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Review article

The Goldilocks model of immune symbiosis with *Mycobacteria* and *Candida* colonizers

Richard T. Robinson[a,*], Anna R. Huppler[a,b,*]

[a] Department of Microbiology and Immunology, Medical College of Wisconsin, Milwaukee, WI, USA
[b] Department of Pediatrics, Division of Infectious Disease, Medical College of Wisconsin, Children's Hospital and Health System, Children's Research Institute, Milwaukee, WI, USA

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ABSTRACT

Mycobacteria and *Candida* species include significant human pathogens that can cause localized or disseminated infections. Although these organisms may appear to have little in common, several shared pathways of immune recognition and response are important for both control and infection-related pathology. In this article, we compare and contrast the innate and adaptive components of the immune system that pertain to these infections in humans and animal models. We also explore a relatively new concept in the mycobacterial field: biological commensalism. Similar to the well-established model of *Candida* infection, *Mycobacteria* species colonize their human hosts in equilibrium with the immune response. Perturbations in the immune response permit the progression to pathologic disease at the expense of the host. Understanding the immune factors required to maintain commensalism may aid with the development of diagnostic and treatment strategies for both categories of pathogens.

1. Introduction

Species in the genera *Mycobacteria* and *Candida* include etiological agents of globally significant diseases, as well as non-pathogens that live in either soil and aquatic environments (i.e. *Mycobacteria*) or on the surface of animals, plants and insects (i.e. *Candida*). *Candida* and *Mycobacteria* species (spp.) have very little in common from a strictly biological perspective: *Candida* spp. are eukaryotes with a diploid genome that is sensitive to external stress and extensively heterozygous [1], replicate primarily via asexual cell division and hyphal extension, and have polysaccharide-rich cell wall. *Mycobacteria* are prokaryotes with a haploid genome that is relatively stable, divide asymmetrically [2], and have a multilayered hydrophobic cell wall. However, despite their biological differences *Candida* and *Mycobacteria* spp. share something in common: both are chronic colonizers of large numbers of humans, but elicit disease in a relative minority of colonized humans. Specifically, an estimated > 30% of the world population is colonized with *Candida* and/or *Mycobacteria* spp., ~90% of whom show no clinical signs of disease.

Several flavors of disease can occur following *Candida* or *Mycobacteria* infection. *Candida* infections are categorized as mucocutaneous or disseminated candidiasis. Mucocutaneous candidiasis is typified by the hallmark infection of oropharyngeal candidiasis, also known as thrush. This disease form can also present as an invasive infection on barrier surfaces of the skin, nails, esophagus, or vulvovaginal mucosa. Disseminated candidiasis includes bloodstream infections (candidemia) and infection of normally sterile organs including liver, spleen, kidney, heart, and brain. The case-fatality rates for disseminated candidiasis are high, with reports of 30–50%, while mucocutaneous candidiasis carries high morbidity for patients [3,4]. Globally, there are an estimated 400,000 cases of candidemia, 10 million cases of thrush, and 2 million cases of esophageal candidiasis annually [3]. Mycobacterial infections similarly impact large portions of the globe, and include nontuberculous mycobacterial infection (NTMI), leprosy, swimming pool granuloma, buruli ulcer, and tuberculosis (TB). TB is particularly significant at the global level, and is caused by aerogenic transmission of *Mycobacterium tuberculosis*, which primarily infects macrophages in the lung alveoli [5]. In its active form, TB is associated with "consumption" of the lung tissue and dissemination of *M. tuberculosis* to other organs; in its latent form, TB is asymptomatic and not infectious. Improved public health practices and the use of effective drug treatment have reduced exposure and disease rates in many countries. However, the efforts to control TB in many other countries are not optimal, casting doubt on the World Health Organization's goal of halving TB incidence by 2050 [6]. For these reasons, it is important to have a data-informed framework for understanding the

* Address: Department of Microbiology and Immunology, Medical College of Wisconsin, Milwaukee, WI, USA (R.T. Robinson and A.R. Huppler).
E-mail addresses: rrobinson@mcw.edu (R.T. Robinson), ahuppler@mcw.edu (A.R. Huppler).

