Virulence Factors of Environmental Microbes in Human Disease
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Abstract
Environmental pathogens are organisms that survive in the outside environment but maintain the capacity to cause diseases in humans. They somehow adapt to the challenges of life in habitats that range from water and soil to the cytosol of the host cells. The key difference between environmental pathogens and other human pathogens is the ability of environmental pathogens to survive and thrive outside the host. Adaptation to wide ranges of temperature conditions, available nutrients and stresses encountered through physical conditions as well as those resulting from host immunological responses requires an ability to sense and rapidly adapt to new territories. Temperature is a critical and ubiquitous environmental signal that governs the development and virulence of diverse microbial species; microbial survival is contingent upon initiating appropriate responses to the cellular stress induced by severe environmental temperature change. In the case of microbial pathogens, development and virulence are often coupled to sensing host physiological temperatures. To escape various host defenses including temperature, these environmental pathogens express various factors as survival strategies in the new environment of the host body which prove to be virulent in the host ultimately making them environmental pathogens.

Keywords: Environmental pathogens; Virulence factors; Pseudomonas; Mycobacteria; Campylobacter, Listeria

Introduction
Environmental pathogens spend a part of their life cycle outside living hosts but these organisms may cause infections resulting in functional or anatomical damage to the host, if they get opportunity to enter the living host. Such organisms are capable of surviving outside the living host in the outside available environment. They may be encountered in the water, soil, air, food and other elements of our surroundings.

Attempts have been made to understand the persistence of these organisms in the environment, the reservoirs they inhabit, the ways they exchange virulence factors, and their diversity. But the main topic of concern is that why not all, but only few environmental microbes behave as human pathogens? The answer to this question may lie in the fact that those few might possess some special virulence factors or resistance factors which may help them to flourish in different settings, the surrounding environment and inside the human body. So in this article, we are reviewing the various factors or properties which switch environmental microbes onto well-known human pathogens.

The association of virulence of the microbes to the environment needs to be explored further. This exploration might help in the differentiation of pathogenic from non-pathogenic microbes. So, virulence in the case of environmental pathogens is not a separate microbial characteristic but, rather, a complex, dynamic, and changeable phenomenon that includes host and environmental factors too.

Host Defenses Needed to be Breached by Pathogens
A microorganism will be able to invade host's body only if it overcomes individual's host defenses which may include:

- Skin and mucosal secretions
- Non-specific local responses (e.g., pH, temperature, bile salt concentration, acidity, osmolarity etc.)
- Non-specific inflammatory responses.
- Specific immune responses (e.g. lymphocytes).

Requirements of Environment Microbes to Establish as Human Pathogens
There are certain essential requirements which have to be fulfilled by environmental microbes to behave as human pathogens. These requirements are discussed as follows:

Route of transmission
In order to begin infection and cause disease, pathogens must find a transmission route. Transmission of an infectious agent can occur in many ways, but it is typically through exposed skin (e.g., a cut, abrasion, puncture, or wound) or mucous membranes (e.g., gastrointestinal tract, respiratory tract, or urogenital tract).

Adherence
After gaining access to the body, microbe must have some means of attaching itself to the host's tissues. This attachment is called adherence and is a necessary step in pathogenicity. If a microorganism cannot adhere to a host cell membrane, disease will not occur.

Invasion
At this point, microbes begin to invade the host. Microorganisms are exposed to many barriers after introduction into the host. Some bacteria are able to cause disease while remaining on the epithelial barriers, while many need to penetrate that barrier. Once this barrier has been penetrated, these pathogens can multiply without competition.

Keywords:
- Environmental pathogens
- Virulence factors
- Pseudomonas
- Mycobacteria
- Campylobacter
- Listeria

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Colonization

Colonization is the multiplication of pathogenic or–ganisms after normal flora are overcome. Pathogens usually colonize host tissues that are in contact with the external environment. For infection to proceed there is a concept of an infectious dose. This is the minimal number of microbes necessary to establish infection. Certain pathogens are less contagious and therefore require larger numbers of pathogens to cause disease.

Breach of host defenses

Pathogens must also avoid or breach host defenses. For this, pathogens can produce certain enzymes which breakdown host defenses or can possess capsules to avoid phagocytosis by the host’s immune system.

