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Impact of life history theory on host compentence through the selection of divergent immunological strategies

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IMPACT OF LIFE HISTORY THEORY ON HOST COMPETENCE THROUGH THE SELECTION OF DIVERGENT IMMUNOLOGICAL STRATEGIES:

UNDERSTANDING WHY RESILIENT SPECIES MIGHT ALSO BE POOR DISEASE DILUTION AGENTS

by

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ABSTRACT

Disease dilution, the reduction in infection risk with increased host diversity, has recently attracted attention as one of the many indispensable services provided by rich ecological communities. Immunological variation seems to play an important role in many dilution mechanisms, with non-competent hosts acting as dead ends for various generalist pathogens. Interestingly, life pace in host species has been previously correlated in literature with two distinct immunological strategies that might directly influence host dilution potential. Evidence that fast-paced organisms evolutionarily approach infection differently than slow-paced ones supports the idea that reproductively prolific species might also be more competent hosts, favoring the persistence and spread of infectious diseases through investing more in tolerance mechanisms. Less ecologically resilient hosts, in this case, would assume the role of less competent hosts that buffer disease transmission, since their evolved immunological strategy is more efficient when dealing with repeated pathogen encounters. Competence to generalist pathogens, therefore, should be maximized in fast paced species and minimized in slow paced species when dictated by either resistance based or tolerance based immunological profiles. Life history variation gradients might help reprioritize conservation efforts and control the spread of emergent infectious diseases by revealing common traits in optimal dilution agents.

INTRODUCTION

Biodiversity loss caused by habitat fragmentation, introduction of invasive species, overharvesting, and pollution is on the rise and has reached a level that approaches that of past mass extinctions (MEA 2005). Organizations such as the Intergovernmental Science Policy Platform on Biodiversity and Ecosystem Services have recently been created in an effort to quantify changes in the structure of ecological communities and their impact on human welfare (Keesing *et al.* 2010). Decline in species richness interferes with important services provided by ecological communities, one of them being the dilution of infectious diseases (Keesing *et al.* 2006). Dilution is defined as lower overall disease prevalence resulting from higher species diversity. Reduced infection of susceptible hosts seems to be largely caused by infection opportunities being wasted on highly resistant hosts that serve as dead ends for parasites (Keesing *et al.* 2010).

Curiously, in several disease dilution studies, the species most likely to be lost from ecological communities as diversity declines are also those likely to reduce overall disease risk when present (Keesing *et al.* 2009, Allan *et al.* 2003). A possible explanation for this observed pattern might lay in the evolutionary relationship between the scheduling of reproductive events over a host's lifespan and its reservoir competence, here defined as the ability to transmit a parasite. Both parasite exposure and resources available to mount distinct immune responses are affected by the life pace of an organism. Selection on short lived organisms to mature faster and produce more offspring per unit time might also favor inflammatory responses that are energetically cheaper to develop and do not take time or energy away from reproduction. This tendency towards nonspecific inflammatory responses in fast paced species upon parasite re-

exposure might, in turn, ultimately result in a tolerance based approach to generalist infections, which could in turn explain the relationship between high ecological resilience and high host competence found in some disease dilution studies. Incorporating the immunological relationship between resistance and tolerance to disease dilution and how these pathways evolved in fast versus slow paced species remains critical in order to understand why ecologically resilient species might be amplifiers of disease transmission.

I. LIFE HISTORY THEORY HELPS EXPLAIN IMMUNOLOGICAL VARIATION

Life history is a set of evolved strategies, including behavioral and physiological adaptations that influence survival and reproductive success (Ricklefs and Wikelski 2002). Environmental factors, such as exposure to different pathogens, climate change, and resource availability push populations to modify phenotype, in order to increase their chance of survival within their respective communities. Optimization of life history traits, however, is constrained by energy limitations that drive different species (and even different populations) to fall along a life pace continuum. When various activities compete for limited energy resources, combination of certain life history characteristics becomes apparent. Fast paced species generally exhibit high reproductive efforts, at the cost of somatic/developmental investments and longevity. Slow paced species, on the other hand, live longer and invest more in somatic maintenance, at the cost of reproductive output. Here, duration of in utero development and longevity are contrasted with

reproductive output for a mouse and an elephant:

