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Chapter 15Evasion of the Toxic Effects of Oxygen

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Oxygen as a Toxic Species

Oxygen is an efficient terminal electron acceptor in respiratory pathways. During aerobic respiration the electron transport chain generates free radical oxygen species as a result of electron leakage; this generation of toxic species is proportional to the oxygen tension (51). In addition, toxic oxygen species (TOS) may be formed exogenously, for example, by chemical processes or through radiation. TOS also result from the oxidative burst of polymorphonuclear leukocytes (PMN). Infection with *Helicobacter pylori* induces an inflammatory response (gastritis), which leads to an increase in the level of TOS in the gastric mucosa and the gastric juice (4, 24–26, 59). This increase in the level of toxic metabolites is probably the result of the generation of the superoxide anion ($O_2^{\cdot -}$), a reactive TOS, formed as part of the oxidative burst of PMN and enzymic activities of gastric epithelial cells. There is evidence that *H. pylori* infection leads to increased production of $O_2^{\cdot -}$ via NADPH oxidase in gastric cells, stimulated by lipopolysaccharide as well as xanthine oxidase, another mechanism for the generation of oxygen-derived free radicals (8, 80). In response to increased superoxide anion production in gastric tissue, changes have been detected in the level of expression of human superoxide dismutase (SOD) (12). Human gastric SOD exists as a cytoplasmic copper-zinc-superoxide dismutase (Cu, Zn-SOD) found in gland cells of the gastric body and antral mucosa, and as a manganese-superoxide dismutase (Mn-SOD) within mitochondria (63). An increase in the amount and activity of Mn-SOD has been observed in response to *H. pylori* infection and gastritis, whereas the amount and activity of the Cu, Zn-SOD remained constant or decreased slightly (39). It has been suggested that the induction of Mn-SOD is in response to increased cytokine production within the inflamed gastric mucosa (39). This situation is reversed following successful treatment of the infection (38). The data suggest that within the gastric environment *H. pylori* may be exposed to increased levels of TOS. In such an environment it is important for bacterial survival that the impact of such TOS be neutralized.

Reducing the Impact of TOS

How do microorganisms manage their exposure to TOS? Several strategies may be adopted, governed in part by determinants such as whether the toxic species are generated endogenously or exogenously. Microorganisms may neutralize TOS by mechanisms that include the enzymes SOD, catalase, peroxidases, and a variety of reductases. Also, they may modulate intracellular oxygen concentration or redox potential, thus minimizing their exposure to oxidative damage, or minimize such damage through the evolution of cellular structures resistant to oxidative damage. Finally, bacterial cells may overcome the effects of oxidative damage through efficient DNA repair mechanisms. There are many studies on such mechanisms in other organisms, and indeed, a great part of our understanding of these mechanisms in *H. pylori* is based predominantly on comparisons with the systems present in other organisms.

Neutralization of TOS

There are two prominent enzymes that facilitate resistance to oxidative damage in *H. pylori*, catalase (KatA) and SOD (43, 54, 65, 67, 77). In addition, there is genetic and biochemical evidence for the presence of at least two other enzyme systems involved in resistance to oxidative damage, alkylhydroperoxide reductase (Ahp) and thioredoxin-linked thiol peroxidase (scavengease).

Catalase

Catalase has been studied quite comprehensively in many eukaryotic and prokaryotic systems, beginning with studies in the 1800s (53). It has been used and still is used today as a diagnostic tool in bacterial identification in medical microbiology. The major function of catalase is to protect cells from the damaging effects of hydrogen peroxide (H_2O_2), catalyzing the dismutation of H_2O_2 into water and oxygen (equation 1). Consequently, catalase is an extremely important enzyme in an organism's response to oxidative stress.

$$2H_2O_2 \rightarrow 2H_2O + O_2 \qquad (1)$$

Hydrogen peroxide is generated as a by-product of aerobic respiration, which uses oxygen as a terminal electron acceptor and can give rise to reactive oxygen species such as $O_2^{\cdot -}$ and H_2O_2. SOD is capable of removing the superoxide anion, but this results in the generation of more H_2O_2 (equation 2).

$$2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2 \qquad (2)$$

Nonetheless, the amounts of hydrogen peroxide and superoxide radicals produced during aerobic respiration are quite small in comparison with the quantity released during the respiratory or oxidative burst produced by PMN.

