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Pathogens Shape Sex Differences in Mammalian Aging

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Understanding the origin of sex differences in lifespan and aging patterns remains a salient challenge in both biogerontology and evolutionary biology. Different factors have been studied but the potential influence of pathogens has never been investigated. Sex differences, especially in hormones and resource allocation, generate a differential response to pathogens and thereby shape sex differences in lifespan or aging. We provide an integrative framework linking host pathogenic environment with both sex-specific selections on immune performance and mortality trajectories. We propose future directions to fill existing knowledge gaps about mechanisms that link sex differences, not only to exposition and sensitivity to pathogens, but also to mortality patterns, whilst emphasizing the urgent need to consider the role of sex in medicine.

Highlights

Years of research in biomedical sciences have revealed that sex-specific immune responses to pathogens can be associated with sex-specific consequences on health.

These effects partly account for the observed sex gap in lifespan, leading women to be longer-lived than males in human populations.

Sexual selection exerted on males and the pathogenic environment may explain, at least partly, the sex-difference in lifespan generally observed across mammalian populations.

Sex Differences in Mammalian Lifespan

In almost all human populations, and consistently throughout history, women live longer than men [1]. This pattern is pervasive in mammals [2], although the difference in **lifespan** (see Glossary) between sexes varies strikingly across species and populations facing contrasted environmental conditions [2,3]. Currently, a large body of research is devoted to the understanding of evolutionary, genetic, and physiological mechanisms that govern these sex differences in lifespan [4,5]. Differences in life-history strategies between sexes, driven by **sexual selection**, are among the most common explanations [6]. However, evidence that sexual selection mostly shapes sex differences in lifespan remains equivocal [2]. Here, we highlight that sexual selection, that is, selecting for traits and behaviors that increase male reproductive success, also leads males to be more exposed to **pathogens** than females. Moreover, earlier **aging** of the immune system can occur in males. This can lead to sex differences in aging, which can be exacerbated in pathogen-rich environments.

Up until now, the literature on the deleterious consequences of infectious diseases has focused on the deterioration of the immune system with increasing age (i.e., the **immunosenescence** process; Box 1). In humans and wild vertebrate populations, aging of the **adaptive immune system** may occur earlier in males [7,8]. These different patterns of immunosenescence could occur between sexes due to a variety of interactions between physiological factors and the local environmental context. For instance, more intense stimulation of immune defenses through a greater pathogen exposure could contribute to an earlier aging of the male immune system, leading to an earlier onset of their **actuarial senescence**. For example, HIV-1-infected individuals experience immunologic changes similar to uninfected elderly persons as a result of the continuous stimulation of their immune system [9]. However, the contribution of immunosenescence to the observed sex differences in lifespan and aging within and across mammals is yet to be deciphered. We argue that sex-specific immune responses and sex differences in energy

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 https://doi.org/10.1016/j.pt.2020.05.004

Box 1. Sex-Specific Immunosenescence

A decline in immune defense with increasing age, defining the immunosenescence process, has been highlighted in numerous species across the tree of life [8]. However, the few results available so far do not support that a sex difference of immunosenescence pattern would cause the observed sex differences of adult mortality [8,36].

Progressive deterioration of the organism results from concomitant retention (or exacerbation) of innate immunity coupled with a dysregulation (or dysfunction) of adaptive immunity [52]. For now, in all studies conducted in humans so far, a universal age-associated immune alteration is consistently observed. The number and proportion of naive peripheral blood CD8+ T cells are reduced as a consequence of the developmentally-programmed thymic involution [52]. Moreover, as the establishment of the innate immune response causes inflammation and reactive oxygen species (ROS) production that induces collateral tissue damage, we can hypothesize that the more an organism is subject to a repeated innate immune response (e.g., due to high exposure to pathogens), the more permanent the damage will be. This potentially accelerates an organism's deterioration, ultimately leading to its death. Similarly, the adaptive immune system is particularly affected by the effect of long-term exposure to a variety of antigenic stimuli. Accordingly, an adaptive immune system highly exposed to pathogens will quickly lose efficiency, leading it to exhaustion, with dramatic consequences, such as high mortality.

