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Review

Flagellar motility of the pathogenic spirochetes

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ABSTRACT

Bacterial pathogens are often classified by their toxicity and invasiveness. The invasiveness of a given bacterium is determined by how capable the bacterium is at invading a broad range of tissues in its host. Of mammalian pathogens, some of the most invasive come from a group of bacteria known as the spirochetes, which cause diseases, such as syphilis, Lyme disease, relapsing fever and leptospirosis. Most of the spirochetes are characterized by their distinct shapes and unique motility. They are long, thin bacteria that can be shaped like flat-waves, helices, or have more irregular morphologies. Like many other bacteria, the spirochetes use long, helical appendages known as flagella to move; however, the spirochetes enclose their flagella in the periplasm, the narrow space between the inner and outer membranes. Rotation of the flagella in the periplasm causes the entire cell body to rotate and/or undulate. These deformations of the bacterium produce the force that drives the motility of these organisms, and it is this unique motility that likely allows these bacteria to be highly invasive in mammals. This review will describe the current state of knowledge on the motility and biophysics of these organisms and provide evidence on how this knowledge can inform our understanding of spirochetal diseases.

Contents

1. Introduction

It is hard to build an all-terrain vehicle. Tires that are best on smooth roads do not fare well on rough, rocky mountain trails and are useless for driving across deep rivers or oceans. The structural design that is best for maneuverability and aerodynamics on relatively flat surfaces is not optimized to prevent tipping on inclines and would not float. While there are man-made vehicles that can traverse this range of environments [1], they often utilize multiple force producing mechanisms (e.g., wheels for roads and propellers for water-based travel) and are not terribly efficient in any modality.

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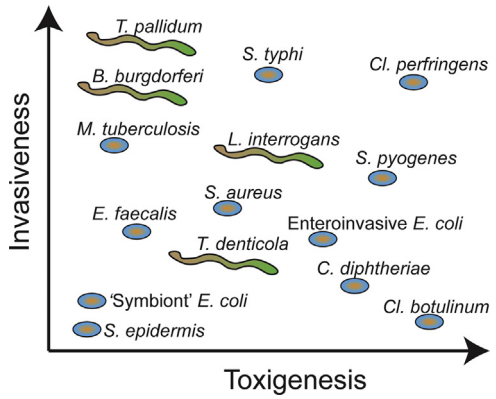

Fig. 1. Relative comparison of the invasiveness and toxin production (toxigenesis) for a number of pathogenic bacteria. The syphilis bacterium (*T. pallidum*) is one of the most invasive but does not release toxins into its host, whereas *Cl. botulinum* is highly toxic but not invasive. Schematic is based on (10).

Pathogens that invade our bodies often have to be able to survive in and, in many cases, move through a range of diverse environments. For example, many bacteria are capable of moving through fluids (swimming) and also along solid or semisolid surfaces (gliding, twitching, and swarming) [2–4]. This transition from swimming to surface-associated motility can be achieved by transitioning from flagellar-based swimming to pili-driven gliding or twitching [5], much like the switch from wheels to propellers in man-made all-terrain vehicles. Likewise, *Vibrio parahaemolyticus* uses polar flagella to swim and lateral flagella to swarm [6]. Some flagellated bacteria, though, can use their flagella to power swarming along surfaces [7]. In other words, bacteria have out-engineered us by figuring out how to make a single motility mechanism work in multiple environments.

Indeed, flagellar-based motility can also move bacteria through complicated environments, such as soft agar gels, where the pore-size in the gel is approximately equal to the diameter of the bacteria [8,9]. However, as the concentration of the polymer in the gel increases, the motility of most flagellated bacteria becomes greatly inhibited [9], likely due to there being few holes large enough for the bacteria to squeeze through. This, though, is not true for the spirochetes, a unique group of bacteria with some highly pathogenic members. One aspect that makes pathogenic spirochetes so capable of setting up infections in mammals is their motility. For example, Lyme disease and syphilis are caused by the spirochetes, *Borrelia burgdorferi* and *Treponema pallidum*, respectively, and these bacteria are some of the most invasive mammalian pathogens (Fig. 1) [10,11]. Both of these bacteria are able to easily move through our skin, break into and out of blood vessels, and can cross the blood–brain barrier [12]. The syphilis bacterium can even cross the placental barrier, which leads to infection of the unborn fetus, known as congenital syphilis [12]. Truly, these bacteria are exceptional and efficient all-terrain vehicles for traversing the mammalian body. Why are they so adept at moving through the broad range of tissues in our bodies?