Exposure to H_2O_2 can be catastrophic for many organisms, yet the reactions between H_2O_2 and organic molecules, such as proteins and DNA, remain unclear. This is largely due to the rapid formation of other reactive oxygen species (ROS), which appear to be more reactive than H_2O_2 (33). The formation of other reactive oxygen radicals is due in part to interactions between H_2O_2 and reduced metallic ions found in all biological systems. The greatest risk that is posed to any cell, in terms of ROS, occurs when H_2O_2 reacts with reduced iron or copper ions (83) to form hydroxyl radicals ($OH^{\cdot}$) in a Fenton reaction (16). The hydroxyl radicals will react with most biological and organic molecules in oxidation reactions. Exposure to hydrogen peroxide, either through direct or indirect action, can result in DNA damage (therefore being mutagenic), lipid damage, and inhibition of the activities of enzymes and other proteins through oxidation. This is a probable explanation for the decreased growth rates observed in bacterial cell cultures in the presence of H_2O_2 (78).

"Typical" catalases characteristic of eukaryotes are homotetrameric with subunit mass between 55 and 65 kDa, and no heme prosthetic group per subunit (53), as indicated by the strong Soret band at 402 to 406 nm, with minor peaks at 500 to 505, 535 to 540, and 620 to 635 nm (45). Typical catalases differ from catalase-peroxidases found in a number of bacterial species in that they do not display peroxidase activity (32). *H. pylori* catalase is homotetrameric; each subunit has a mass of 58.7 kDa (as determined by the inferred amino acid sequence) and one heme prosthetic group (43, 54, 65). The enzyme is a mono-functional catalase, i.e., it lacks peroxidase activity (43). The activity of the *H. pylori* catalase is pH independent, with no difference between pH 5.25 and 8.95 (43). The enzyme has good thermostability, retaining catalytic activity after incubation at 56°C for 1 h (43). These properties are consistent with those of typical eukaryote catalases (43, 58).

Catalase is expressed in the cytoplasm and probably in the periplasm of *H. pylori*. There is some limited evidence supporting the presence of catalase on the cell surface, a unique occurrence in *H. pylori*, and possibly owing to autolytic events (43, 68, 71). However, Mori et al. (57) were unable to detect catalase activity in the supernatant of culture media after 24 h of growth, concluding that it was unlikely that the enzyme is secreted into the surrounding environment. The sequence does not show a cleavable *N*-terminal signal peptide, as is the case with many other periplasmic proteins (41), thus the putative translocation of the enzyme to the periplasm would be Sec-independent. *H. pylori* catalase is expressed during exponential growth and is not induced when the cells enter stationary

phase as is the case with some bacterial catalases/catalase-peroxidases, for example, in *Escherichia coli* (43, 55).

A unique property of *H. pylori* catalase is an isoelectric point (pI) in the range of 9.0 to 9.3 (43). To date it is the only basic catalase that has been characterized. Catalases produced by other organisms usually have a pI in the range of 4.5 to 5.0 (58). The basic pI of *H. pylori* catalase is largely due to the high lysine and arginine content in the enzyme. The release of the genome made it clear that many proteins of *H. pylori* have a basic pI (2, 82). The biological relevance of the pI of catalase and other proteins of *H. pylori* has yet to be determined.

Catalase in *H. pylori* is distinctive because in situ there is a very rapid breakdown of hydrogen peroxide. The formation of oxygen occurs extremely fast, giving an "explosive" appearance of oxygen bubbles that is characteristic of catalase tests performed on whole *H. pylori* cells. The kinetic properties of the enzyme do not necessarily shed light on the activity observed when whole cells are exposed to H_2O_2. *Helicobacter pylori* catalase has a K_m of 43 ± 3 mM and a V_{max} of 60 ± 3 mmol/min/mg of protein (43). The K_m is 3 to 10 times higher than those of other bacterial catalases, suggesting that the enzyme is relatively inefficient. Although the affinity of the protein for the substrate is not as high as those of some other catalases, it is likely that the high activity characteristic of *H. pylori* cells is due to the amount of enzyme present, typically accounting for >1% of the cells' total protein content (42, 43, 54), and/or the rapid turnover of substrate.