As increased solicitation of the immune system leads to an acceleration of its dysregulation and efficiency, we suggest that in the presence of pathogens, males undergo stronger immunosenescence than females because of their higher exposure and tolerance to infectious agents. This results in the observed higher mortality rate and shorter lifespan of males compared with females. For example, Zeng *et al.* [53] highlighted that two immune pathways, the cytokine interleukin 6 (IL-6) and toll-like receptor 3 (TLR3) proinflammatory signaling pathways, are positively associated with the lifespan of centenarian men but not women. This suggests that dysregulation of these proinflammatory pathways with age makes elderly men more susceptible to infectious pathogens than elderly women. However, while numerous researchers asked for more longitudinal studies to define more accurately immunosenescence profiles and identify the underlining mechanisms [52], sex remains overlooked in biological research despite its critical consequences in veterinarian and human medicine.

allocation strategies driven by sexual selection, leading to differences in both exposure and susceptibility to pathogens, should result in an accelerated immunosenescence in males through immune exhaustion. If this hypothesis is correct, sex differences in lifespan, through either direct (host mortality) or indirect (faster immunosenescence) effects, could be modulated according to the pathogenic environment of populations [2] (Figure 1) and have direct consequences on human as well as veterinarian medicine (Box 2). Although the sample size was limited, a preliminary analysis of currently available data supports this hypothesis, with sex differences in mean adult lifespan increasing in favor of females when pathogen richness increases (Box 3).

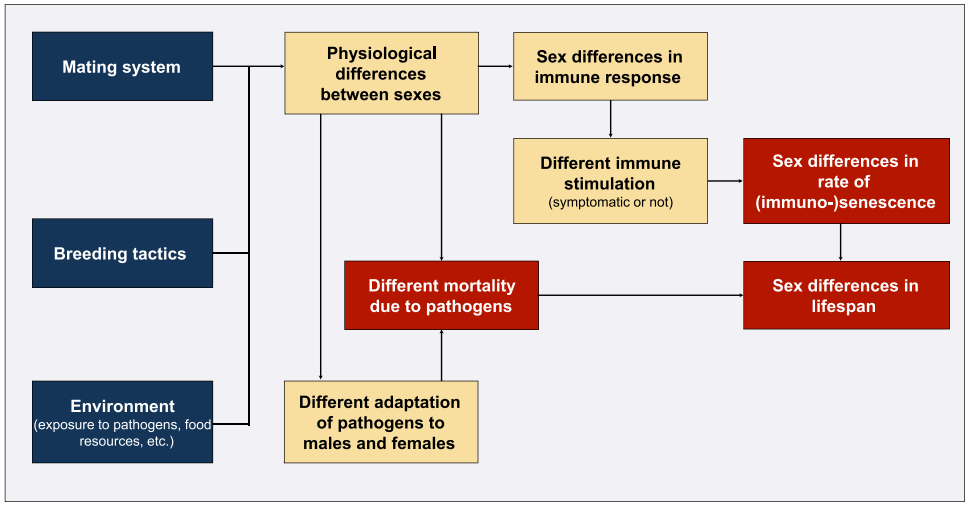

Figure 1. Different Selective Strength between Sexes Driving the Evolution of Sex Differences. These differences include those in life-history traits (blue boxes), in physiology and the immune response to pathogens (yellow boxes), and in aging and lifespan (red boxes).

