Mechanobiology: How pathogens use mechanics to modulate host interactions

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Mechanobiology explores how cells sense and respond to mechanical cues and how mechanics guide cell function, physiology, and disease. In this issue of *Cell*, Thacker and colleagues reveal how the tuberculosis-causing pathogen exploits the mechanical behavior of cord-like structures to promote infection, impacting immune response, antibiotic susceptibility, and treatment strategies.

At the crossroads of biology and physics, mechanobiology is a fascinating research area that aims at elucidating how living cells sense and respond to mechanical cues and how physical forces guide cell function and disease. The past decades have witnessed remarkable advances in our understanding of the role of mechanical properties and perturbations in cell signaling, development, division, differentiation, and disease.[1–3] Central to the growth of mechanobiology is the development of advanced methods to study mechanical forces at relevant length scales. At the (multi)cellular level, mechanics are traditionally investigated using microscale engineering and microscopy platforms. Micropillar and traction force microscopy experiments, which measure the forces generated by cells and cell assemblies, have shed light on the forces associated with pili retraction and growing bacteria. Atomic force microscopy (AFM) has become one of the most powerful and versatile tools to explore forces in cellular systems.[4,5] AFM-based force spectroscopy enables researchers to capture the mechanical strength and dynamics of adhesion from the cellular to the single-molecule levels and to quantify cell mechanics and its regulation in relation to function. Notably, elasticity can be spatially mapped across single live cells with nanoscale resolution, revealing that many cell types show local variations of stiffness that are of biological relevance. Optical and magnetic tweezers are valuable complementary techniques to study forces in cells and molecules while molecular dynamics simulations are being increasingly used to unveil their molecular and atomic origins.

Over the years, there has been tremendous progress in understanding the mechanics of mammalian cells at various length scales. Yet, the mechanobiology of microbes has long been overlooked and is the focus of Thacker et al. in the current issue of *Cell*.[6] The main reason for our lack of understanding mechanobiology of bacterial infections is the tiny size of these cells and of their machineries and the lack of appropriate tools to study their mechanical properties. However, evidence is growing that mechanics also influence the behavior of microbes, including bacterial pathogens. Bacteria adhering on surfaces, whether biomaterials or host tissues, are subjected to physical stress like hydrodynamic stresses from fluid flow and compressive and tensile stresses brought on by intercellular contacts and tissue deformations (Figure 1A). The external shear and tension to which bacteria and their individual surface components are exposed play important roles in modulating cellular function.[7,8] Essentially, the main breakthroughs in recent mechanomicrobiology are that (1) under external applied forces, microbes feature a variety of mechanosensitive feedbacks to enhance motility and adhesion, and (2) mechanosensing and mechanotransduction mechanisms enable microbial cells to sense forces and transduce them via cellular machineries to regulate various phenotypes, like gene expression and pathogenicity. Hence, it has become clear that forces can profoundly impact bacterial physiology and pathogenesis, but what is much less understood is whether and how pathogens can exert mechanical action inside host cells and tissues to promote infection.

In this issue of *Cell*, Thacker and colleagues[6] address this fascinating issue by investigating a new mechanobiology aspect of infection: how the pathogen *Mycobacterium tuberculosis* (Mtb) applies mechanical pressures against host cells to promote infection. Mtb cells organize into multicellular structures called cords *in vitro* and during infection. While cords are known to play a part in Mtb virulence, how they do so is unclear. Using advanced lung-on-chip and mouse infection models as well as confocal and electron microscopy, the authors[6] find that cords envelop and compress the nuclei of alveolar macrophages (Figure 1B). This mechanical deformation results in altered histone deacetylase activity, which mediates an attenuated inflammatory response favoring Mtb persistence despite the inflammatory nature of Mtb surface lipids.

