cell functions, reflecting the molecular entanglement of the genome. Here, we provide a network-based model of human antioxidant genes together with a comprehensive classification. This approach can be used to evaluate the systemic properties of antioxidant genes. For this purpose, we provide on the web the HAG website (Human Antioxidant Genes website), which is designed to search database information in order to facilitate the analysis of high-throughput data focusing on human antioxidant defenses. The evaluation of expression patterns of the human antioxidant gene network in transcriptomes from patients of several diseases associated with oxidative stress may provide new insights to understand the role of reactive species in such

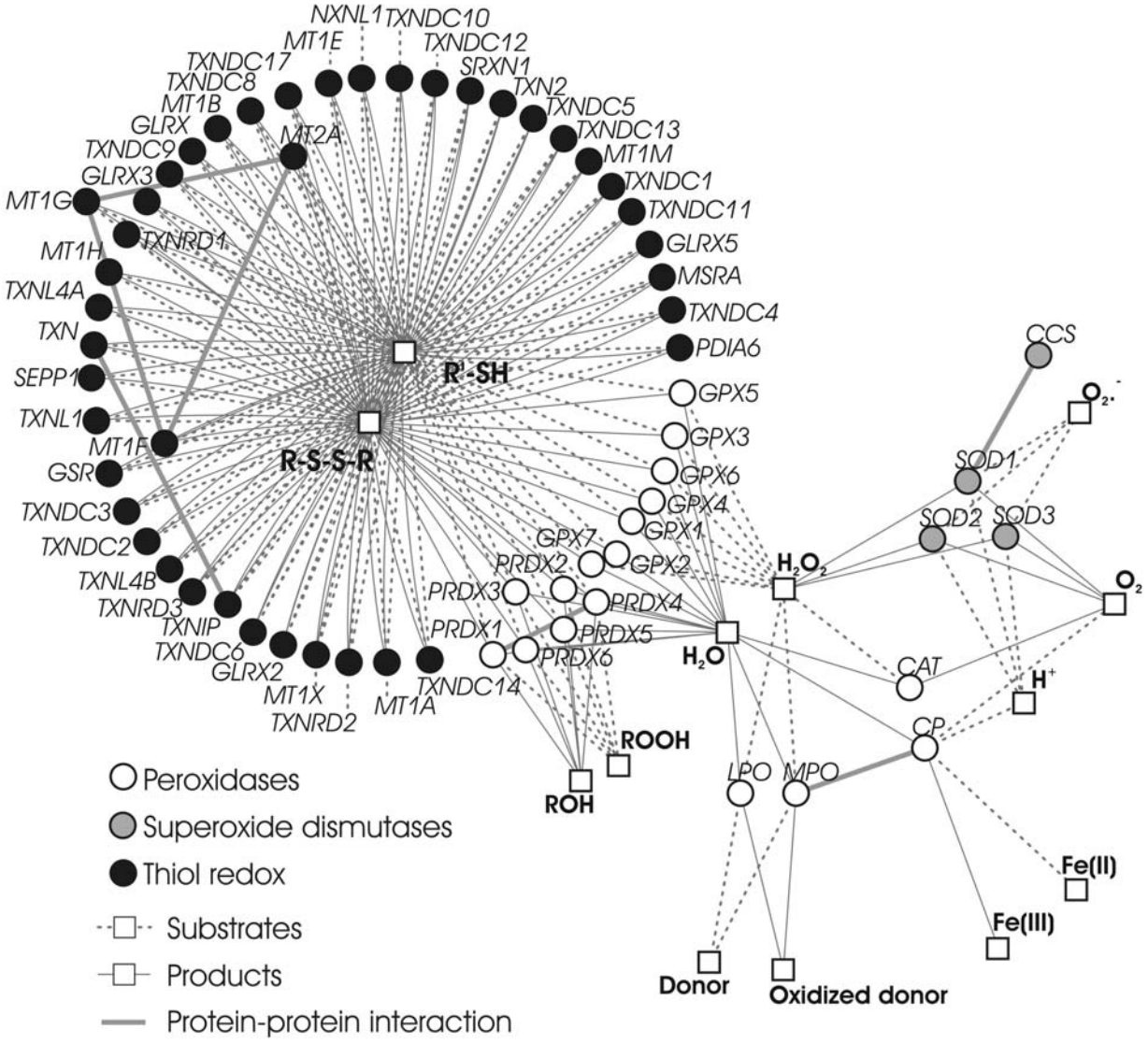

Figure 1. Human antioxidant gene network. This graph presents a network-based model of human antioxidant genes characterizing the interactions existing among different antioxidant genes and its substrates. Each node corresponds to a gene-network node (GNN), while the lines represent direct (physical) and/or indirect (functional) associations as described in the text. The underlying principle of this model is simple, but nontrivial, and is founded in a metabolic context, that is, all genes with prime antioxidant function are considered together with their substrate/product reactions to construct the network interactions. Given that many related antioxidant genes can code different protein isoforms, this model in fact expands those nodes representing enzymes in the redox reactions, which leads to substrate/product centrality onto the network map. Different groups are represented in different colors. Online version available at http://www.ufrgs.br/icbs/hag, including links to access several database resources (*e.g.*, RefSeq, Ensembl, the HUGO Gene Nomenclature Committee database and the NCBI Entrez database).

conditions. This approach may also be applied using transcriptomes from cell cultures subjected to diverse controlled conditions.