Glossary

Actuarial senescence: also called survival aging. Actuarial senescence corresponds to the decrease in survival rates with increasing age.
Adaptive immune system: antigen-specific immune responses characterized by immunological memory that makes future responses against a specific antigen more efficient.
Aging: decline in the age-specific contribution to fitness throughout life. As a consequence, the aging process is mostly studied in the two main fitness components: survival and reproduction.
Immunosenescence: decline of immune parameters with increasing age, associated with detrimental clinical outcome (e.g., high risk of contracting and dying from infectious diseases).
Intensity of infection: pathogen load within an individual at a given time.
Lifespan: time interval between the birth and the death of a given individual.
Lifetime reproductive success: number of living offspring produced by an individual at some life stage (usually birth, weaning, or 1 year of age) during its entire lifetime.
Pathogen: organism that causes disease to the host. They include, in particular, ectoparasites, protozoans, helminths, viruses, bacteria, and fungi.
Pathogenesis: progression of a disease. It encompasses the complete sequence of events accompanying acute and persistent infections.
Prevalence: proportion of infected individuals within a population at a given time, which encompasses both old and new cases.
Reproductive senescence: also known as reproductive aging. Reproductive senescence corresponds to the decrease in reproductive rates with increasing age.
Sexual selection: evolutionary process arising either through mating choice (i.e., preference by one sex for certain characteristics, for example, form, color, or behavior, in individuals of the other sex) or through intrasexual competition (i.e., competition among mature individuals of one sex to monopolize access to mate with individuals of the other sex). Both ways select for a large sexual size dimorphism and extravagant secondary sexual characters, such as ornaments or weapons, when sexual selection is strong.

Box 2. The Urgent Need to Consider Sex in Medicine

Investigating the role of pathogens on sex differences in aging highlighted how much males and females differ regarding their immune system and their response to infectious diseases. In spite of this, physicians still tend to prescribe the same treatment to both male and female patients for a given diagnosis. One reason for this is that sex differences in immune functions are not yet well understood.

During the past 30 years, most biomedical research routinely used only males in both cohort and animal model studies because the cyclic hormonal fluctuations of females introduce additional experimental variation [54]. This could explain the higher number of secondary effects observed in women than in men following the commercialization of a given drug [55]. Upon vaccination, women not only develop a higher antibody immune response, but also more frequent and severe adverse side effects than men [56]. The application of sex-specific medicine is thus urgently required [55]. The American National Institutes of Health recently declared that clinical trials not taking sex-specific responses into account will no longer be funded [57].

A great deal of knowledge about sex differences in immune functions comes from laboratory animals, notably the mouse model, which have been used extensively to develop research and test therapies before they are used in humans. However, very little is known about how much information from inbred and laboratory-adapted mice can be extrapolated to mammalian immune responses in the wild [58]. First, the selection of laboratory mice has resulted in the alteration of life-history traits, such as reproduction or lifespan [59], and immunological traits of individuals. Second, as argued previously, animals' immune responses are just one dimension of a wider life-history strategy to maximize fitness within the constraints of the environmental context. Laboratory conditions strongly differ from the environment individuals face in the wild, which can have serious consequences on the immune response they mount. Comparison between male and female immune functions in wild and laboratory animals is thus crucially needed to reveal both the relevance and limitations of laboratory animals as immunological models. Linking wild and laboratory animal immunology using tools and concepts of immunology, and also of ecology and evolutionary biology, is badly needed. In that respect, companion animals, which live in the same environment as their owners and are exposed to similar pathogens [60], may potentially serve as bridges between laboratory and wild species. The affordability of new 'omic' approaches and the availability of new trusted biomarkers (e.g., antibodies, cytokines, cellular responses) and immunological reagents (e.g., monoclonal antibodies) will help to quantify male and female exposition to microbes and the dysregulation of immune parameters with increasing age in a wider range of mammalian species, aiding immunologists, ecologists, and evolutionary biologists to work together.

How Biological Differences between Males and Females Contribute to Disease Dimorphism?