Catalases, like other proteins, are susceptible to damage by hydrogen peroxide, but the catalase of *H. pylori* appears to be quite stable at very high concentrations of hydrogen peroxide. This property appears to be shared with only a few other catalases, for example, of some *Mycobacterium* spp. (36, 43, 58). It may be hypothesized that the stability of the catalase of these bacteria in the presence of high concentrations of hydrogen peroxide is an adaptation by these organisms to environments comparatively rich in reactive oxygen species.

The *H. pylori* catalase gene *katA* from four different strains of the bacterium has been sequenced (2, 54, 65, 82). Not surprisingly, all sequences are almost identical with very few nucleotide variations. The inferred amino acid sequence of catalase revealed the presence of an NADPH-like binding motif similar to that of bovine liver catalase and other typical catalases. The residues involved in NADPH binding in bovine liver catalase are R-202, D-212, K-236 (all binding to the O2′ phosphate of $NADP^+$), and H-304 (binding to the pyrophosphate group) (34). This sequence appears to be semiconserved in the *H. pylori* catalase; R-184, D-194, H-218 (conserved replacement), and L-286 (nonconservative change). Whether this sequence allows for NADPH binding remains to be determined. However, other data suggest that *H. pylori* catalase may bind NADH rather than NADPH (54). The inferred amino acid sequence of the protein reveals an adenylate-binding motif (GXGXXG) consistent with NADH binding, different from the NADPH adenylate-binding motif (GXGXXA) (72).

In typical catalases the presence of NADPH is important to maintain an active enzyme. The dismutation of H_2O_2 occurs by way of an intermediate form of catalase termed "compound I." The formation and decomposition of this intermediate occurs too rapidly for it to be detected by spectroscopy (47). Compound I (a nominal Fe^{5+} state) is formed by a two-electron oxidation involving H_2O_2 (equation 3), which then reacts with a second molecule of H_2O_2, returning the enzyme to its original state (Fe^{3+}) (equation 4) (23). In the presence of excess H_2O_2 (or with other hydrogen donors), a second intermediate, termed "compound II," is formed (equation 5). Compound II is the result of the one electron oxidation of catalase (thus forming an Fe^{4+} intermediate). This enzyme intermediate does not react with H_2O_2 and thus the accumulation of compound II leads to the deactivation of catalase (11).

$$\text{catalase } (Fe^{3+}) + H_2O_2 \rightarrow \text{compound I } (Fe^{5+}) \quad (3)$$

$$\text{compound I } (Fe^{5+}) + H_2O_2 \rightarrow \text{catalase } (Fe^{3+}) + H_2O + 1/2O_2 \quad (4)$$

$$\text{catalase } (Fe^{3+}) + XH_2O_2 \rightarrow \text{compound II } (Fe^{4+}) \quad (X = \text{steady flow}) \quad (5)$$

Formation of compound II can be reversed or inhibited by NADPH bound to catalase (11, 44). Four molecules of NADPH bind to the tetrameric structure of bovine liver catalase (49). This reduced dinucleotide is not essential for the catalytic action of the enzyme, but it is believed that NADPH reduces compound II via a one electron transfer reaction to yield $NADP^+$ and the active native catalase (11).

All strains sequenced have the same genes flanking *katA*; upstream is *frpB* coding for an iron-binding protein, and downstream is an open reading frame (ORF) of unknown function. On the basis of sequence homology, a putative Fur-Box (ferric uptake regulator) has been identified upstream of *katA* (54, 65). Usually, the Fur protein mediates iron repression in gram-negative bacteria, and it would appear that the expression of *katA* might be regulated by this putative Fur-Box (Fig. 1). Although limited studies have been performed on the regulation of *katA* (54, 65), the level of catalase activity drops when *H. pylori* is grown in blood-based media, as opposed to serum-based media, suggesting that iron availability may have a role in the expression of *katA* (43). Studies by Bereswill et al. indicate that the *H. pylori* Fur homolog is functional as an iron-dependent transcriptional repressor (9). In *Campylobacter jejuni*, a bacterium of the same family as *H. pylori*, expression of catalase (*katA*) is repressed by iron, and regulation of catalase appears to be mediated by both Fur and the peroxide stress regulator PerR (84, 85). These findings would support the hypothesis that the putative Fur-Box of *H. pylori* is functional.

Catalase is not essential for growth and survival of *H. pylori* in vitro (54, 65, 89). Vaccine studies indicate that the enzyme is a highly effective antigen, suggesting that it may be essential in vivo (71). However, proof that catalase is essential in vivo remains to be established, as no catalase-negative mutants have been employed in animal model studies.