This review focuses on describing the unique motility of the spirochetes and seeks to use our current knowledge about how these organisms move to inform some aspects of the pathogenesis of spirochetal diseases. I begin in Section 2 by describing the more prevalent diseases that are caused by spirochetes, focusing on the role of motility. Then, I discuss the current state of our knowledge about the biophysics for how these bacteria create their unique shapes (Section 3) and movements (Section 4). Though much of the research on spirochete motility has focused on the swimming of these organisms through liquid media, recent work has investigated their motility in extracellular matrix-like environments and in living mammals and ticks. Section 5 will describe how these environments affect motility. Section 6 discusses how biophysical data on motility can aid our understanding of the early stages of Lyme disease. Section 7 concludes with a discussion of where the field of spirochetal motility stands and what major outstanding questions remain.

2. Spirochetal diseases

A vast array of mammalian diseases are caused by spirochetes, including the notorious human diseases syphilis and Lyme disease. In humans, spirochetes also cause yaws (*Treponema pallidum* subsp. *pertenue*), pinta (*Treponema carateum*), relapsing fever (*Borrelia* species), leptospirosis (*Leptospiraceae*) and periodontal disease (*Treponema* species) [13,14]. In this section, I briefly review these diseases, focusing on the spirochetal behaviors that largely influence pathogenesis.

2.1. Syphilis

Relatively few diseases are as recognized and carry such a stigma as syphilis, the sexually transmitted form of which is caused by *T. pallidum* subspecies *pallidum*. Venereal syphilis is primarily acquired either through sexual intercourse with an individual in the primary or secondary stages of the disease or congenitally, being transmitted from a mother to the unborn fetus [12]. During the primary and secondary stages of the disease, mucocutaneous lesions are present, which readily enable spirochetes from the infected individual to come into contact with mucosa or skin on the uninfected partner. Surprisingly, few treponemes are required to initiate syphilis: If approximately 57 organisms are inoculated onto an individual, there is a 50% chance that they will contract the disease [15]. *T. pallidum* then rapidly disseminates, as exemplified in animal studies where treponemes were found in the blood, lymph nodes, bone marrow, spleen, and testes within 48 h after inoculation [16,17]. *T. pallidum* also readily breaches the blood–brain barrier and infects the central nervous system [12]. Congenital syphilis also highlights the invasiveness of *T. pallidum*, as very few bacteria are capable of transplacental transmission, yet treponemes can be found in fetuses as early as nine weeks [18,19].

Syphilis begins with a 9–90-day incubation period, during which time the patient is asymptomatic. Replication of the spirochetes at the inoculation site induces a local inflammatory response that generates a papule, which subsequently ulcerates [12]. This chancre is the defining lesion of primary syphilis. In the chancre, *T. pallidum* are found in the dermis in close proximity to blood vessels [20]. Interestingly, the chancre is often painless, which may be due to infiltration of cutaneous sensory nerves by the bacteria [21,22]. Secondary syphilis begins four to ten weeks after primary syphilis. In secondary syphilis, the spirochetes have disseminated throughout the body. While mucocutaneous lesions are the primary manifestation of secondary syphilis, virtually any organ can be affected [23]. The lesions associated with secondary syphilis typically resolve in three to twelve weeks, after which there can be periods of latency where the patient is asymptomatic [12]. Periods where there are high burdens of spirochetes in the blood (spirochetemia) occur during the early years of syphilis, and at least 30% of untreated patients will develop tertiary syphilis, which include gummatous, cardiovascular and neurological complications [12].

2.2. Yaws, bejel, and pinta

Other subspecies of *T. pallidum* cause the related diseases of yaws (*pertenue*) and endemic syphilis (also known as bejel or nonvenereal syphilis and caused by the subspecies *endemicum*) [13,14]. A related species, *T. carateum*, causes pinta [12]. These diseases