As a general rule, **prevalence**, **pathogenesis**, and **intensity of infections** caused by diverse pathogens (i.e., viruses, bacteria, parasites, and fungi) are higher in males than in females in humans, domesticated animals, companion animals, laboratory rodents, and numerous species in the wild [10]. For example, in adult mice (*Mus musculus*), males display more symptoms of sickness than females when they are exposed to bacteria that cause an illness with symptoms similar to the flu [11]. In addition, women have more than 40% less HIV-1 RNA loads than men [12], while Italian men infected by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) are approximately twice as likely to die than infected women [13]. Beyond obvious morphological, anatomical, and behavioral differences (e.g., aggressiveness) that might affect exposure to pathogens, many other biological differences may contribute to observed sex differences in the susceptibility or disease progression [14]. Yet these differences remain little studied and data on the underlying biological mechanisms are surprisingly scarce, although they lead to different responsiveness to treatment between sexes [14] (Box 2).

Sex, Hormones, and Immunity

It has become increasingly clear that males and females differ in immune responses [15]. As a general rule, females exhibit greater capability of producing antibodies than males [16]. They are less susceptible to infectious diseases [15] but can develop a stronger predisposition to autoimmune or inflammatory diseases than males [15]. However, the consequences in terms of sex differences in lifespan and aging are yet to be accurately quantified [17].

Differences in disease prevalence and expression between males and females are mainly attributed to sex steroids (e.g., estrogens, testosterone, and progesterone), which, by binding to hormone

Box 3. Relationship between Sex Differences in Mean Adult Lifespan and Increased Pathogen Richness

Using between-sex differences in mean adult lifespan in 13 mammalian species (eight carnivores and five primates, Table S1 in the supplemental information online), a preliminary analysis (Figure I) reveals that between-sex differences in lifespan increases (0.335 ± 0.139, $P = 0.03$) in favor of females when pathogen richness increases. The mean adult lifespan for the 13 species was obtained from [2]. Pathogen richness is defined as the cumulative number of pathogen species inventoried (arthropods, helminths, protozoans, virus, and bacteria) for each carnivore and primate species, males and females combined (extracted from literature and standardized for a given sampling effort). Linear models have been fitted with between-sex differences in mean adult lifespan as the response variable, and pathogen richness and 'family' (Carnivora or Primates as factors) as explanatory variables. For each species considered, the number of studies inventorying one or several pathogen species was recorded as an indication of the sampling effort exerted on the species and included in the analysis: pathogen richness values correspond to the residuals of the linear model with real pathogen richness in response variable and the sampling effort as an explanatory variable.

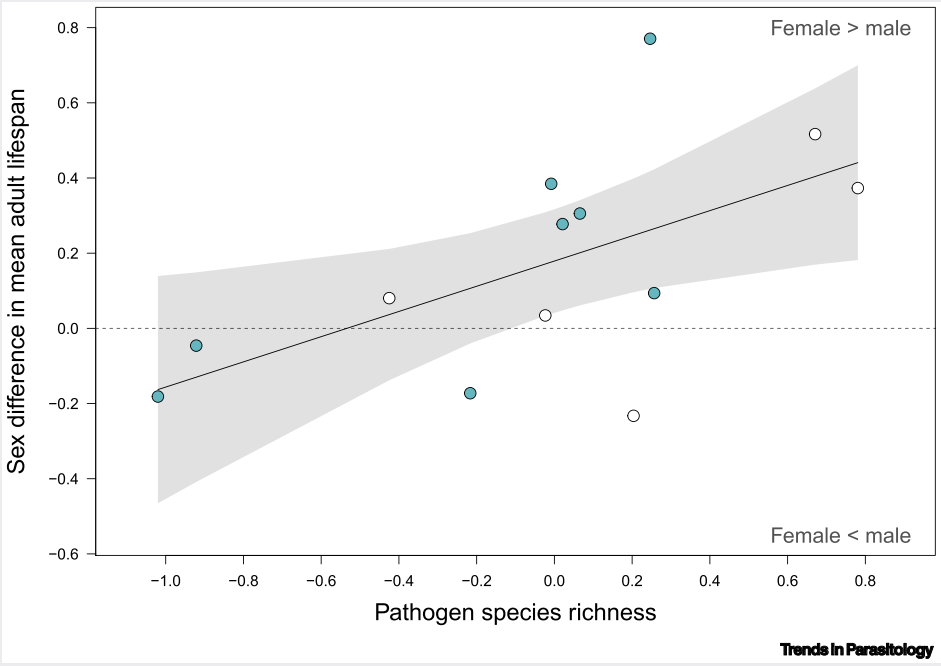

Figure I. Increase of Sex Differences in Mean Adult Lifespan in Favor of Females When Pathogen Richness Increases for Eight Carnivore (Colored Circle) and Five Primate (White Circle) Species.