SOD

SOD catalyzes the dismutation of superoxide ions to hydrogen peroxide, which may be deactivated by catalase or peroxidase. The SOD of *H. pylori* is a typical prokaryotic iron-containing enzyme (Fe-SOD), consisting of two identical subunits each with an apparent molecular mass of 24 kDa (77). Three electromorphs or isoforms of Fe-SOD have been identified in different strains of *H. pylori*. These isoforms are the products of mutations leading to an altered pI (10). Unlike other bacteria that may express either an Mn-SOD or Cu, Zn-SOD, these forms of the enzyme were not detected in *H. pylori* by Spiegelhalder et al. (77), nor are they found in the genome (2, 82).

The different types of superoxide dismutase, Cu, Zn-SOD, Fe-SOD, and Mn-SOD, appear to support various functions in resistance to oxidative stress by cells. The dimeric prokaryotic Cu, Zn-SOD, which differs from the corresponding eukaryotic SOD, is usually expressed in the periplasm of gram-negative bacteria (27, 35). The Cu, Zn-SOD of *E. coli* is more resistant to inactivation by H_2O_2 than the eukaryotic enzyme and appears to be an important virulence determinant conferring resistance to oxidative damage induced by the respiratory burst of phagocytic cells (6). Indeed, the Cu, Zn-SOD of *Salmonella* appears essential to serious systemic disease (33).

In contrast, Mn-SOD is found in the cytosol and does not appear to be a critical virulence determinant. Instead, it appears to fulfill a "housekeeping" role, protecting against superoxide generated endogenously in bacteria such as *Bordetella pertussis* (40). Similarly, the Fe-SOD are cytosolic enzymes important in the management of endogenously generated superoxide (37). In *H. pylori* the absence of a leader sequence suggests that its Fe-SOD is also cytosolic (77). Interestingly, Fe-SOD show strong structural conservation between the prokaryotic and eukaryotic enzymes, as is the case for the *H. pylori* enzyme (37, 77).

In members of the *Enterobacteriaceae* periplasmic Cu, Zn-SOD appears to be much more important than the cytosolic SOD as a virulence determinant (37). However, there is evidence that Fe-SOD may enhance intracellular survival of *C. jejuni* (67) and may also be important to the virulence of *Trichomonas vaginalis* (87). The significance of such observations in relation to the Fe-SOD of *H. pylori* has yet to be ascertained.

Alkylhydroperoxide reductase

Alkylhydroperoxide reductase (2, 67, 82) catalyzes the reduction of alkylhydroperoxide to the corresponding alcohol. In most bacteria alkylhydroperoxide reductase is a two-component system consisting of the proteins AhpF and AhpO; the latter is responsible for the peroxide reductase activity, while the accessory flavoenzyme, AhpF, possesses NADH or NADPH oxidase activities. The *H. pylori* gene *tsaA* is orthologous to *E. coli ahpC* (69, 70). Although a homolog of *ahpF* has not been identified in the genome of *H. pylori*, there is ample experimental evidence for the presence of NADH oxidase activity in the bacterium (74). Niimura et al. demonstrated that in *Salmonella enterica* serovar Typhimurium, in the absence of AhpF, NADH oxidase or NADH oxidase-like activities coupled to AhpC are sufficient to generate alkylhydroperoxide reductase activity (61, 62).

Little is known about the alkylhydroperoxide reductase of *H. pylori*. Yet this enzyme may be common within this family of bacteria. Baillon et al. (5) identified a homolog of *ahpC* in the microaerophile *C. jejuni*. Like *H. pylori, C. jejuni* appears to lack *ahpF*, encoding the large accessory flavoenzyme of alkylhydroperoxide reductase. Importantly however, insertional mutagenesis of *ahpC* in *C. jejuni* resulted in an increased sensitivity to oxidative stresses induced by cumene hydroperoxide and atmospheric air (5). These data suggest that it is likely that alkylhydroperoxide reductase is functional in *H. pylori*.

Thioredoxin-linked thiol peroxidase

Thiol peroxidase (scavengease) belongs to a recently identified family of bacterial antioxidant enzymes possessing thioredoxin-linked activity (92). Direct biochemical evidence for the existence of thiol peroxidase in *H. pylori* has been provided by an assay for antioxidant activity (88). These findings are supported by data from the genome indicating the presence of the gene HP390 (jhp991) encoding a putative thiol peroxidase (2, 82).