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relationship between humans and *Candida* and *Mycobacteria* pathogens.

Here we will introduce a novel concept regarding the biological relationship between immune cells and *Mycobacteria* pathogens that is modeled on established concepts regarding the host relationship with *Candida* spp. Namely, we advocate that humans' relationship with *Candida* and *Mycobacteria* spp. is best described in terms of biological commensalism, and that most individuals maintain the human:commensal equilibrium via innate and T cell-associated cytokines. In a relative minority of individuals, too little or too much of select cytokines offsets this equilibrium and leads to a diseased state. We term this model the "Goldilocks Model." To support this model, we will review data demonstrating that recognition of *Candida* and *Mycobacteria* spp. by overlapping pattern recognition receptors (PRRs) leads to similar innate cytokine profiles, which consequently direct T cell differentiation. We also review data concerning how T cells govern *Candida* and *Mycobacterial* disease outcome, as well as the polymorphisms in PRR and cytokine response genes that associate with disease susceptibility.

2. Human colonization as a survival strategy for *Candida* and *Mycobacteria*

Natural selection is the force behind both prokaryotic and eukaryotic evolution, and is the process whereby heritable traits that increase a species likelihood of survival become more common over successive generations. We can therefore assume that during human history the ancestors of what are now *Candida* and *Mycobacteria* pathogens found the human niche to give them a selective advantage. Their adaptation to humans is understandable, as the human niche is stable relative to many other environments, with a regulated temperature and wealth of nutrients from the food we ingest. Competition with other bacteria is also limited in the human niche: while a common microbial environment such as soil may contain up to $\sim 3 \times 10$ [8] CFU per gram of soil [7], the human niche is relatively sterile (the gut being an exception, with $\sim 3 \times 10$ [11] CFU per gram [8]). For several *Mycobacterial* and *Candida* spp., co-evolution has led to humans now being their only niche. Since most individuals fail to develop disease following initial *Mycobacteria* or *Candida* colonization, *Mycobacteria* and *Candida* spp. are best described in ecological terms as *commensals* in the majority of chronically colonized individuals, and *exploiters* in the minority of chronically colonized individuals (Fig. 1A).

Candida and *Mycobacteria* spp. use of chronic colonization as a survival strategy contrasts with pathogens that solely cause acute disease. Fig. 1B depicts the life cycle of two human pathogens that employ distinct survival mechanisms: *Yersinia pestis* and *Mycobacterium tuberculosis*. *Y. pestis* caused the Black Death of the 14th century, and passages between rodents and fleas until infecting a human via a flea bite. Human to human transmission of pneumonic plague can also occur. *Y. pestis* employs a rapid bacterial replication rate at the expense of host survival, and is best described in ecological terms as an exploiter of humans (Fig. 1A). By the time its human host dies (a matter of days), *Y. pestis* will have replicated N times (N being an arbitrary number). Contrasting with the life cycle of *Y. pestis* is that of *M. tuberculosis*, which does not have a non-human host and passes between humans via aerosolization of infected sputum. In most infected individuals, *M. tuberculosis* enters a slowly replicating, dormant state that does not cause clinical disease. By the time its latently infected host dies (a matter of years and/or decades), *M. tuberculosis* will have also replicated N times. A minority of infected individuals ($\sim$10%) develop active disease and produce the infected sputum that allows for *M. tuberculosis* transmission to a new generation of hosts. For these reasons, we propose that *M. tuberculosis* is best described in ecological terms as a commensal of most infected individuals, and an exploiter in the minority of infected individuals (Fig. 1A). In contrast to the relative novelty of the commensal status of *Mycobacteria* spp., it is well-established that *Candida* spp. live primarily as commensals. The ecological niche for *Candida* spp. is primarily on animal or plant hosts, and the relationship is generally benign to the host. Certain species are commensals in humans that transmit via physical contact (e.g. the touch of caregivers), which correlates with the species that can act as the most common opportunistic pathogens in humans (including *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. lusitaniae* and *C. krusei*). *Candida* spp. colonize the majority of humans in the oral cavity, gastrointestinal tract or genital tract. Colonization usually precedes invasive infection and is a key predictor of subsequent disease [9]. In spite of this and the moderate replication rate of *Candida* spp., the majority of colonized humans never develop invasive infection and do not require anti-fungal treatment to maintain normal health. Invasive infection occurs with breaches in normal host immune or barrier function. Thus, through three distinct survival strategies *Y. pestis*, *M. tuberculosis* and *C. albicans* will have both replicated the same N times. However, we consider the strategy of *M. tuberculosis* and *C. albicans* to be more successful in the long term (a matter of millennia) given that neither species cause the rapid, deleterious effects on their host population that were characteristic of the Black Death.