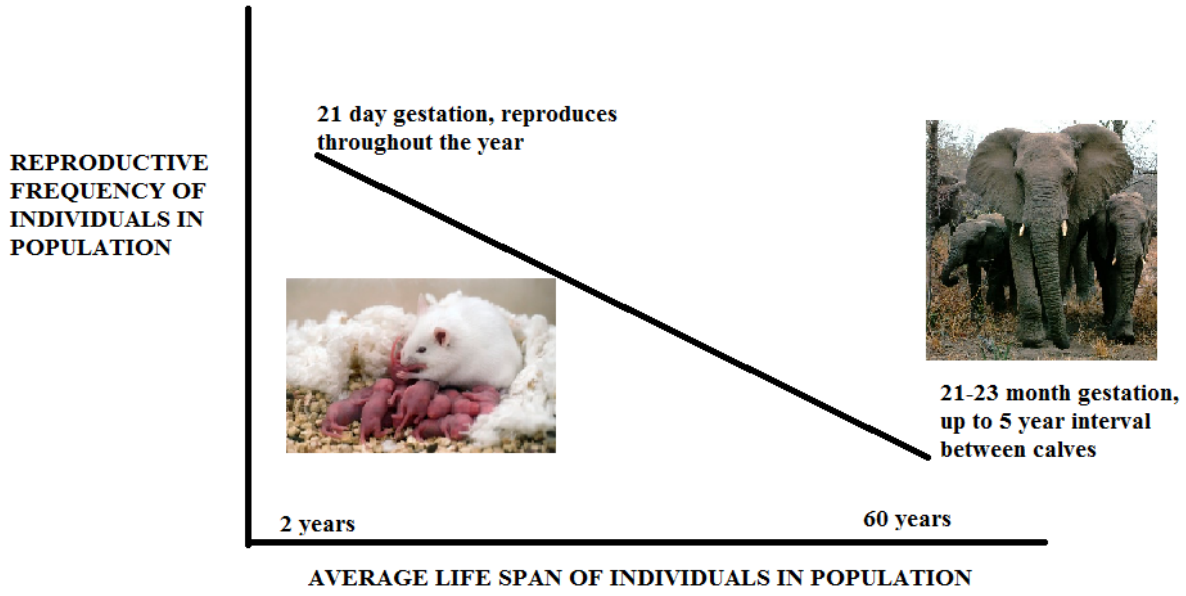

Fig 1. Life History Patterns Observed in Nature. This pattern extends to virtually all organisms. Animals with shorter life spans and that develop faster tend to reproduce more prolifically and rely less in somatic maintenance.

A species immune function also seems to be affected by this life history continuum, since the development of distinct immunological profiles also requires energetic investment (Norris *et al.* 1994). In order to understand commonly encountered immunological strategies, one must have a general understanding of the main components of the immune system. Immunological responses have been historically classified as innate and adaptive. Innate responses are mediated by similarly diverse macrophages, NK cells, granulocytes, and various blood born factors (Adelman and Martin 2009). Adaptive responses are mediated by B cells and T cells and take longer to engage than innate responses. Most importantly, the adaptive branch of the vertebrate immune system is responsible for the selection of useful antibodies and the proliferation of these

antibodies during the development of an immunological memory (Elgert 2009). Also, during refinement of immunological memory, lymphocyte receptors that recognize self-antigens are eliminated, so to prevent autoimmune damage (Elgert 2009). Innate and adaptive immunological arms work together and activate each other's' components through a variety of feedback mechanisms.

Even though developing methods to access to which degree each immunological arm is involved in a given response has been problematic, a pattern seems to emerge when correlating life pace characteristics to innate and adaptive immunological variables. Species that develop quickly and reproduce prolifically (fast paced) appear to rely mostly on inflammatory, nonspecific, fast acting immune defenses. Slow paced species characterized by lower reproductive output, longer life spams, and slow maturation, on the other hand, exhibit intricate adaptive responses that are anti-inflammatory and slow to engage. *Peromyscus* species seem to either be proficient at killing *E. coli* (innate response) or generating antibodies against a novel protein (adaptive response), however, not both (Martin *et al.* 2007). The species that are more fast paced seem to invest less in generating and proliferating specific antibodies against the novel proteins and more in inflammatory and bactericidal responses. Also, correlation between immune response specificity and clutch size has been established for tree sparrows and house sparrows, with tree sparrows exhibiting larger clutch sizes and investing less in T-cell mediated defenses (Lee *et al.* 2006b). Fast paced garter snakes exhibit more bactericidal power and complement-mediated lysis – both considered measures of constitutive innate immunity - than slow-paced ones (Sparkman and Palacios 2009). Finally, domesticated egg-layer lines of chickens exhibit stronger inflammatory responses to the same infection than did broiler chicken lines (Leshchinsky and Klasing 2001). A possible explanation for these findings is that the

developmental costs of a diverse lymphocyte receptor repertoire, along with selection and proliferation of useful antibodies, are minimized in fast paced species in order to favor large litter/clutch sizes, fast maturation, and shorter reproductive cycles energetically (Lee *et al.* 2008). Sickness behaviors that accompany the time-consuming engagement of adaptive immunology could also compromise mating opportunities in fast paced individuals by preventing them from searching for mates or displaying reproductive traits that signal phenotypic quality , for example (Sears *et al.* 2009). Also, short lived species are less likely to experience repeated pathogen encounters, which minimizes the need for investing in a developmentally expensive adaptive immune system (Sears *et al.* 2009).