Thiol peroxidase is usually a small protein (~20 to 30 kDa) found in both prokaryotic and eukaryotic organisms including *Haemophilus influenzae, Vibrio cholerae, E. coli*, streptococci, and *Entamoeba histolytica* (15, 21, 22). Thiol peroxidase protects from inactivation enzymes sensitive to oxidative stress such as glutamine synthetase, by removing H_2O_2 in a metal-catalyzed oxidation system (equation 6).

$$2RSH + H_2O_2 \rightarrow RSSR + 2H_2O \qquad (6)$$

The thiol specificity of the enzyme is determined by the observation that the oxidized form of thiol peroxidase is reactivated (converted back to its sulfhydryl form) by treatment with thiols (15, 60). This observation relates to the finding that one cysteine residue, Cys-94 in the *E. coli* enzyme, appears to be central to peroxidase activity (21).

In *E. coli* oxidative stress induces higher levels of expression of the enzyme (48), which is located in the periplasm (21). It has been suggested that thiol peroxidase complements the cytosolic enzymes in protecting bacteria from oxidative damage (21). However, in the amoeba *E. histolytica* the enzyme is located in the cytosol, not on the surface or extracellularly (15), thus its role may include protection from both endogenously and exogenously generated reactive oxygen metabolites.

Management of Redox Potential

The oxidation-reduction (redox) status of *H. pylori* is important, as changing the environmental oxygen concentration and hence the redox status of the cell can greatly affect metabolic processes and clinical outcomes. The redox state of a cell may be defined as the sum of the oxidized and reduced molecular species present, but it is usually expressed in relation to the ratio of the oxidized and reduced thiols. Oxidation of thiols leads to an increase in the disulfide forms of both proteins and smaller compounds such as glutathione (γ-glutamylcysteinylglycine), the major free thiol in most cells. Reduced glutathione (GSH) plays an important role in the maintenance of the redox balance of cells, as it can scavenge free radicals and be converted to oxidized glutathione (GSSG). The cycling of glutathione is critical for detoxification of free radicals in many organisms, with GSSG normally converted back to GSH by the enzyme glutathione reductase.

However, there is little evidence that GSH is important to the maintenance of the redox balance in *H. pylori*. On the basis of genome analyses, the bacterium does not appear to have a homolog of the gene encoding for typical glutathione reductases (2, 82). There is evidence that the major free thiol compound within *H. pylori* is cysteine (Jorgensen et al., unpublished data). This observation is consistent with data from a number of microaerobic protozoan species that lack detectable levels of glutathione and use cysteine as their major free thiol compound (13, 30, 31, 76). Cysteine appears not to be an appropriate free thiol compound for aerobic organisms, because in the presence of a metal catalyst it is oxidized much faster than glutathione. Indeed, cystine (oxidized cysteine) markedly enhances the cytotoxic response of *E. coli* to H_2O_2 and may impair the cell defense machinery through thiol-disulfide exchange reactions at the cell membrane (18). This does not appear to be as critical in microaerophiles. If cysteine is the primary free thiol compound in *H. pylori*, cycling of oxidized cysteine, that is, the maintenance of a reduced state, may depend on a thioredoxin-like reductase as has been proposed for *Giardia duodenalis* (14).

H. pylori contains two ORFs encoding putative thioredoxin reductases, designated HP0825 (jhp764) and HP1164 (JHP1091), and two ORFs encoding putative thioredoxins, designated HP0824 (jhp763) and HP1458 (JHP1351) (2, 82). Thioredoxin and thioredoxin reductase form an NADPH-linked thiol-dependent redox system able to reduce proteins selectively. The proteins encoded by HP0825 (jhp764) and HP0824 (jhp763) appear to be typical thioredoxin reductase and thioredoxin components of the thioredoxin system involved in stress response (90). The "alternative" thioredoxin reductase and thioredoxin encoded by HP1164 (JHP1091) and HP1458/JHP1351, respectively, may fulfill the role of the thioredoxin-like reductase of *G. duodenalis* necessary for the maintenance of free cysteine (14), and hence the redox state of the cell.

