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Review Article

Analysis of Sex Differential Immunity and its Impacts on Health: A Comprehensive Review

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Abstract— Sex as a bio-variable affects both male and female immunity. Immunologically and phylogenetically both males and females are separated in terms of their innate and adaptive immunity and responses to self and non self antigens also and there are several influencing factors involved. Some sex differences in immune responses persist life long, while others become visible only after adolescence and before old age , indicating many immune regulatory genes(those on sex chromosomes) and sex hormones are equally engaged. There are four different life stages viz. fetal stage, childhood, adolescence and aging stage are characterized by sex differential levels of immunocytes, sex hormones and immune responsiveness . In addition ,microbiomes are influenced by early environmental exposures that also leads to sex differential immune responses. As well as micronutrient supplementations provide female-biased immunity. Henceforth, these sex differential immunity leads to variations in the frequency of some immunosuppressive diseases such as diseases caused by autoimmunity and malignant cancers, proneness to communicable diseases. Similarly differential vaccine efficiency are also seen in men and women and these differences affect their overall survival.

Keywords— Sex, Innate immunity, Adaptive immunity, Genetic factors, Hormonal factors, External factors, Immunosuppressive diseases, Vaccine

1. Introduction

Sex is a set of bio-attributes in animal kingdom . It becomes effective on immunity when exposing self and non-self antigens (e.g. antigens from pathogens & allergens). Sex and gender is different from each other in that the former is designated as the discriminatory association of chromosomes, sex organs, and sex hormones whereas later include some specific attitudes and functionalities those are already fixed in human civilization. Although both sex and gender influence the immune response but sex playing major roles to discriminate physiology and morphology, so the living organism is being to be exposed, recognise, and transmit microbes sex differentially, while gender showing some manners that lead to either increase or decrease the chances of infection.

Evidences showed males and females have immune responses to various diseases are quite different. E.g. 80% of autoimmune diseases and inflammatory diseases occur in women rather than men. Men exhibit approx 2 times greater chance of mortality from life-threatening cancers but these are comparatively low in women. Sex chromosomal genes and sex steroids may also influence the pathogenicity of such diseases sex-differentially . Previous studies also determine that women have enhanced vaccine efficacy and ability to faster pathogenic clearance than in men probably due to stronger feminine innate and adaptive immune responses. As well as women show adverse side effects following vaccination rather than men. Apart from non-communicable diseases, males are more prone to communicable i.e. infectious diseases than females (most mammals). If we look back at the time of birth, it will be seen that male babies are severely threatened from septicemia [1]; chances for developing phthisis (also known as TB) are greater in men from childhood to last of the adult stages in compared to women . Nutritional status of male fetuses and infants may also lead to their immunosuppressiveness. Men suffered from various bacterial and viral diseases severely, for instance, pulmonary diseases(COVID 19, MERS, Legionellosis, Aspergillosis etc.), gastrointestinal diseases (Amoebiasis, Schistosomiasis, Hepatitis B etc.). Many immune-related diseases are implicated with genetic, hormonal and other factors, so this comprehensive study is important for conceptualization of proper and factor-based sex-specific treatments/ therapeutic interventions. For that, this review paper is attempted to find out some important informations about sex differential immunity and there involving

hormonal, genetic and environmental/external factors that affect the immune system.

2. Methodology

This review provides many useful facts regarding sex differential immunity. For these, the author searched previous experimental and non experimental studies through these internet databases — Google scholar, PubMed, Researchgate, Science Direct in the search engine. Research articles published from 1965 and 2021 are searched and the final dataset is prepared.

3. Analyses

3.1. Evolutionary Analysis of Sex Differences in Immunity

Previous theories indicate that males are less immunocompetent thereby causes high microbial infection that adversely affects on some traits or characteristics that indirectly responsible for increment of breeding success and existence. Evolutionary changes occurred in the immunity in both sexes of different small to large sized organisms at the prehistoric period of life; it has been seen that males exhibit drastically reduced inborn and acquired immunity in compared to females (All species). For instance, fruit fly, *Drosophila melanogaster* , showing genes on X chromosome that encoding different immune regulatory molecules having sex-biased immune responses to any pathogenic infection [2]. Another fly viz. scorpion fly (*Panorpa vulgaris*) shows high levels of hemolysis and phagocytosis in females rather than in males [3]. But some bivalved molluscs represent slightly different scenarios — male oysters (in case Hong Kong Oyster ,*Crassostrea hongkongensis*) show greater number of immunocompetent haemocytes than females , suggesting that males after completion of breeding stage represent strong immunity in compared to female oysters [4]. In case of sea urchin (*Paracentrotus lividus*), females show greater number of immunocytes , higher cytotoxic, phagocytic and haemolytic activities than that of males [5]. In case of lizards (for instance , *Podarcis muralis*) female lizards exhibit higher degree of phagocytosis performed by macrophages than male lizards resulting from high androgenic influences on male phagocytes [6]. Similarly in certain avian species, immunoglobulin functions and cellular immunity are greater in females and such type of immune effectiveness have become increased at the seasonal period of mating while androgenic concentrations being superior [7]. Likewise, human females also exhibit greater innate and adaptive immune responsiveness (humoral and cellular immune responses) than males [8].