Intrinsic characteristics of host species are indeed as important for mitigation of infectious diseases as interspecific interactions within ecological communities (Lee *et al.* 2006a). In a study involving the trematode *Ribeiroia ondatrae* , for example, Johnson and Thieltges discovered that the addition of a competent host (*B. americanus*) to a monospecific community increased total metacercariae abundance, while the addition of a non-competent host (*H. versicolor*) induced the opposite effect regardless of relative host densities or average species biomass/size (2010). Another example is increased diversity of non-passerine birds - less competent hosts for West Nile Virus compared to passerines - associated with decreased viral infection in humans (Ezenwa *et al.* 2006, Allan *et al.* 2009). Finally, neither filter-feeding cockles and barnacles nor filamentous algae interfered with the transmission of cercariae to juvenile stalk-eyed mud crabs (*Macrophthalmus hirtipes*), whereas anemones (*Anthopleura aureoradiata*) caused a strong reduction in parasites acquired by crabs (Hopper *et al.* 2008). According to these studies, immunological variation amongst species is an important mechanism through which disease dilution operates. Studying this immunological variation, however, has

proven a challenge due to the complexity of pathway interactions participating in an immune response. Fortunately, life history theory reveals how energy allocation selects for commonly encountered combinations of life pace and immune strategy.

II. TOLERANCE AS AN IMMUNOLOGICAL STRATEGY AND A DETERMINANT OF HOST COMPETENCE

Host defenses can also be divided into two major components: tolerance and resistance. Resistance consists of any efforts aimed specifically at decreasing parasite burden (Raberg *et al.* 2009, Sears *et al.* 2011, Schneider 2008). Tolerance consists of mechanisms aimed at reducing costs of parasite burden and immunopathology, such as tissue damage resulting from severe inflammation (Sears *et al.* 2011, Schneider *et al.* 2008). One example of tolerance engagement occurs when high levels of TNFα (tumor necrosis factor alpha) continuously released by hyper activated macrophages cause neutrophil death (Sears *et al.* 2011). Phagocytosis of these neutrophils in turn induces phenotype changes in the macrophages themselves, causing them to produce anti-inflammatory cytokine IL-10 (Sears *et al.* 2011). Parasite virulence as indicated by pathogen-associated molecular patterns used in antigen recognition and tissue vulnerability or immunological constituents at infection site are some of the factors that determine when tolerance mechanisms become necessary during the course of a resistance based response (Sears *et al.* 2011, Medzhitov *et al.* 2011, Pagan *et al.* 2009).

Tolerance in fast paced species should also be evolutionarily favored, since autoimmune damage from repeated inflammatory responses could turn out fatal in the case of parasite persistence. Slow paced species, on the other hand, should show a resistance based response to

infection all the way to adaptive antibody recruitment. Not considering shifts from tolerance to resistance (and vice versa) due to changes in pathogen load or due to parasite interactions, fast paced species should, in theory, be able to support higher parasite burdens through investing more in tolerance mechanisms. Slow paced species that rely more heavily on immunological memory would serve as buffers of disease transmission within ecological systems by effectively clearing parasites with specific antibody receptors developed during previous infections. Competence, therefore, should be maximized in fast paced species and minimized in slow paced species and determined by how much they rely on tolerance mechanisms aimed at preventing auto immune damage by nonspecific responses.

III. CONNECTING THE DOTS: ECOLOGICAL RESILIENCE, HOST COMPETENCE, AND DISEASE DILUTION

If distinct life history traits indeed select for immunological strategy, it would be reasonable to state that species that are reproductively prolific or ecologically resilient should also be the most competent hosts. A study on aphid vectored virus in plants supports this life pace-competence relation, with short lived hosts with fast metabolism and abundance of nutrients exhibiting higher susceptibility and ability to support vector populations (Cronin *et al.* 2010). A single slow-fast axis describing host physiological phenotype seems to explain host competence in this case. The very species that have traits permitting persistence ("weedy" characteristics in Johnson and colleagues' study) were more likely to carry high pathogen burden, with the immune-reproductive trade off possibly resulting in a tolerance based approach to infection. Studies on disease dilution seem to point in the same direction. In habitats degraded

by anthropogenic forces, species with life history characteristics that allow them to persist are also the ones responsible for the highest transmission rate, such the white footed mouse as a reservoir host for Lyme disease. In contrast, a host with strong buffering effect, the opossum, was absent from most degraded forests where mice were abundant. If indeed selection in fast paced species operates in a way that creates an increased need for tolerance and consequentially increases competence, important dilution agents would most likely be slow paced species, which rely on specific immune responses that severely undermine infection upon repeated exposure. Slow paced species, however, should also be less resilient to extinction due to overall lower reproductive output (Keesing *et al.* 2010). Robust empirical support for tolerance predisposition in fast paced species would enlighten our understanding of how competence regarding generalist parasites evolves across species. This particular intercession in the fields of disease ecology and immunology might help us in the future to recognize super spreaders (or organisms more prone to engage in tolerance within communities) by accessing their developmental investments towards reproductive output and maturation.