receptors on the surface of immune cells, modulate in different manner the functioning of moleculesof immune system [7,15]. Most of them express multiple sex hormone receptors that drive sex-specific immune responses following antigen stimulation [7]. Males and females differ in steroid concentrations: males have a higher concentration of testosterone and females a greater concentration of estrogen and progesterone. Estrogen receptors are detected in immune cell populations, including lymphocytes, monocytes, and macrophages [18], and have an immunoenhancing effect as well as diverse protective effects [19]. On the contrary, progesterone and testosterone have mainly immunosuppressive effects [20]. Folstad and Karter [21] proposed that testosterone has, in fact, a 'double-edged sword' effect that increases the probability of mating for a male while decreasing its ability to fight pathogens. For instance, territorial male chamois (*Rupicapra rupicapra*) have almost six times more fecal androgen metabolites and are three times more parasitized during the rut period than nonterritorial males [22]. Hence, we may expect that males will develop stronger disease symptoms, resulting in a lower probability of survival, and consequently increased between-sex differences in lifespan in pathogen-rich environments. However, inconsistencies among studies of vertebrate species (e.g., Cape ground squirrels, *Xerus inauris* [23]) suggest that testosterone is not the whole story.

Immune System and Reproduction

Major physiological changes occur during reproductive seasons or cycles. Typically, testosterone production is increased in males when competing for fecund females, while pregnancy induces a decrease in estrogen and an increase in progesterone concentration to avoid the immunologic aggression of the fetus [24]. However, infectious diseases that are acquired during pregnancy or lactation are often associated with lower birth mass and reduced breast milk in humans, suggesting that females reactivate the formally quiescent immune system [25] to combat infection at the expense of reproduction. For example, women who contract malaria during pregnancy have higher circulating levels of proinflammatory cytokines, which in turn are associated with lower birth weight [26]. This suggests that females should show a lower **lifetime reproductive success** in an environment with high pathogenetic load, but their lifespan should be much less affected than that of males.

The Evolutionary Roots of Sex Differences in Response to Pathogens

From an evolutionary viewpoint, the immune response is a key fitness-related trait, but the energy it requires should inevitably be traded for allocation to life-history traits governing other biological functions [27]. For instance, the growth and maintenance of secondary sexual traits impair male immune performance through a resource-based allocation trade-off [28], making them more sensitive to pathogens [29] (Figure 1). Many observations in rodents, birds, and insects document substantial energetic, reproductive, and survival costs of immune activation [30]. Hence, organismal responses to pathogens should involve sex differences, given that the optimal solution to the trade-off between reproduction and survival differs between sexes, with females allocating more than males to their immune responses in order not to jeopardize their survival, thereby increasing their lifetime reproductive success [27]. We can even expect that iteroparous females should rapidly redirect their energy to immune functions at the expense of fetus/offspring survival when exposed to a pathogen during pregnancy. The optimal strategy should be radically different in semelparous females who only have one opportunity to reproduce. For example, parasite removal reduces reproducing female survival in the Taiwan field mouse (*Apodemus semotus*), possibly by allowing breeding females to increase maternal investment (i.e., allocation at the cost of their future survival [31]). By contrast, in males, immune performance is impaired by the growth and maintenance of secondary sexual traits, which makes them more sensitive to pathogens [28]. In mice, increased aggression is costly and is associated with reduced resistance to disease [32]. As a consequence, sex differences in lifespan should increase in favor of females when pathogen load increases (Box 3).

