Experimental Gerontology 104 (2018) 17–27

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Could age and aging change the host response to systemic parasitic infections? A systematic review of preclinical evidence

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ARTICLE INFO

Keywords:
Aging
Immunosenescence
Infectious diseases
Methodological bias
Preclinical research

ABSTRACT

The impact of age and aging in the evolution of systemic parasitic infections remains poorly understood. We conducted a systematic review from preclinical models of Chagas disease, leishmaniasis, malaria, sleeping sickness and toxoplasmosis. From a structured and comprehensive search in electronic databases, 29 studies were recovered and included in the review. Beyond the characteristics of the experimental models, parasitological and immunological outcomes, we also discussed the quality of current evidence. Our findings indicated that throughout aging, parasitemia and mortality were consistently reduced in Chagas disease and malaria, but were similar or increased in leishmaniasis and highly variable in toxoplasmosis. While a marked humoral response in older animals was related to the anti-*T. cruzi* protective phenotype, cellular responses mediated by a polarized Th1 phenotype were associated with a more effective defense against Plasmodium infection. Conversely, in leishmaniasis, severe infections and high mortality rates were potentially related to attenuation of humoral response and an imbalance between Th1 and Th2 phenotypes. Due to the heterogeneous parasitological outcomes and limited immunological data, the role of aging on toxoplasmosis evolution remains unclear. From a detailed description of the methodological bias, more controlled researches could avoid the systematic reproduction of inconsistent and poorly reproducible experimental designs.

1. Introduction

Malaria, leishmaniasis, toxoplasmosis, African (sleeping sickness) and American (Chagas disease) trypanosomiasis are systemic protozooses responsible for dramatic economic and medico-social impact worldwide (Pollitt et al., 2011; Lozano et al., 2012). Taken together, they are the main neglected diseases responsible for the highest morbidity and mortality rates reported for parasitic diseases in tropical and subtropical regions (Mackey et al., 2014). The etiological agents of each disease are hyperendemic in developing countries, especially in Africa, the Middle East, Central and South Americas; areas with favorable environmental conditions for parasite development, poor socio-economic status and limited access to formal health services (Kettler and Marjanovic, 2004; Rassi et al., 2010; Antinori et al., 2017). Children and the elderly are the most susceptible to parasitic diseases, developing severe forms of infection and suffering disproportionately high mortality rates compared to intermediate age groups (Simon et al., 2015). In these vulnerable groups, infection susceptibility has been attributed to an immunological inability to contain the infection, especially due to incomplete immunological maturation in children and immunosenescence in aged people (Simon et al., 2015). Understanding the biological cycle of each etiological agent and the physiopathological mechanism linked to the infections is essential to control transmission and treat human protozooses (Molyneux, 2006). Furthermore, the rational design of more effective public health programs also depends on the identification of vulnerable population groups, as well as on clear delimitation of factors associated with the greater susceptibility to infections (Giefing-Kröll et al., 2015), including those determined by age and aging (Fernández-Mayoralas et al., 2015).

Malaria is the most frequent systemic protozoozis worldwide. This disease is caused by parasites of the genus *Plasmodium*, which are transmitted through the bites of female *Anopheles* mosquitoes (Cox-Singh et al., 2008; Oliveira-Ferreira et al., 2010). According to recent estimates, > 212 million new cases of malaria were registered

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https://doi.org/10.1016/j.exger.2018.01.022
Received 27 December 2017; Received in revised form 17 January 2018; Accepted 19 January 2018

worldwide in 2015, especially in Africa (90%), South-East Asia (7%) and Eastern Mediterranean areas (2%). For the same period, about 438,000 deaths were reported, 92% of which occurred in African countries (WHO, 2017a). Without treatment, the infection progresses with fever, headache and vomiting to marked anemia, respiratory distress and cerebral malaria, which is the severe condition leading most often to death (WHO, 2017a).

Leishmaniasis is an anthropopathy and zoonotic disease caused by protozoan parasites of the genus *Leishmania*, which are transmitted by the bite of female phlebotomine sand flies. This disease is endemic in Africa, the Middle East, Central Asia, South and Central America (WHO, 2017b). Leishmaniasis closely correlated to poverty, poor domestic sanitary conditions, malnutrition, immunological debility, and precarious socio-environmental support (Alvar et al., 2006). Recent estimates indicated an annual occurrence of 700,000 to 1 million new cases, and 20,000 to 30,000 deaths worldwide (WHO, 2017b). Leishmaniasis encompasses three different clinical forms: cutaneous, mucosal, and visceral. Visceral leishmaniasis the most severe form, and affects multiple organs such as spleen, liver, and bone marrow, and causes vomiting, diarrhea, malnutrition, weight loss, hepatosplenomegaly, pancytopenia, jaundice and eventually death (PAHO, 2014).

The protozoan parasite *Toxoplasma gondii* is the etiological agent of toxoplasmosis (CDC, 2015). Due to its wide distribution (< 10 to 95% in some populations) this disease represents an important health problem worldwide (Torgerson and Mastroiacovo, 2013), especially in areas with precarious hygiene and eating habits (Babaie et al., 2013). In the United States toxoplasmosis is a leading cause of death due to foodborne illness (Oz, 2014). In this country, at least 11% of the population of 6 years and older is infected by *T. gondii* (CDC, 2015), in contrast with countries such as Korea and Brazil, in which seroprevalence is around 6.7% and 68.6%, respectively (Shin et al., 2009; Sroka et al., 2010). Food borne, animal-to-human (zoonotic), and mother-to-child (congenital) are the main forms of *T. gondii* infection. Although limited tissue damage and symptoms are reported in immunocompetent individuals, pregnant women and immunocompromised people can develop severe toxoplasmosis, which causes pulmonary necrosis, myocarditis, hepatitis, chorioretinitis, encephalitis and death (Bhopale, 2003).