They further find that after inducing cell lysis, Mtb cords continue growing through the tight junctions between adjacent epithelial cells thereby allowing bacterial dissemination that can lead to cavitary lesion formation and Mtb transmission. The ability of Mtb cords to exert a force on their surrounding host cells and tissues depends upon their architectures. Wild-type Mtb cords have high aspect ratios with individual bacteria mainly organized parallel to each other. On the other hand, mutant Mtb cells lacking *cis* cyclopropane rings in the mycolic acids of their outer membrane do not produce microcolonies with high aspect ratios. These do not compress alveolar macrophage nuclei nor do they infiltrate the tight junctions between adjacent epithelial cells.

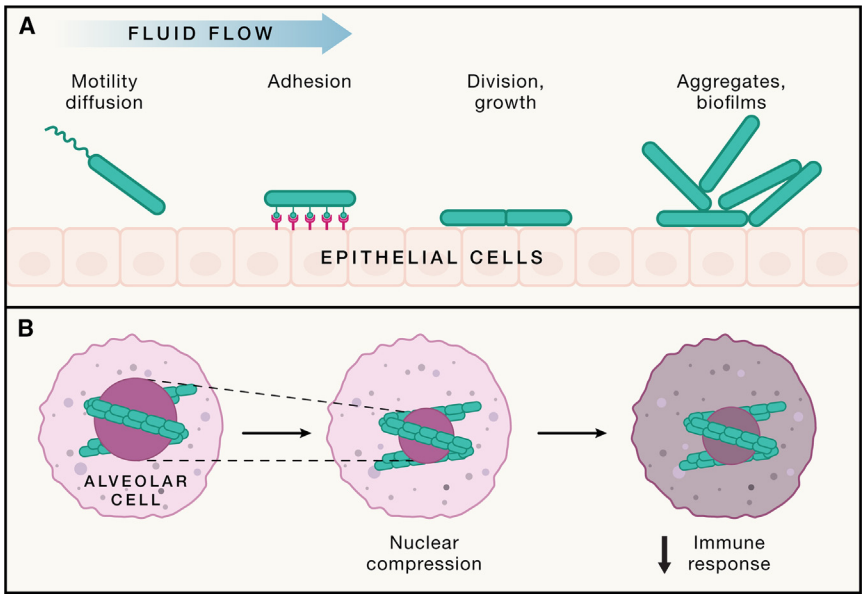

Figure 1. Pathogens and mechanical forces

(A) Bacterial pathogens experience various mechanical cues as they adhere to host tissues and biomaterials under fluid flow. Upon contacting a surface, microbes engage into specific mechanical bonds for adhesion and divide, grow, and finally form multicellular colonies and biofilms.

(B) *Mycobacterium tuberculosis* (Mtb) cords envelope host cell nuclei thereby exerting a mechanical pressure on them. This modulates histone deacetalyase-mediated inflammatory responses to Mtb, favoring infection.

Interestingly, the ability of Mtb cords to exert force on their surroundings relies on their mechanical rigidity, which is determined by strong interbacterial adhesion within cords and energy storage within the mycomembrane due to the compressibility of its constituent lipids. Cord stiffness extends to antibiotic tolerance as tightly packed bacteria within cords display a remarkable capacity to survive antibiotic treatments. The therapeutic implications of Mtb biofilm-like cords are striking. The limited penetration of antibiotics within cord structures challenges effective drug delivery, allowing bacteria to remain resilient even in the presence of therapeutic concentrations. This highlights the need to develop strategies that can target bacteria within these architectural niches.

In conclusion, this study emphasizes that bacteria are capable of producing multicellular assemblies that can exert mechanical force on host intracellular structures to enhance pathogenesis. The findings unveil the pivotal roles of biofilm-like Mtb cord mechanics in shaping the immune response, bacterial dissemination, and antibiotic susceptibility. This prompts intriguing questions about the broader implications of the mechanobiology of microbial biofilm architectures in infection dynamics and therapeutic outcomes. As we delve deeper into the complex interplay between pathogen mechanics and host responses, new avenues for combating tuberculosis, and other diseases, are poised to emerge.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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