Finally, males and females correspond to markedly different environments for pathogens, which may shape their evolution. Hence, the observed sex-biased disease prevalence and/or severity might be the result of the parasite having adapted to grow in a specific host sex [33]. Úbeda and Jansen [34] formalized this idea and suggested that natural selection can act differently on pathogens in males and females depending on the transmission route of the pathogen. In Japan, where the transmission of HTLV-1 (human T cell lymphotropic virus type 1) occurs through breastfeeding rather than through sexual transmission, the progression to adult T cell leukemia is slower in women than men. Sex-specific adaptation of HTLV-1 to preserve women as a viral route could be a potential explanation for this puzzling observation [34].

The Need to Consider Sex-Specific Immune Performance and Pathogen Exposure in Evolutionary Biology

Challenges within Species

The immune system includes many different immune cell types, each having its own unique function, and collectively protecting the host against pathogens. The reliable measurement of multiple markers of both immunity (e.g., cellular components, T cell repertoire) and aging (e.g., epigenetic markers of biological age [35]) remains challenging. However, such data are required to allow a

better understanding of the ecological (pathogen exposure) and evolutionary forces that shape the sex-specific decline of immune responses and between-sex differences in lifespan. Ideally, these measures should be made in wild populations that display a large variation in the magnitude of sex differences in lifespan [2] because of differential risk-taking behavior, food requirements, mortality due to direct sexual competition, or exposition to commensal and pathogenic organisms. Longitudinal studies are thus required to assess how immunosenescence patterns are shaped according to sex (e.g., [36] and references in [8]) and also to identify mortality causes, which allows deciphering the different ways through which pathogens reduce individuals' lifespan (through early deaths from lethal diseases or through advanced immunosenescence due to immune exhaustion). This has rarely been investigated in wild populations yet ([37] being an exception).

Even though studies of rodents (reviewed in [38]) show that reaching this aim is possible in wild populations, it remains a complex task. Populations living in protected conditions (e.g., wild species in zoos, domestic animals and companion animals living with humans, laboratory animals) would offer excellent simplified systems to explore more deeply the deterioration of immune functions with increasing age and its role in between-sex mortality patterns, [39] provides an example in mice. This would allow an investigation into how the level of pathogen exposure, as well as the virulence of pathogens to which hosts are exposed, shapes the immunosenescence profile and, thus, the mortality rate and lifespan of males and females. Captive mammalian populations could also provide insightful information on the potential effect of chronic and putatively asymptomatic infections on the differential rates of immunosenescence between sexes, which is currently totally underestimated. Research on human health has provided important and somewhat unexpected results in this field. Notably, chronic infection by the common CMV (cytomegalovirus) is involved in the remodeling of the immune system. Hence, chronic exposition to any microbial agent (i.e., not only known pathogens) could be involved in shaping sex-specific immunosenescence [40]. Only long-term monitoring of individuals from birth to death, in which wherein molecular and cellular markers of adaptive and innate functions are recorded repeatedly throughout an individual's lifetime, together with reliable estimate of the infection date, will allow a deeper understanding of the influence of age and sex on immunosenescence in relation to microbial agent exposure.

Additionally, the comparative analysis of populations within a single species occupying multiple habitat types can offer important insights into the intraspecific variation in immunosenescence and its consequences on life-history traits, such as lifespan, in both sexes. Selection is expected to produce the immune response that maximizes individual fitness, in interaction with other selective pressures imposed by the environmental context (i.e., resource availability, weather conditions), the social and mating systems, and the pathogen exposure. Thus, the immune system of rodents from different populations and environments in the wild differs from that of laboratory rodents, the former being continuously exposed to commensal and pathogenic organisms (reviewed in [38]). It would thus be interesting to evaluate how such excessive energetic demands to activate the immune system compromise other fitness components of laboratory rodents according to their pathogenic environment, notably actuarial senescence patterns, and to investigate whether these effects are sex-specific.

