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Review

The role and regulation of catalase in respiratory tract opportunistic bacterial pathogens

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ABSTRACT

Respiratory tract bacterial pathogens are the etiologic agents of a variety of illnesses. The ability of these bacteria to cause disease is imparted through survival within the host and avoidance of pathogen clearance by the immune system. Respiratory tract pathogens are continually bombarded by reactive oxygen species (ROS), which may be produced by competing bacteria, normal metabolic function, or host immunological responses. In order to survive and proliferate, bacteria have adapted defense mechanisms to circumvent the effects of ROS. Bacteria employ the use of anti-oxidant enzymes, catalases and catalase-peroxidases, to relieve the effects of the oxidative stressors to which they are continually exposed. The decomposition of ROS has been shown to provide favorable conditions in which respiratory tract opportunistic bacterial pathogens such as *Haemophilus influenzae, Mycobacterium tuberculosis, Legionella pneumophila,* and *Neisseria meningitidis* are able to withstand exposure to highly reactive molecules and yet survive. Bacteria possessing mutations in the catalase gene have a decreased survival rate, yet may be able to compensate for the lack of catalatic activity if peroxidatic activity is present. An incomplete knowledge of the mechanisms by which catalase and catalase-peroxidases are regulated still persists, however, in some bacterial species, a regulatory factor known as OxyR has been shown to either up-regulate or down-regulate catalase gene expression. Yet, more research is still needed to increase the knowledge base in relation to this enzyme class. As with this review, we focus on major respiratory tract opportunistic bacterial pathogens in order to elucidate the function and regulation of catalases. The importance of the research could lead to the development of novel treatments against respiratory bacterial infections.

1. Introduction

The upper respiratory tract of humans is asymptomatically colonized by a variety of commensal microbiota, such as *Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus,* and hemolytic streptococci [7]. In healthy individuals, the normal flora found in this region generally does not cause disease. However, infection may develop when bacteria are able to gain entry into normally sterile areas such as the middle ear space, lung, and paranasal sinuses [58]. Respiratory pathogens are the etiologic agents for a variety of illnesses such as otitis media, sinusitis, bronchitis, pneumonia, meningitis, and septicemia [7,41]. Each year, it is estimated that two million deaths occur in young children and infants due to acute respiratory infections (ARI); ARI's are the main cause of acute illnesses worldwide [60–62]. Protection against infection is mediated by the immune system, which utilizes a variety of defense mechanisms to rid the body of foreign invaders.

As part of the nonspecific immune response during the progression of pathogenesis, invading microbes encounter granulocytes, which contain an array of antimicrobial agents [46]. The primary and most abundant granulocytes responsible for phagocytosis and release of cytotoxic molecules are neutrophils [38]. Neutrophils utilize substances contained within their granules such as peroxidase, lysozyme, collagenase, lactoferrin, and various other hydrolytic enzymes to destroy invaders. In addition, neutrophils incorporate the use of oxygen-dependent pathways in order to generate reactive oxygen species (ROS), which serve to facilitate pathogen clearance [46,50]. Within the respiratory tract, macrophages and neutrophils are considered to be the primary source of ROS [42].

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Microorganisms residing in the respiratory tract are continually bombarded by reactive oxygen species, which are generated through normal metabolism and host defenses. Yet, these colonizers and other pathogens are able to persist and cause disease by circumventing the toxic effects of ROS. Bacteria have adapted to their respiratory niche by developing systems that are capable of relieving the oxidative stresses to which they are exposed. Because of the high rate of morbidity and increasing antimicrobial resistance by respiratory pathogens, many studies have been conducted in order to elucidate the mechanisms by which bacteria are able to survive the toxic effects of ROS [25]. It has been proposed that bacterial pathogens utilize a catalatic mechanism as a virulence strategy to confer protection against potentially lethal oxidative bursts generated by host immune cells [5].

The discovery of hydrogen peroxide in 1818 by chemist Louis-Jacques Thenard leads to the postulation of a substance responsible for H_2O_2's decomposition [17]. In 1900, Oscar Loew suggested hydrogen peroxide was a byproduct of aerobic metabolism and that its decomposition was due to its interaction with an enzyme, which he termed as catalase [35] and [43]. In 1937, Sumner and Dounce crystallized catalase from cow liver and later in 1938, the molecular weight was determined by Sumner and Gralén [53]. Ever since catalase's proposed existence, it has become one of the most studied enzymes in the biological field. Its ubiquity in aerobic organisms and cellular importance has catapulted catalase into the spotlight for many decades [10]. The purpose of this review is to characterize and examine the role of catalase in colonization and pathogenesis during respiratory tract infection.

