„Pathogen heterogeneity during infection: impact on disease progression and therapy“

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Infectious diseases remain a major cause of death worldwide. Lack of efficacious vaccines against important pathogens, and rapidly rising antimicrobial resistance pose a major threat to human health. Infection research has discovered many host-pathogen interactions, but most in vivo studies use bulk average readouts that cannot capture the vast and dynamic complexity of individual encounters in infected tissues. We have recently developed single-cell techniques that report on survival/killing, stress exposure, and growth rates of individual *Salmonella* cells in infected mouse tissues. In addition, we are currently developing 3D imaging approaches to localize individual *Salmonella* in tissue microenvironments at nm to cm scale. Our results show that after oral infection, individual *Salmonella* arrive from gut-associated tissues at various sites throughout the entire spleen. Distinct microenvironments expose *Salmonella* to widely different levels of oxidative and nitrosative stress, resulting in massive death of *Salmonella* subsets in inflammatory lesions, but successful local adaptation and stress defense in other regions. Surviving *Salmonella* grow at vastly divergent rates as a consequence of highly heterogeneous access to host nutrients. A small fast growing *Salmonella* subset drives disease progression with little contribution of moderately growing *Salmonella*. On the other hand, slow growing *Salmonella* are tolerant against antibiotics and can cause treatment failures. These results show that salmonellosis consists of strikingly heterogeneous and dynamic *Salmonella*-host encounters involving diverse tissue regions, cell types, and molecular mechanisms. Overall disease progression results from failures in host control or antibiotic therapy at some tissue sites, despite successful simultaneous eradication elsewhere. Disparate pathogen-host encounters thus make the difference between lethal disease and successful control, and offer new opportunities for improving disease control.