Interspecific Comparisons

Taking into account the evolutionary history of mammals, their pathogen species richness, which varies largely across species [41], may help explain between-sex differences in lifespan. In the presence of numerous pathogens, males from species subjected to strong sexual selection should be more exposed to pathogens compared with females than males from species with a low sexual selection [42]. This could partly explain sex differences in immunosenescence (e.g., [8]) and highlight how these differences are likely determined by fine-scale interactions between sex-specific physiological pathways and the local environment in pathogens [2].

Variation in pathogen richness, infection rate, and pathogen load correlates with numerous morphological and ecological traits, mostly driven by sexual selection, which are also related to the lifespan variation in mammals [43]. Among these traits, variation in host body size [44], mating system and sexual size dimorphism [42], MHC allelic diversity [45], geographical range [46], social group size [47], population density [48], and phylogeny [6,41] have been identified as playing a role. However, most cross-species studies that investigate the interaction between pathogens and host ecological and life-history traits performed to date did not include between-sex differences in pathogens or their consequences in terms of sex-specific lifespan (e.g., [49]). Although male-biased parasitism is positively correlated with the level of polygyny in mammals [42], the level of polygyny also correlates with a shorter lifespan and a more pronounced aging in males compared with females, at least across captive populations of large herbivores [6].

All of these challenges will be made possible thanks to databases, gathering longitudinal data that measure accurately sex differences in lifespan, which are becoming increasingly available (e.g., [2]). Several databases recording the number of pathogen species found in mammals, such as the World Register of Marine Species (WoRMS[i]), Pathogen–Host Interactions (Phi-base[ii]) [50], or the Database of Bat-associated Viruses (DBatVir[iii]) [51], have been developed. These databases provide a large amount of information about the diversity and the richness of parasites across mammalian species displaying contrasted lifestyles. Combining these databases should allow better understanding of the role of pathogens in between-sex differences in lifespan and aging (e.g., in terms of both onset and rate of actuarial and/or **reproductive senescence** patterns) across mammalian species (Box 3). In our view, this information should inform on how pathogens shape sex differences rather than how sex differences shape responses to pathogens because the magnitude of sex differences seems to be context-specific [2]. Thus, it might be difficult to envisage mammals evolving differential responses to pathogens mediated by sex differences if the magnitude of sex differences is so labile.

Concluding Remarks

Understanding the determinants of differences in male and female outcomes is becoming a crucial, recognized challenge in infectious disease research in humans as well as in veterinary clinical research, such as identifying the true contribution of pathogens to overall mammalian mortality. Available information so far calls for an appropriate inclusion of sex differences over the whole human lifespan to anchor medicine in the real word (Box 2). Longitudinal studies combining detailed immunological and nonimmunological follow-ups for individuals of each sex should help to understand aging of the immune processes and how it differs between sexes and environments. By taking into account the evolutionary history of mammalian species, such a holistic approach could help explain between-sex differences in lifespan. For instance, studies should focus on consequences of resistance and tolerance to pathogens on lifespan across mammals (see Outstanding Questions). We encourage the scientific community to adopt this holistic approach, which is necessary in order to embrace all the methodological, theoretical, and conceptual challenges raised by pathogens regarding sex differences in lifespan. The increasing availability of required data offers great opportunities to formulate and test new hypotheses.

Outstanding Questions

What is the true contribution of pathogens to overall mammalian mortality?

Do between-sex differences of immunosenescence really occur in mammals?

Is there a differential effect of resistance and tolerance on between-sex differences in lifespan across mammalian species in relation to variation in generation time?

Do immunosenescence patterns vary with the intensity of pathogen exposure?

Are sex-specific immunosenescence patterns associated with between-sex differences in lifespan and aging across mammals?

Acknowledgments

This work was supported by the Laboratoire d'Excellence (LabEx) ECOFECT 'Eco-Evolutionary Dynamics of Infectious Diseases' (ANR-11-LABX-0048) of Université de Lyon. We thank three anonymous referees for their helpful comments.

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.pt.2020.05.004.

Resources

[i]www.marinespecies.org/

[ii]www.phi-base.org/

[iii]www.mgc.ac.cn/DBatVir/

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