Cause damage or disease to the host

Pathogens must cause damage to the host by secreting exotoxins or enzymes or by endotoxins.

Exiting the host

A pathogen must exit the body to infect newer hosts. This occurs through various routes. Examples include sneezing, coughing, diarrhea, pus, blood, body fluids or insect bites.

Survival outside the host

Finally, a pathogen must be able to survive in the environment long enough to be transmitted to another host. Some are hardy and can survive for several weeks before a new host is found. There are others that survive in animal reservoirs or require direct contact because they are fragile.

Virulence Factors Possessed by Environmental Pathogens

Environmental pathogens contain certain virulence factors that promote disease formation and provide the opportunity for a microbe to infect and cause disease. These factors are discussed by taking examples of some environmental pathogens:

Nontuberculous mycobacteria

The nontuberculous mycobacteria (NTM) include those Mycobacterium species that are not members of the Mycobacterium tuberculosis complex. Nontuberculous Mycobacteria (NTM) are important environmental opportunistic pathogens of humans, animals, poultry, and fish [1,2]. Several studies indicate that they are normal inhabitants of a variety of environmental habitats shared with humans and animals which include natural waters, drinking water distribution systems, and soils [1,3]. The cell wall characteristcs allow the mycobacterium species to survive in different environments (e.g., in biofilms in water habitats or particulate matter in soils and water. The major structural feature of NTM is the lipid-rich outer membrane rich in unique mycolic acids [4]. These long-chain mycolic acids form a hydrophobic barrier that promote the attachment of NTM to surfaces permitting their persistence in habitats where they could be washed out like in drinking water distribution systems and household plumbing. Hydrophobicity also drives the adherence of NTM to soil particles [5] and thus, they can be readily aerosolized as dusts produced from dry soils. The Mycobacterium cell walls with very low permeability also contributes to their resistance to wide range of therapeutic agents [4]. The most significant of the environmental mycobacteria are the MAC and M. ulcerans. M. ulcerans is the causative agent of Buruli ulcer, a debilitating disease characterized by large necrotic skin ulcers. M. ulcerans is closely related to the fish pathogen M. marinum. M. marinum causes a tuberculoid disease in fish and other poikilotherms and a relatively minor skin infection in humans. In contrast, is not known to cause disease in fish and in humans it produces large necrotic skin lesions caused by massive necrosis of subcutaneous fat. This type of pathogenesis is due to the presence of a macrolide toxin produced by M. ulcerans called mycolactone [6] which is not produced by M. marinum. The mode of M. ulcerans transmission is controversial. Definitely there is absence of person to person transmission [7]. Indeed, the bacterium has been detected in infected mosquito species and predatory water bug’s salivary glands, indicative of the possibility of human transmission by water bug bites. Insect-borne transmission is a minor route of transmission compared to direct transmission which can occur through cuts and wounds on skin when it comes in contact with mud or water contaminated with M. ulcerans.

Campylobacter

Campylobacter are Gram negative, microaerophilic, curved or spiral rod shaped bacteria. Campylobacter are found in humans and many animal species like cattle, sheep, poultry birds etc. Campylobacter spp., particularly C. jejuni and C. coli, are a major cause of enteritis in humans. Humans are infected most commonly after the ingestion of contaminated or undercooked meat (especially poultry), raw milk or other dairy products, and other contaminated foods such as unwashed vegetables. Untreated water is another potential source of infection. Campylobacter sp. is also transmitted to humans through contact with infected pets or livestock. Campylobacter species do not tolerate drying or heating but can often survive for a long time in moist environments. Campylobacter can survive for weeks in water at 4°C, but only a few days in water above 15°C. C. jejuni may remain viable for up to 9 days in feces, 3 days in milk and 2 to 5 days in water. C. jejuni and C. coli can remain infective in moist poultry litter for prolonged periods. C. fetus can survive in liquid manure for 24 hours and soil for up to 20 days [8,9].

