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The evolution of greater humoral immunity in females than males: implications for vaccine efficacy

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Abstract

Males and females differ in their effector and memory immune responses to foreign and self-antigens. The difference in antibody responses (i.e., humoral immunity), in particular, is one of the most well conserved sex differences in immunology. Certain sex differences in humoral immunity are present throughout life, whereas others are only apparent after puberty and prior to reproductive senescence, suggesting that both genes and hormones are involved. Importantly, these sex-based differences in humoral immunity contribute to variation in the responses to vaccines and may explain some disparities in vaccine efficacy between the sexes. Elevated humoral immunity in females compared with males is phylogenetically well conserved, suggesting an adaptive advantage of elevated antibody for reproductive success, including for the transfer of protective antibodies to offspring.

Keywords

antibody; B lymphocyte; estrogen; immunization; influenza; X chromosome

The term ‘sex’ is a biological construct that defines males and females by the basic organization of chromosomes, reproductive organs, and circulating sex steroid hormone concentrations. There is a growing appreciation that sex is a biological variable that can impact immune responses through genetic and hormonal regulation of immune cells [1]. One of the most well conserved immunological differences between the sexes is in antibody responses to foreign antigens [2]. Generally, among adults of reproductive ages, females have greater antibody responses than males, higher basal immunoglobulin (Ig) levels, and higher B cell numbers [3–5]. Adult females also have higher antibody responses to diverse vaccines against, influenza, hepatitis B, yellow fever, rabies, herpes, and smallpox viruses [2]. Higher antibody responses to vaccine antigens imply that the efficacy of vaccines should be greater in females than males, which has not been adequately analyzed in

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Conflict of interest statement

Nothing to declare

epidemiological studies. The phylogenetic and ontogenetic development of sex differences in humoral immunity illustrate that this conserved immunological difference between the sexes has functional significance, including for vaccine efficacy, and is profoundly affected by both genes and hormones.

Ontogeny of sex differences in humoral immunity

The effects of age on the humoral immune response to vaccination are well documented, yet very few studies consider both age and sex as biological variables. Sex differences are most profound in individuals after sexual maturation, and the underlying mechanisms for these differences have been attributed to both hormonal and genetic effects on the immune system. However, the interplay between age, specifically prior to sexual maturation and following reproductive senescence, and the differential outcomes between the sexes following immune stimulation requires greater consideration.

Pre-puberty

The humoral immune response to vaccinations in children prior to puberty is functionally and quantitatively different compared with that of older children and adults. After birth, infants are exposed to various foreign antigens and their immune system functions to reach a balance between immunotolerance and immunoreactivity. The CD4+ T cell responses in infants are skewed toward anti-inflammatory T-helper (Th)-2 and T-regulatory (Treg) responses, correlating with a lower capacity of antigen presenting cells to produce Th1 polarizing cytokines [6]. The B cell arm of the adaptive immune response also differs between young children and adults. Naïve B cells in infants have lower expression of the co-receptors CD80, CD86, CD40, and HLA-peptide, that interact with T cell ligands during T cell-dependent B cell activation and production of antibody [7,8]. Infants also have lower levels of CD21, the receptor for the C3 complement activation component C3d, which also dampens T cell-dependent B cell activation and impairs germinal center activation [9]. Furthermore, early-life B cells show decreased somatic hypermutation, and bone marrow stromal cells fail to support long-term plasmablast survival and differentiation into plasma cells [10,11]. As a result, infant antibody responses are generally delayed, have lower affinity for the target antigen, and decline more rapidly than those elicited in adults.

There are few reports of sex differences in the humoral immune response in infants and children prior to puberty. Numbers of B cells and levels of IgG and IgM are equivalent between the sexes; whereas infant males are reported to have higher IgA and IgE than females [1]. Sex differences in the B-cell activating factor (BAFF) are present in cord blood from infants, with girls having greater levels of BAFF at birth than boys [12]. The sexes differ in immature/naïve CD5+ B cells during the first three years of life, with boys having greater proportions of CD5+ B cells at birth to 5 days, 4 months, and 36 months of age relative to girls [12]. The observed combination of lower levels of BAFF and higher proportions of CD5+ B cells in boys as compared with girls suggests that sex differences in the humoral immune response may be present at birth, with boys having a more immature/naïve immune system, in general.