3.2. Analysis of Innate Immune Responses in Both Sexes

Aforementioned that sexual disparities occur in the class – Mammalia. Two sexes of all species are discriminated in terms of their inborn immunity, that indicate the germlines somehow encoding certain sexual distinctions; e.g. Pathogen associated Molecular Patterns (PAMPs) are triggered by pattern recognition receptors (PRRs) sex differentially . Proteins translated from X-linked Toll like Receptor 7 (TLR7) genes are highly expressive in feminine organisms. In vitro study reveals that when TLR 7 ligands bind to peripheral blood mononuclear cells (PBMCs) as a consequence, interferon – alpha(IFN- alpha) generated largely in these cells in females in comparison with males [9]. Plasmacytoid dendritic cells (pDCs) in women show enhanced level of TLR7 expression and interferon-alpha production than men. Previous genetic studies reported that sexual differentiations in the genetic expressions occur in toll-like receptor pathways that induce interferon-1 responsiveness. Thereby if adult humans get vaccinated or viral infection occur in adult rats, then certain genes that are responsible to up-regulate inflammation(e.g. toll-like receptor 7, interferon-gamma, interferon regulatory factor 7, RIGI, interferon-beta, NF-kB ,etc.) and toll-like receptor signaling cascades will highly expressed in case of females than that of males [10]. But it has also evidenced that TLR9 stimulated PBMCs produce higher levels of IL-10 in males than that of females . Sex differential neutrophilic expressions also occur –male neutrophils represent greater degree of expression of toll-like receptor 4 and generate adequate tumor necrosis factors after activation with LPS (Lipopolysaccharide) [11]. Male mice peritoneal macrophages exhibit greater degree of TLR4 expression alongwith generate larger amount of CXCL10 after activation with lipopolysaccharide than feminine peritoneal macrophages. Due to masculine innate immunocompetent cells showing such results hence these cells produce cytokines that are responsible to up-regulate inflammation enormously after activation with lipopolysaccharide ,whereas feminine innate immunocompetent cells express toll-like receptor 7 greatly in compared to males resulting higher generation of cytokines in them and there involves sex chromosomal expressiveness. Males have relatively high number of natural killer (NK) cells. Level of phagocytosis induced by feminine neutrophils is higher than male neutrophils. APC efficacy in presenting antigenic peptides is simultaneously greater in women but lower in men (Figure 1).

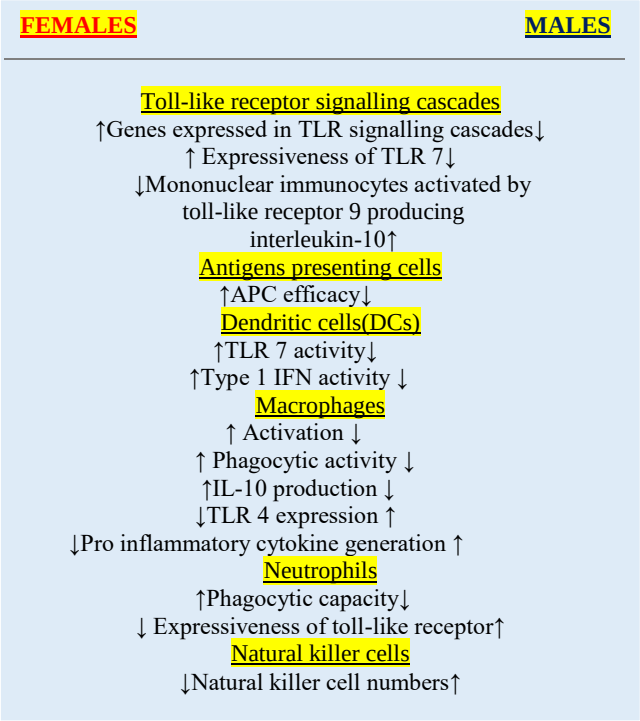

Figure 1. Sex differential innate immunity in adults

3.3. Analysis of Adaptive Immune Responses in Both Sexes

Sexual dimorphisms in adaptive immunity was reported in several studies. The thymus, a central lymphoid organ take a part to constitute adaptive immunity and generating mature T cells that are circulated throughout the blood and lymphatic vessels. Notably, male rats (initial stages of life) having macro thymuses , higher thymic cell numbers than female rats and show sex differential distribution of thymocyte subsets [12] .