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8. REFERENCES

1. Athena A. Andreadis, Stanley L. Hazen, Suzy A. A. Comhair and Serpil C. Erzurum: Oxidative and nitrosative events in asthma. *Free Radic Biol Med* 35, 213-225 (2003)

2. Igor B. Afanas'ev: Signaling functions of free radicals superoxide & nitric oxide under physiological & pathological conditions. *Mol Biotechnol* 37, 2-4 (2007)

3. Barry Halliwell and John Gutteridge: Antioxidant defenses: endogenous and diet derived. In: Free Radicals in Biology and Medice. Eds: Barry Halliwell and John Gutteridge, Oxford University Press, New York (2007)

4. Petr Jezek and Lydie Hlavata: Mitochondria in homeostasis of reactive oxygen species in cell, tissues, and organism. *Int J Biochem Cell Biol* 37, 2478-2503 (2005)

5. José M. Matés and Francisca Sánchez-Jiménez: Antioxidant enzymes and their implications in pathophysiologic processes. *Front Biosci* 4, D339-D345 (1999)

6. Gilberto Pérez Trueba, Gregorio Martínez Sánchez and Atilia Giuliani: Oxygen free radical and antioxidant defense mechanism in cancer. *Front Biosci* 9, 2029-2044 (2004)

7. Christian von Mering, Lars J. Jensen, Michael Kuhn, Samuel Chaffron, Tobias Doerks, Beate Kruger, Berend Snel and Peer Bork: STRING 7--recent developments in the integration and prediction of protein interactions. *Nucl Acids Res* 35, D358-D362 (2007)

8. Hester M. Wain, Michael J. Lush, Fabrice Ducluzeau, Varsha K. Khodiyar and Sue Povey: Genew: the Human Gene Nomenclature Database, 2004 updates. *Nucl Acids Res* 32, D255-D257 (2004)

9. T. D. Rae, P. J. Schmidt, R. A. Pufahl, V. C. Culotta and T. V. O'Halloran: Undetectable intracellular free copper: the requirement of a copper chaperone for superoxide dismutase. *Science* 284, 805-808 (1999)

10. Britton Chance, Helmut Sies and Alberto Boveris: Hydroperoxide metabolism in mammalian organs. *Physiol Rev* 59, 527-605 (1979)

11. Xiaoyan Li, Hainan Chen and Paul N. Epstein: Metallothionein Protects Islets from Hypoxia and Extends Islet Graft Survival by Scavenging Most Kinds of Reactive Oxygen Species. *J Biol Chem* 279, 765-771 (2004)

12. Mauro A. A. Castro, Jose C. M. Mombach, Rita M. C. de Almeida and Jose C. F. Moreira: Impaired expression of NER gene network in sporadic solid tumors. *Nucl Acids Res* 35, 1859-1867 (2007)

13. E. Birney, D. Andrews, M. Caccamo, Y. Chen, L. Clarke, G. Coates, T. Cox, F. Cunningham, V. Curwen, T. Cutts, T. Down, R. Durbin, X. M. Fernandez-Suarez, P. Flicek, S. Graf, M. Hammond, J. Herrero, K. Howe, V. Iyer, K. Jekosch, A. Kahari, A. Kasprzyk, D. Keefe, F. Kokocinski, E. Kulesha, D. London, I. Longden, C. Melsopp, P. Meidl, B. Overduin, A. Parker, G. Proctor, A. Prlic, M. Rae, D. Rios, S. Redmond, M. Schuster, I. Sealy, S. Searle, J. Severin, G. Slater, D. Smedley, J. Smith, A. Stabenau, J. Stalker, S. Trevanion, A. Ureta-Vidal, J. Vogel, S. White, C. Woodwark and T. J. P. Hubbard: Ensembl 2006. *Nucl Acids Res* 34, D556-D561 (2006)

14. Sean D. Hooper and Peer Bork: Medusa: a simple tool for interaction graph analysis. *Bioinformatics* 21, 4432-4433 (2005)

15. Minoru Kanehisa, Susumu Goto, Masahiro Hattori, Kiyoko F. Aoki-Kinoshita, Masumi Itoh, Shuichi Kawashima, Toshiaki Katayama, Michihiro Araki and Mika Hirakawa: From genomics to chemical genomics: new developments in KEGG. *Nucl Acids Res* 34, D354-D357 (2006)

16. Joe Healy, Keith Tipton. Ceruloplasmin and what it might do. *J Neural Transm* 114, 777-81 (2207)

17. Britton Chance, Helmut Sies, Alberto Boveris. Hydroperoxide metabolism in mammalian organs. *Physiol Rev* 59, 527-605 (1979).

Abbreviations: SOD, superoxide dismutase; ROS, reactive oxygen species; RNS, reactive nitrogen species; KEGG, Kyoto Encyclopedia of Genes and Genomes; HUGO, the Human Genome Organisation; HGNC, HUGO Gene Nomenclature Committee; STRING, search tool for the retrieval of interacting genes/proteins.

Key Words: Antioxidant, Oxidative Stress, Gene Network, Reactive Oxygen Species, Peroxidases, Superoxide Dismutases, Thiol-redox, Systems Biology, Review

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