Reproductive Ages

Adult females of diverse species tend to have higher antibody responses than males [1]. In adult nonhuman primates, following vaccination against simian immunodeficiency virus (SIV), females show increased local IgA antibody titers, numbers of memory B cells, and numbers of plasma cells as compared to males [13,14]. SIV-vaccinated females also have elevated levels of virus-specific IgG1, IgG2, and IgG3 antibodies as compared to males, with anti-SIV IgG3 antibody levels correlating with antibody mediated cytotoxicity and phagocytic activity, suggesting that the quality of the antibody response is greater in females than males [13]. Studies in mice further illustrate that following vaccination or challenge, females develop higher systemic and mucosal antibody responses than males [15], suggesting that mice are a representative model to study sex differences in humoral immunity.

In humans, global analysis of B cell gene expression signatures reveals that the majority of genes differentially expressed between the sexes are significantly upregulated in B cells from adult females compared with males [16]. Whether these differences in B cell activity reflect intrinsic, genetic differences in B cells between the sexes, or environmental factors, such as hormones, that regulate the functioning of B cells requires greater consideration. The observation that estrogen induces somatic hypermutation and class switch recombination in B cells via the upregulation of activation-induced deaminase, which contains an estrogen response element [17], illustrates that the hormonal milieu can have profound effects on the regulation of B cell activity and antibody production.

Reproductive Senescence

The period of reproductive senescence overlaps with a profound remodeling and decline of the immune system [8]. Changes in the humoral immune response during aging are associated with an increased susceptibility to infectious diseases and increased morbidity and mortality in older adults [18], but the extent to which the age-related decline in the humoral immune response differs between the sexes is poorly understood. Males and females appear to experience the same immune related changes with age, but these changes occur earlier in males as compared with females. For example, males experience a more dramatic decrease in total numbers of T and B cells and larger increases in senescent CD8+ T effector memory cells that re-express the naïve marker CD45 RA (T_{EMRA}) as compared with females [19–23]. In addition, a greater proportion of aged males than females demonstrate an inverted CD4:CD8 T cell ratio, an age-related phenotype that is also associated with decreased levels of CD19+ B cells and CD8+CD28- senescent T cells [20]. In contrast, aged females have greater numbers of age associated B cells (ABC) than young females and males of all ages [24,25]. This phenomenon has also been reported in animal models where investigators determined that the mechanism of ABC induction relies on the presence of toll-like receptor 7 (TLR-7) signaling [25,26]. The TLR-7 gene is located on the X chromosome, has biallelic expression in B cells, and may explain how numbers of ABCs are greater in females than males [25,27].

The hormonal milieu changes dramatically with age, in which ovarian function in women and the testicular production of sex steroids in men both decline over time, but at much

different rates [28]. In females, the hormonal changes during menopause, specifically declining levels of estrogen and progesterone, occur rapidly [29]; whereas in males, the reduction in testosterone is much more gradual [28,29]. Changes in sex steroid concentrations as well as sex steroid receptor signaling likely contribute to the age and sex-specific changes and dysfunction in the humoral immune response [30]. The hormonal changes associated with menopause (surgical or naturally occurring) in females are directly associated with increased concentrations of proinflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) and decreased numbers of T and B cells [31–33]. Furthermore, the use of hormone replacement therapy in post-menopausal women is known to increase numbers of circulating B cells and reduce baseline concentrations of proinflammatory cytokines as compared to post-menopausal women who are not receiving hormone replacement therapy [32,34]. Males experience a similar decline in numbers of circulating B cells with age but whether or not this is directly a result of decreased testosterone levels has not been determined.

Functional significance of sex differences in humoral immunity for vaccines

Increased susceptibility to infections in infants has led to the development of many vaccines that provide protection prior to exposure. Sex differences have been reported in the antibody responses to many childhood vaccines, however these data are conflicting and limited by the number of studies that report the sex of the individuals and/or partition their data by sex. Antibody responses to diphtheria, pertussis, hepatitis A, hepatitis B, pneumococcal, rabies, human papilloma virus (HPV), and rubella vaccines, as well as to the candidate malaria vaccine RTS,S/ASO2 are higher in girls as compared with boys [1,35–39]. Sex differences have also been reported in the antibody responses to the measles vaccine where girls have higher titers as compared to boys, however these data are inconsistent and depend on the vaccine formulation [40]. In contrast, no sex differences have been observed in antibody responses to infant whole cell and acellular pertussis, infant diphtheria and tetanus, meningococcus A and C, or varicella vaccines in children [36,39,41].

Sex differences in the immune responses to vaccines in adults of reproductive ages are well documented, in which females consistently generate greater antibody responses to both live and inactivated vaccines (e.g. influenza, hepatitis B, yellow fever, rabies, herpes, and smallpox) as compared to males [1]. Sex difference in the antibody responses to influenza vaccines are particularly well studied where elevated neutralizing antibody titers are observed against H1N1, H3N2, and influenza B viruses. In adults aged 18–49, receipt of either a half dose or full dose of the seasonal trivalent inactivated vaccine results in hemagglutination inhibition antibody titers that are twice as high in females as compared with males [42]. In response to the hepatitis B vaccine males have an increased nonresponse rate and a more rapid decline in antibody titers with age as compared with females [43].