The concept of *Mycobacteria* spp. being human commensals may initially seem to conflict with the fact that *Mycobacteria* spp. also cause significant global mortality. Historical perspective is needed to reconcile this dissonance. Using *M. tuberculosis* as an example: the relationship between *M. tuberculosis* and humans is ancient, having evolved alongside humans for the past 10K-70K years [10]. The organism's ability to enter latency is important for this long relationship, allowing it to infect an individual without impacting her/his evolutionary fitness until she/he becomes immunocompromised with age [11]. While latent TB is asymptomatic and not infectious, active TB is associated with "consumption" of the lung tissue and dissemination of *M. tuberculosis* into the airways; the extensive coughing that ensues can then spread *M. tuberculosis* into the air and enable its infection of a new generation of hosts [12]. The organism's need to balance between activity versus latency not only ensures the survival of *M. tuberculosis*: it has also selected against *M. tuberculosis* variants that are more pathogenic and, thus, more capable of killing its only natural reservoir [10]. Whatever equilibrium may have existed between *M. tuberculosis* and its human hosts was altered in the 1970s, the beginning of the HIV/AIDS pandemic [13]. HIV is a retrovirus that is transmitted through sexual intercourse (via semen or vaginal fluid), blood contamination (via shared needles), or from mother to child perinatally (intrauterine, intrapartum or via breastmilk). The ability of HIV to infect and affect immune lineages that keep *M. tuberculosis* in latency, including T cells and macrophages [14], results in HIV-positive (HIV^+) individuals being more likely to develop active TB than HIV-negative (HIV^-) individuals [15–18]. The HIV/AIDS pandemic has also allowed for the outgrowth of more pathogenic clinical isolates since selective barriers are diminished [10,19]. Thus, whereas the organism's transition from latency to active disease may take decades in HIV^- individuals (a phenotype consistent with the ecological commensals), the recent evolution of HIV and its ability to accelerate the loss of T cells and macrophage lineages results in higher rates of active disease (a phenotype consistent with ecological exploiters).

In many respects, our immune symbiosis with *M. tuberculosis* mirrors that we have with non-tuberculous mycobacteria (NTM). NTM include species that colonize human epithelia, as well as species that are ubiquitous in soil and aquatic environments [20,21]. NTM spp. that colonize human epithelia are rarely pathogenic, include constituents of the healthy microbiota, and can be found along the urogenital tract (*M. smegmatis*, *M. lentiflavum*) [22–24], gastrointestinal tract (*M. lentiflavum*) [24], mouth or respiratory tract (*M. confluentis*, *M. branderi*, *M. bohemicum*, *M. interjectum*, *M. intermedium, M. conspicuum*) [25–31], and skin (*M. smegmatis*, *M. bohemicum*, *M. intermedium*) [32–34]. NTM spp. that are found primarily in soil and aquatic environments include *M. vaccae*, the *M. avium* complex (MAC, *M. avium* and *M. intracellulare*), and *M. abscessus* complex (MABSC, *M. abscessus* subspecies *abscessus*,