2. Reactive oxygen species

Prokaryotic aerobic and microaerophilic organisms require molecular oxygen for normal metabolism. However, the use of oxygen leads to the production of reactive oxygen species (ROS), which have a detrimental effect on aerobic organisms [47]. ROS are molecules that have the ability to damage deoxyribonucleic acid (DNA), oxidize proteins and lipids, and interfere with cell signaling pathways [27,42]. Formation of reactive oxygen species commonly occurs during normal cellular metabolism or as part of a host defense mechanism. The proclivity of oxygen to form radicals is due to its structure of two unpaired electrons in separate orbitals in the outer electron shell. Some of the most common ROS formed are the hydroxyl ion, hydrogen peroxide, hydroxyl radical, peroxide, and the superoxide radical (Fig. 1) [24]. If these molecules were allowed to accumulate to a level favoring a pro-oxidative state, known as oxidative stress, the survival of aerobic organisms would be endangered [24].

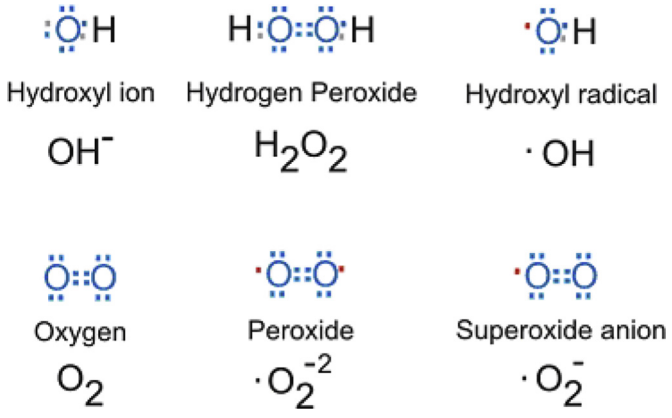

Fig. 1. Reactive oxygen species.

Removal of reactive oxygen species is carried out through the utilization of anti-oxidants and anti-oxidant enzymes such as superoxide dismutase, peroxidase, and catalase [42]. Peroxidases mostly catalyze the decomposition of hydrogen peroxide (H_2O_2), but may also utilize organic peroxides or azo-molecules as substrates [23]. The function of superoxide dismutase (SOD) is to convert superoxide radicals into hydrogen peroxide and diatomic oxygen [17]. The ROS product of the aforementioned reaction, hydrogen peroxide, has the ability to interact with sulfur clusters and cysteine residues of proteins, but typically displays little reactivity with other cellular components [15]. Hydrogen peroxide's toxicity is derived from the products of its interaction with ferrous iron through the Fenton reaction [65]: $H_2O_2 + Fe^{2+} \rightarrow OH^- + FeO^{2+} + H^+ \rightarrow Fe^{3+} + OH^- + \bullet OH$.

In the presence of ferrous iron (Fe^{2+}), H_2O_2 is reduced to a hydroxyl anion (OH^-) and a hydroxyl radical (•OH). The hydroxyl radical is nonselective and highly reactive as an oxidant. Due to its non-selectivity, •OH generally reacts with organic molecules such as DNA, within the vicinity of its creation [27]. In the presence of iron, a mere 10 min exposure to H_2O_2 at low millimolar levels is enough to mutagenize DNA or even kill the majority of bacteria [27]. In order to prevent such a deleterious reaction from occurring, microorganisms have developed an extremely efficient H_2O_2 scavenging system involving the use of the enzyme catalase, which degrades H_2O_2 into water and oxygen [10,30].

3. Catalase families

Catalase can be found in both eukaryotic and prokaryotic organisms. In humans, it serves to relieve oxidative stress, has functions relating to host defense mechanisms, cellular apoptosis, aging, inflammation, tumor formation, and mutagenesis [11,65]. Improperly functioning catalases in humans can lead to a variety of morbid states [11]. In contrast to humans, catalase's pivotal role in prokaryotic human respiratory organisms is to detoxify peroxides generated from the oxidative chemicals released from immune cells and competing bacteria during the colonization and progression of infection [5]. Since prokaryotic organisms may be found in a variety of environments and have highly complex interactions between self and host, the catalase family has diversified and evolved into three sub-families [11,31,65]: mono-functional (typical) catalases, bi-functional catalase-peroxidases (KatG), non-heme (manganese) and minor catalases.

3.1. Mono-functional catalases

Mono-functional catalases are heme-containing, homotetrameric and are considered to be the most common group [34,64,65]. Based upon phylogenetic analysis, this group has been further subdivided into three clades [65]. Clade 1 catalases contain a heme *b* prosthetic group and are comprised of small subunits (55–65 kDa); this clade is predominately of plant origin, but also includes a few algal and bacterial catalases [10,11,54,65]. Clade 2 is comprised of the larger subunit (75–84 kDa) catalases with a heme *d* prosthetic group and a flavodoxin-like domain; included in this clade are archaea, bacteria, and fungi catalases [15,65]. Catalases in clade 3 are the most abundant of the mono-functional enzymes and are found in plants, animals, protists, fungi, archaea, and bacteria [15]. A large proportion of bacteria possessing clade 3 catalases also possess catalase gene paralogues from clades 1 and 2. Similar to clade 1, many clade 3 catalases have small subunits (43–75 kDa) and contain heme *b*, but have an additional second redox-active cofactor, NADPH [65].