In aged individuals, sex differences in antibody responses to vaccines are less consistent and depend on the vaccine antigen. Among individual 65+ years of age, hemagglutination inhibition antibody titers to both the standard and high dose seasonal trivalent inactivated influenza vaccine are significantly higher in females as compared to males [44]. In contrast,

aged males have higher antibody responses to the tetanus diphtheria and pertussis vaccines as well as the 7-valent and 23-valent pneumococcal vaccines [45–49]. The variability observed in the sex differences in responses to vaccines in the elderly are likely a reflection of both biological and behavioral differences between the sexes. Furthermore, the evidence for sex-specific differences in both the rate at which the immune system ages and the differential changes in immune cell populations between the sexes during aging, highlights a need to better consider how age and sex impact the immune responses to vaccines administered to the elderly.

A very limited number of studies have evaluated the impact of sex steroids on immune responses to vaccines. Estradiol, at physiological concentrations, can stimulate antibody production by B cells [50], including antibody responses to an inactivated influenza vaccine administered in mice [51] suggesting one possible mechanism mediating higher antibody production in females, at least prior to reproductive senescence. In humans, reduced neutralizing antibody responses to influenza vaccination are correlated with higher serum testosterone concentrations [5]. Elevated testosterone concentrations in males are also associated with greater lipid metabolism, suggesting that the immunosuppressive role of testosterone and the reduced antibody responses to vaccines in males may be mediated by the expression of genes involved in lipid metabolism that are associated with the suppression of inflammatory responses [5].

Phylogeny of sex differences in humoral immunity

Sex differences in humoral immune responses have evolved in diverse species. In birds, for example, females exhibit higher antibody and cell-mediated immune responses to immune challenges and these effects are often most pronounced during the mating season when male testosterone concentrations are highest [52,53]. Mounting adaptive immune responses that are necessary for clearance of microbes requires metabolic resources that might otherwise be used for other biological processes, such as growth, maintenance of secondary sex characteristics, and reproduction. Trade-offs likely exist for life strategies that impact survival and reproduction [54]. Several theories posit that increased microbial loads and reduced immune function among males are an adverse side effect of positive selection for other traits or characteristics, such as aggressive behavior and the development of male secondary sex characteristics, that increase reproductive success and survival [54].

Although considerable attention has been paid to the evolution of reduced immunity in males, less attention has been paid to the evolution of greater immunity in females. When offspring are young (i.e., during the neonatal period), their immune system has not matured (see above), and protection against infection is primarily mediated by passive immunity from maternal-derived IgG antibodies against microbes. In humans, a majority of maternal antibodies are transferred into fetal circulation, prior to birth, through the placenta [55]. In some mammals, transfer of maternal antibodies can also occur through colostrum immediately following birth and in milk for a long duration after birth [55]. Regardless of species, elevated production of antibodies caused by either vaccination or infection of females enhances the transfer of antibodies to the fetus or neonate to protect them during a critical period of infectious disease susceptibility. We postulate that natural selection favors

increased antibody production in females compared with males of reproductive ages because transfer of maternal antibodies from mother to young increases reproductive success by minimizing the detrimental effects of infection on offspring survival.

Concluding remarks

Males and females are biologically different, which impacts adaptive immune responses to diverse antigens, including vaccine antigens. The mechanisms mediating these differences, both hormonal and genetic factors, can alter humoral immune responses to vaccination and may result in sex-specific difference in vaccine efficacy across the life course. Consideration of sex differences in the design of vaccines, including those that protect against influenza, may increase vaccine efficacy. The evolutionary advantage of elevated humoral immunity in females might be the ability to transmit antibodies generated against specific microbes across the placenta and in milk to protect offspring early in life when they are most susceptible to infectious diseases.

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Highlights

- Among vertebrates, females develop higher antibody responses to diverse antigens than males.
- Sex differences in antibody responses are reported across the lifespan, but are greatest during reproductive ages (i.e., after puberty and prior to reproductive senescence).
- Sex differences in humoral immunity likely involve both genetic and hormonal influences that differentially impact B cell functioning in males and females.
- Higher B cell activity, including antibody production and activity of memory B cells, in females might improve vaccine efficacy in females compared with males.
- The evolutionary advantage of elevated humoral immunity in females might be the ability to transmit antibodies generated against specific microbes across the placenta and in milk to protect offspring early in life when they are most susceptible to infectious diseases.