In Campylobacter, bacterial chemotaxis is a complex signal transduction system by which bacteria are able to sense environmental stimuli and respond to them by flagellar rotation [10]. In Campylobacter, other important virulent factors include cytolethal distending toxin and hemolysin. Hemolysin helps it in iron acquisition from the host which is a necessary action for establishing infection. Chick colonization assays indicate that Campylobacter mutants defective in enterobactin-mediated iron acquisition are unable to colonize the gastrointestinal tract [11]. Cells’ major defense mechanisms include superoxide dismutase which breaks down superoxide molecules to hydrogen peroxide and dioxygen thereby protecting several cell components including cytoplasmic enzymes, DNA and membrane factors. [12]. A study by Van Deun K indicates that bile-salt resistance and more pronounced Cytolethal Distention toxin production are associated with the Campylobacter strains causing enteritis in human [13].

Pseudomonas

Pseudomonas aeruginosa is a Gram- negative bacteria usually found both in aquatic and terrestrial environments. Basically, a natural soil inhabitant, it has a versatile metabolic potential, which allows it to survive in a number of natural and hospital environments. The combination of environmental persistence and ability to employ multiple virulence factors allows P. aeruginosa to be extremely effective as a human opportunistic pathogen. This organism has one of the
largest genomes in the world with extraordinary large number of regulatory genes suggesting that \textit{P. aeruginosa} has a great competitive capacity to move between and adapt to new environmental conditions [14]. \textit{P. aeruginosa} normally residing in natural environments can move successfully to highly different and stressful environmental settings including the airways of humans and persist for hundreds or even thousands of generations without a significant number of genetic adaptive changes. Being a soil inhabitant, \textit{P. aeruginosa} in its wild-type configuration is naturally resistant to many antibiotics, and when confronted with antimicrobial agents, it is be able to develop tolerance to their increased levels [15]. This capacity to resist antimicrobial treatment is an important reason why \textit{P. aeruginosa} has become the dominant airway infection problem for Cystic fibrosis (CF) patients. It is also a leading cause of hospital-acquired infections in injured, burned or immunocompromised patients. Some of the most common phenotypic traits reported for \textit{P. aeruginosa} isolates from chronically infected CF patients include slow growth, auxotrophy, alginate overproduction (mucoidy), antibiotic resistance, loss of virulence factors and motility [16,17].

**Listeria**

\textit{Listeria monocytogenes} is a gram-positive bacterium which is a natural inhabitant of soil, groundwater, silage and decaying vegetation [18] but when it encounters a living host it behaves as an intracellular bacterial pathogen capable of causing serious infections. \textit{Listeria monocytogenes} occasionally causes outbreaks with symptoms usually associated with foodborne illness such as nausea and non-bloody diarrhea. Several foods, including corn, chocolate milk, shrimp, and rice salad, have been reported as vehicles [19]. The transformation between mild soil bacterium and a deadly human pathogen appears to be mediated through complex regulatory pathways that modulate the expression of virulence factors in response to environmental cues. It consists of various virulence factors responsible for its virulence character. Internalin A on the surface of listerial cells binds to a surface protein, E-cadherin, on the surface of host epithelial cells. This interaction apparently stimulates the phagocytosis of \textit{L. monocytogenes} cells [20]. Another surface protein on \textit{L. monocytogenes}, p104, has recently been identified and shown to play a role in adhesion to intestinal cells [21] in order to adapt to adverse environmental conditions (high or low pH, temperature, osmotic conditions), Listeria have chaperone proteins that assist in the proper refolding of proteins. Some of the Clp (caseinolytic proteins) group of proteins, which act both as chaperones and as proteolytic enzymes, have been identified as having a role in the pathogenesis of \textit{L. monocytogenes}. ATPase is a general stress protein that aids in disruption of the vacuolar membrane and the intracellular survival of listeriae [22]. Listeriae can survive and grow at low temperatures (4-25°C), but they normalize at 37°C within 2 hours. Therefore, it is likely that Listeriae in refrigerated foods would recover their infectivity during passage through the intestinal tract of warm blooded animals and cause foodborne illness.

**Conclusion**

Environmental pathogens in the time of transition from their peaceful environment to the body of the host develop different virulent factors to escape the host defenses such as phagocytosis, temperature, oxidation etc. The genes for these factors are already present in their genome as their survival strategy such as flagella to access nutritive substances, other surface proteins, adhesions, toxins, hemolysins etc. which ultimately prove to be damaging to the host's body when these microbes try to flourish and establish themselves in the host's body resulting in various infectious diseases. In this way the environmental microbes switch on to environmental pathogens.

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