Managing the concentration of dissolved intracellular oxygen is another way to regulate the redox potential of the cell. NADH oxidases are used to regulate the oxygen concentration in different microaerobic organisms. This family of enzymes directly reduces molecular oxygen to hydrogen peroxide or water. In the genome of *H. pylori* no ORF homologous to typical NADH oxidases is apparent, but cytosolic NAD(P)H oxidase activities have been measured in the bacterium (75). However, it is possible that such NAD(P)H oxidase activities are the product of electron leakage from the reduced flavin cofactor of flavoprotein enzymes such as alkylhydroperoxide reductase, thioredoxin reductase, glutathione reductase, mercuric reductase, and dihydrolipoamide dehydrogenase (3, 17, 19, 20, 52, 64, 91).

In addition to the enzyme activities outlined above, the pentose phosphate pathway also plays a role in resistance to oxidative stress; among its several roles, it generates reducing power in the form of NADPH. In yeasts, mutations of enzymes of the pentose phosphate pathway lead to increased sensitivity to oxidative stress, and the pathway is required for the maintenance of the cellular redox state (46, 73). Indeed, in mammalian systems, glucose 6-phosphate dehydrogenase, which catalyzes the first step in the pentose phosphate pathway and which provides reductive potential in the form of NADPH, has been found to be essential in protecting cells against oxidative stress, yet it is not essential for pentose synthesis (66). The pentose phosphate pathway was one of the first complete biochemical pathways identified in *H. pylori* (56), but its role in the maintenance of the redox status has not been investigated.

Gene Regulation and Repair Mechanisms

A surprising finding in the genome of *H. pylori* was the absence of homologs of genes encoding the transcription regulatory sigma factors σ^{32} (heat shock) and σ^{S} (stress/stationary-phase) (2, 82). Notwithstanding the absence of genes coding for σ^{32}, homologs of genes encoding GroEL, GroES, DnaK, DanJ, and GrpE were identified in the genome regulated by housekeeping σ^{70}-like sigma factors (1, 2, 7, 79, 82) (reviewed further in chapter 29).

The induction of an inflammatory response by *H. pylori* infection leads to increased potential for oxidative damage of the bacterium. While *H. pylori* has the enzymatic capacity to deal with such oxidative stress, no homologs of the oxidative stress regulators OxyR, SoxR, SoxS, or SOS present in other bacteria (28, 29, 86), have been found in *H. pylori* DNA (2, 82). Together with the absence of sigma factor σ^{S}, these data suggest that either *H. pylori* has adapted to an environment of constant oxidative stress or the bacterium contains novel systems of protection yet to be discovered.

H. pylori appears able to perform mismatch repair, as suggested by the coding capacity for methyl transferases, DNA glycosylases, and MutS and UvrD proteins, involved in error-free and error-prone repairs (2, 82). The RecBCD pathway is the major pathway for recombination in wild-type *E. coli* cells (50), but this system appears to be absent in *H. pylori*. Homologous recombination may be performed by *H. pylori* through the RecF pathway. In *E. coli*, this pathway generally depends on the RecA, RecJ, RecN, RecR, RecG, and RuvABC proteins, whose genes are present in the *H. pylori* chromosome (reviewed further in chapter 24); and Thompson and Blaser demonstrated that *recA H. pylori* mutants were highly sensitive to UV light, methyl methanesulfonate, and exposure to mutagenic antibiotics such as metronidazole (81).

C. jejuni does not encode OxyR and, as discussed above, the regulation of catalase expression in this bacterium appears to be mediated by both Fur and PerR (84, 85). It has been suggested that PerR functions as a nonhomologous substitute for OxyR (84). *H. pylori*, like *C. jejuni*, does not encode OxyR, and we are left to ponder the potential for the existence of previously unidentified oxidative stress regulators encoded by its genome.

Conclusion

H. pylori is a microaerophile that colonizes the inflamed gastric mucosa of humans. These two facts suggest the presence of a network of systems needed to manage both the oxygen to which *H. pylori* is exposed and the oxidative stress induced by endogenous and exogenous processes. That oxygen and TOS are constant companions of *H. pylori* in vivo is reflected in the enzymes expressed to manage them and the regulatory and repair mechanisms developed by the bacterium to cope with this type of stress. Nonetheless, our understanding of how *H. pylori* evades and avoids toxic oxygen effects is far from complete; and despite the importance of the topic, the management of oxygen and oxidative stress in *H. pylori* is a relatively neglected subject area.

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