iron overload. The free iron accumulated is the catalytically active form referred to as a low molecular weight chelatable ion (LMWX-Fe). LMWX-Fe has been shown to mediate reactive oxygen species formation, while the definite source (mitochondria or cytoplasm) remains undefined. As a consequence of lipid per-oxidation reactive intermediates such as reactive aldehydes (MDA; 4-HNE; HHE) are formed [1,2] and these, in turn form cross-linked intermediates subsequent to protein-reactive aldehyde adduct formation. Subsequently, replication failure in genomic DNA results, in strand break and eventual loss of genomic integrity. Attempts to repair the defective genome result in altered conformation and loss of genomic DNA, with the loss of the genes that confer resistance to drugs that are employed in cancer treatment. This deficiency causes the impairment of drug sensitivity resulting in drug resistance [3,4].

The amino acid residues such as lysine, tryptophan, histidine, methionine, proline, arginine and lysine undergo oxidative modification under a sustained lipid per-oxidation environment. Carbonylation, lipid per-oxidation of the protein confers alterations in protein structure impairing the functional property, and also sustained modification and alteration of the proteins increased susceptibility and proteolytic degradation. Both structural and functional proteins subjected to the alteration due to the oxidative stress have been shown to escape the detoxification mechanism of the cell.

Also, proteins with a substantial loss of conformation are a potential source of "neo-antigens," for which auto antibodies are formed as the host recognize these neo-antigens as foreign [5,6]. The rational for the origins of the neo-antigens, induction of the auto-immunity and interplay remains imperceptible. Functional impairment of spleen function results in lowered or defective immunoglobulin synthesis, phagocytosis of damaged erythrocytes, and antigen presented by the MHC molecules. Due to an auto-reactivity, immune complexes are formed which are known to play a pivotal in glomeruler deposition and kidney dysfunction. Collectively, these factors exacerbate immune reactions and thus lead to autoimmunity.

References


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do:10.1016/j.mehy.2004.11.006

Choice of drugs to manage anthrax

Penicillin is the drug of choice for the treatment of many pulmonary pathogens including Bacillus anthracis. Because of the continuous spread and recent genetically engineered threat of penicillin-resistant bacterial strains, fluoroquinolones like ciprofloxacin have become the obvious choice for the empiric treatment of clinically evident inhalation anthrax. Penicillin kills pathogens by targeting an enzyme called penicillin-binding protein (PBP), which is required for bacterial cell wall synthesis. As a defensive measure, bacteria produce an enzyme, β-lactamase, which disables penicillin and other β-lactams to confer resistance [1]. Inhalation anthrax is always fatal as
diagnosis is rarely possible. Patients with meningitic form of anthrax die despite treatment with high dose of penicillin [2]. This finding does not explain the ineffectiveness of penicillin and the same result would have been expected if patients were treated with ciprofloxacin. The reason for this is that by the time the bacilli were diagnosed in the cerebrospinal fluid they had already crossed the blood brain barrier.

β-lactam drug resistance is a complex procedure involving four mechanisms: (a) modulation of drug entry through the porin channels; (b) alteration of target proteins, PBPs; (c) production of β-lactamases; (d) activation of efflux pump; where bacteria can use one or a combination of all four acquire resistance. Whereas, the mechanism of quinolone resistance is less complicated as it can occur easily by acquisition of a point mutation in the target gene topoisomerase-IV, a key enzyme required for bacterial DNA synthesis. Results with quinolone-resistant clinical isolates indicated that repeated exposure of increasing concentrations of drugs resulted in resistance development that is associated with either target gene mutation or activation of efflux pump depending on the doses used [4]. Appropriate drug selection and dosage are thus very important factors to control this problem.

It has been reported that the mutant β-lactamase produced by a clinical isolate hydrolyzes almost all β-lactam drugs at a much higher rate than the wild-type enzyme. Use of β-lactamase inhibitors, clavulanic acid, or sulbactam increases the susceptibility towards β-lactam drugs [3]. These findings raise the intriguing possibility of further study to reemploy penicillin as the clinician's choice of drug to manage pathogens like B. anthracis in combination therapy with β-lactamase inhibitors. Moreover, crystal structure determination of the other mutant variant of β-lactamases will open up potential opportunities for designing novel β-lactamase stable drugs.

Recent advances in genomics and the availability of complete pathogen genetic sequences have increased the possibilities of mixing and matching traits from different deadly bacteria including those responsible for tuberculosis, leprosy, and cholera. These traits could then be transferred to nonpathogenic microorganisms to make them undetectable or untreatable. This raises major concerns about the potential abuses of releasing DNA sequence data into publicly accessible databases but it is also very important to stimulate research for the development of new vaccines, drugs, and diagnostics to combat these possibilities.

Recent studies also revealed that a β-lactamase inhibitor protein-II (BLIP-II) inhibits β-lactamase. The most important finding with gene knockout studies indicates that this protein acts as a key component of the signaling pathway in initiating sporulation of the bacteria [5]. This finding suggests that the in vivo natural targets are structurally very similar to β-lactamases and PBPs are the likely candidate. This discovery could open up a new era in designing drugs that will kill bacteria at the spore level prior to germination.

Although most of the bacterial strains are still susceptible to fluoroquinolones, these drugs are limited in choice because of their severe side effects, particularly in children and pregnant mothers. Effective reemployment of β-lactam drugs in the therapy of these deadly pathogens needs to be considered carefully.

References


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doi:10.1016/j.mehy.2004.11.001