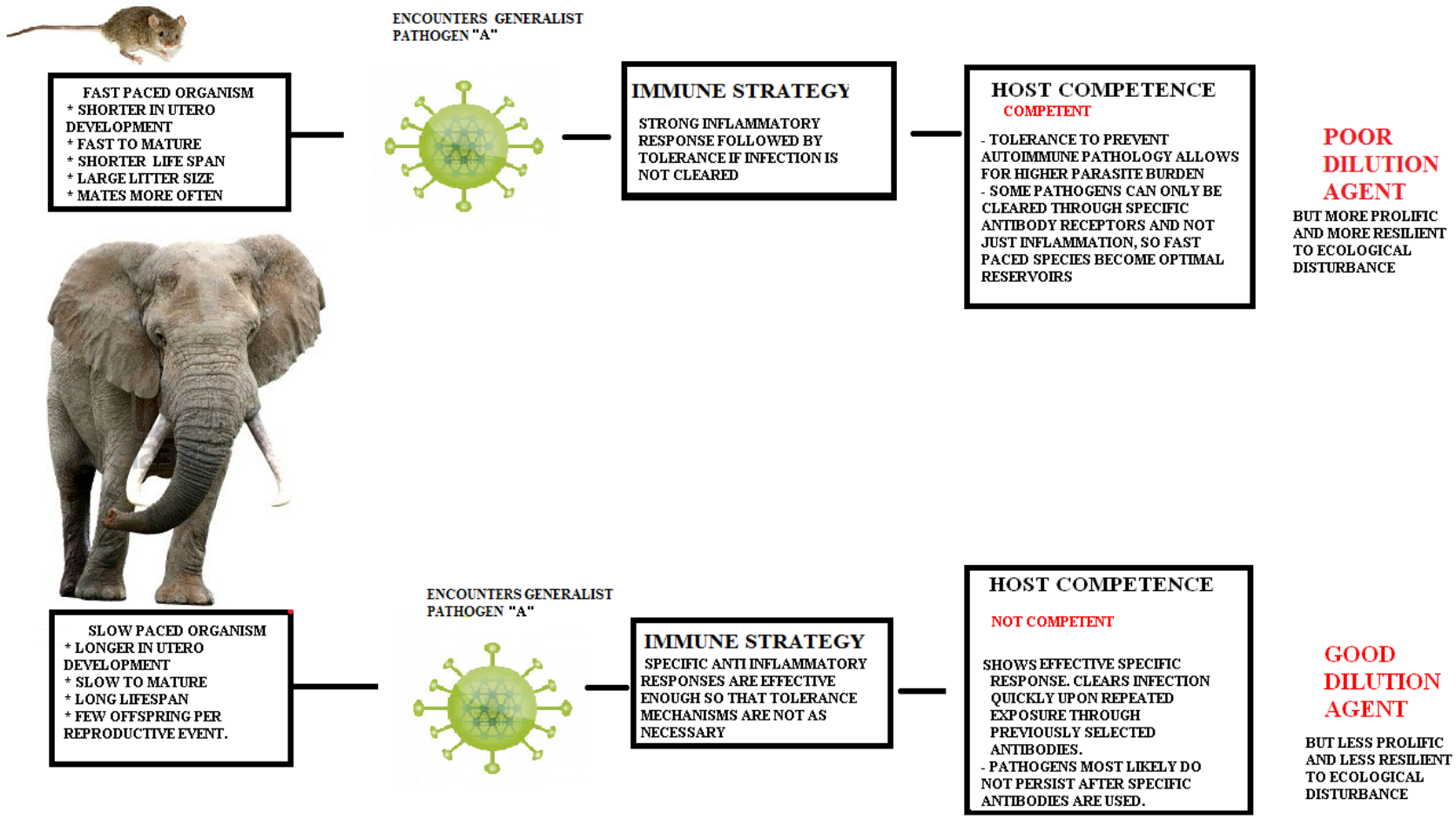

Fig 2. Establishing a Connection between Dilution Effectiveness and Life Pace in Hosts. Hosts who exhibit slow life pace characteristics are most likely to be better dilution agents because of heavier investment on adaptive immune strategies. Since slow paced hosts do not invest as much in reproductive output as fast paced hosts, they are also likely to be less resilient to ecological disturbances.

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