Title:	The Cost of Adaptation: Physiological and Evolutionary Trade -offs in Response to different routes of infection
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Abstract:	Resistance and Disease tolerance are the two main immunity mechanisms that govern host response to an invading pathogen. Mechanisms of resistance pertain to the capacity of the host to actively limit and/or eliminate pathogen numbers. Disease tolerance includes the mechanisms by which the host endures damage incurred during the infection process without any direct action on the pathogen. Hence, the evolution of host response to infection is predicted to balance fitness costs through a combination, at a mechanistic level, of pathogen load reduction/elimination (resistance), with tolerance to the damage caused during the infection process. However, little is known empirically about the relative contribution of these two mechanisms or their interaction, let alone in large natural populations. For example, we do not know how previous adaptive history of the host impacts its response to a new infection or to re- infection by the same pathogen, or how the response to changes in route of infection may also be contingent upon it. Here, we took advantage of an outbred population of Drosophila melanogaster previously adapted to a systemic infection with its natural pathogen Pseudomonas entomophila, to test its response to infection through an oral route. In addition, we sought to disentangle between disease tolerance and resistance mechanisms by changing the nature of the immune response trigger, feeding flies with either heat-killed or live P. entomophila. Indeed, we expect infection by a live pathogen to activate mechanisms of resistance as well as disease tolerance, whereas exposure to heat-killed pathogen will only reveal costs pertaining to mechanisms of disease tolerance. We observe that, despite more than 100 generations of relaxed selection, female flies of the aforementioned population infected orally with live Pseudomonas entomophila, still survive significantly more than control population, while this isn't true for males. Furthermore, our tests for the evolution of tolerance in this population reveal that disease tolerance mechanisms may have evolved alongside resistance toward the systemic mode of infection. And finally, to assess whether pre-existing adaptation toward systemic infection would be a constraint on adaptation toward the oral route of infection, we evolved this population against the oral route using both live and HK forms of P. entomophila. From the preliminary data from the oral selection regime using live pathogen, we predict the lack of a stringent constraint on evolution of resistance among different infection routes. In contrast, we speculate the existence of an evolutionary trade-off from the oral regime with HK pathogen. This implies that while the agent for selection toward resistance among different routes of infection may be common, that might not be the case for disease tolerance mechanisms. Our study introduces an efficient system to disentangle resistance and disease tolerance. Moreover, our results reveal the extent of mechanistic overlap between responses to different infection routes laying the foundations for an interpretation of the role of historical contingency in adaptation to infection through alternating routes.
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