Sleeping sickness is a vector-borne disease caused by protozoan parasites belonging to the genus *Trypanosoma,* which are transmitted by tsetse flies (*Glossina* genus). While *Trypanosoma brucei gambiense* is endemic in 24 countries in west and central Africa and accounts for 97–98% of infection cases, *Trypanosoma brucei rhodesiense* is endemic in 13 countries in eastern and southern Africa, representing about 2–3% of all infection cases (WHO, 2017c). In 2015, 2804 cases of sleeping sickness were recorded, and currently, about 20,000 cases are estimated; being that 65 million people still live in areas at risk of infection. The initial stages of infection proceeds with fever, headaches, joint pains and itching, progressing to central nervous system infection, sensorial and motor disturbances, meningoencephalitis and death (Pereira et al., 2017; WHO, 2017c).

Chagas disease is caused by the protozoan *Trypanosoma cruzi*, which is mainly transmitted by contact with feces or urine of triatomine bugs. This disease is endemic in 21 Central and South American countries, and about 70 million people are at risk of infection. Approximately 6 to 7 million people are infected and 12,000 deaths are recorded per year worldwide (WHO, 2017d). Increasing incidence and prevalence rates of *T. cruzi* infection have been described in non-endemic areas, especially the United States, Europe and Australia; aspects directly related to the migratory flow of infected individuals from endemic countries (Antinori et al., 2017). Chronic Chagas cardiomyopathy is the most severe and incapacitating manifestation of *T. cruzi* infection (Cunha-Neto and Chevillard, 2014; Pereira et al., 2017), which is responsible for varying mortality rates according to the severity of heart damage (Medeiros et al., 2017).

Although the etiological agents, infection pathways and pathogenesis are widely variable in human systemic protozooses, the immunological system invariably constitutes the pivotal host defense line in all infectious diseases (Podack and Munson, 2016). From this immunological dependence, it seems consistent that increased immunological fragility at the extremes of population age groups is associated with disproportionately high susceptibility to infectious diseases (Giefing-Kröll et al., 2015). Given that the world undergoes a gradual process of demographic transition, the elderly age groups have assumed increasing importance as vulnerable population segments (WHO, 2015). Estimates indicate that between 2015 and 2050, the world's population of 60 years and older will nearly double, from 12 to 22%, so that at least 80% of these older people will be living in low- and middle-income countries. Furthermore, by 2020 the number of people over 60 years will outnumber children younger than 5 years (WHO, 2015).

Although aging is associated with the progressive morphofunctional decline in all biological systems and general homeostatic mechanisms (Gupta et al., 2013; Goronzy and Weyand, 2014; Pawelec et al., 2014), immunosenescence is of special relevance in host-pathogen interaction and infectious disease development (Krone et al., 2014). Immunosenescence is a complex and multifactorial process, characterized by general and progressive dysfunction of innate and acquired immunological mechanisms, which increases the susceptibility of aged organisms to autoimmune, neoplastic and infectious diseases (Passtoors et al., 2015). In parasitic diseases caused by intracellular protozoa, immunosenescence is potentially dangerous, due to poor modulation of immunological phenotypes (Th1 and Th2) that establish the interface of the host-pathogen relationship and the interactions that direct the infection to the ecological balance, either in favor of the host, maintaining the disease stable or leading to cure, or in favor of the parasite, which determines disease progression and eventually death (Torrão et al., 2014). Taken into account that the impact of the age of the host on the evolution of parasitic diseases is poorly understood, investigating how these diseases develop in response to variants of the aging process, especially immunosenescence, may represent a rational and valuable strategy to elucidate the host-pathogen relationship. Furthermore, this strategy can be useful in identifying specific mechanisms underlying resistance and susceptibility to infection, with a direct impact on the understanding of pivotal variables that make older organisms more vulnerable. Considering that the literature provides only fragmented data, and no objective overview on the impact of age and aging on the evolution of parasitic diseases, we conducted a systematic review of preclinical models of human systemic protozooses. Our focus was to define the accumulated evidence on how malaria, leishmaniasis, toxoplasmosis, African and American trypanosomiasis develop in different-age hosts, determining in detail the characteristics and relevance of the preclinical models used; the potential convergences and divergences in physiopathological mechanisms; and the pathological manifestations of important neglected tropical diseases worldwide. From a detailed bias analysis, the methodological quality of current evidence was also evaluated, pointing out the main sources of bias that constitute important research barriers in the area and hinder advances in the understanding of the relationship between host age and parasitic diseases.

2. Methodology

2.1. Search strategy

All studies included in the systematic review were selected according the standardized guideline PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) (Moher et al., 2009). A two-level search was designed to identify relevant studies on the influence of aging on the host response against protozoan parasites associated with human systemic protozoozes. The primary (direct) search was based on three comprehensive electronic databases in biomedical