Between the two subsets of T cell, T_H (helper)cells (containing surface molecule– cluster of differentiation 4(CD4)) and CD4/CD8 proportions are higher in females (both children and adults) than males of same age groups , while males showing greater T_C (cytotoxic)cell counts (containing surface molecule – cluster of differentiation 8(CD8)). Previous studies reported that activated peripheral blood mononuclear cells enhance the counts of stimulated T_H and T_C cells , respectively and T cell proliferation in human females than males. The functionality and dissemination of T_H cell subpopulations are sexually different. Females (using a model of mature mouse) generate more cytokines (e.g. IFN gamma) derived from T_H 1 cells than males in such protozoan diseases, including cutaneous leishmaniasis and African rodent malaria and males are less secured in these diseases. Again, females have higher levels of cytokines (such as, interleukin-4, interleukin-10) derived from T_H2 cells than males in such cases during which human PBMCs become polyclonally activated with mitogen phytohemagglutinin (PHA) and female PBMCs produced and released these cytokines . T helper 1 and T helper 2 cell biasness occur in men and women , respectively with women are more biased to T helper 2 cells whereas men show T helper 1 cell biasness. T_H0 cells produce preferentially IFN gamma in females and IL-17 in males depending upon how much T cells are active and pure. Regulatory T cell (T_{reg}) study in different sexes in both mice and humans show discriminatory results where, in mouse , regulatory T cells are involved in several organ malfunctioning but analyses on man reveal that healthy men have more regulatory T cell counts than women . T helper 2 cell biased females generally have more B cell counts; greater antibody responses as well as higher basal immunoglobulin concentrations than males, irrespective to age (Figure. 2).

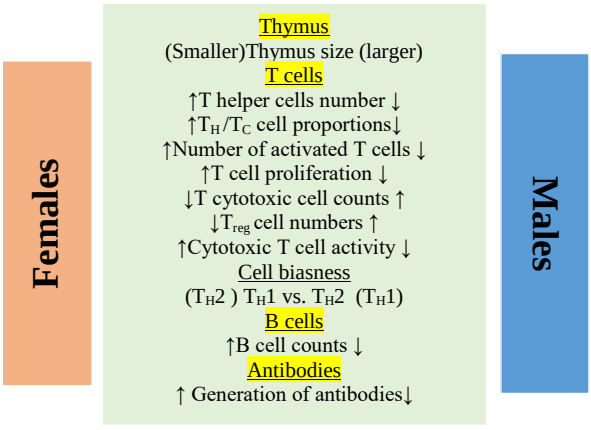

Figure 2. Sex differential adaptive immunity in adults. CD, cluster of differentiation; T_{reg} , regulatory T cell; T_H , T- helper cell

4. Impact of Genetic Factors on Sex Differential Immunity

4.1. Sex chromosomes

In humans, males have heterologous sex chromosomes (XY) and females have homologous (XX). The human Y chromosome consists of almost 100 genes, containing SRY and other immune response regulatory genes [13]. On the other hand, human X chromosome is composed of 1000 + genes, which is approx five percent of the human genome alongwith contain some important immunoregulatory genes , for example, TLR7, TLR 8 , GATA1 , IRAK1, CD40 L, FOXP3 etc. Approx 54 functional genes have been estimated that are homologous to both chromosomes . DNA of these sex chromosomes to be exchanged at the pseudoautosomal regions (PARs)to maintain correct segregational events in masculine meiotic division (PARs – tiny regions of homologous sequence situated at the apex of sex chromosomes of mammals). Both X and Y chromosomes of human contain one pair of PARs – PAR1 (location –terminal part of p-arms(short arms)) and PAR2 (location –terminal part of q-arms (long arms)). PARs of both sex chromosomes contain 29 homologous genes, and the remaining genes are present in the region where recombination doesn't occur. X-linked genes that are present exterior to PARs, in which one set of genes become silent that assure only one set of genes become active in each sex. X chromosomes contain X inactivation centre (XIC) that is located in the q-arm and consists of *XIST* gene that initiate silencing. The p-arm is involved in translocation with autosomes.

However many genes get away X chromosome silencing in both human and mouse and the percentage of such genes are slightly greater in humans than that of mice. Females have gradually larger number of copies than males. Several X genes control immune function and take part in modulation of sexually differentiated progression of immunocompromised diseases . Human Y chromosome contains several immunoregulatory genes which play pivotal roles in autoimmunity and communicable diseases and polymorphic Y chromosome affects sex dependent susceptibility to viral infections [13].

Activity of female X genes enhance and over responsive their immunity. As feminine sex chromosomal complement is XX so there will be a chance to develop dual dosage effects of proteins. But actually this is not happens , single X chromosome is only active and continue to perform all biological functions lifelong from the initial embryonic stages of females and to avoid double dosages of proteins. Due to X inactivation (The procedure held in eutherian females where single X chromosome is genetically inexpressive between the two and the other remains active throughput the life assuring the similarity between the expression of feminine and masculine X genes) females develop cellular mosaics i.e. approx. 50% cells show expression of X genes that are coming from mother while remaining 50% cells show expression of X genes that are coming from father. Hence deleterious or harmful mutations in X linked genes (if occur) will lead to the formation of dysfunctional or less functional

molecules that affect every masculine cells but only 50% feminine cells.

Aforementioned, X genes affect on immunity and natural diversifications in a single set of genes may lead to 2 different alleles which play distinctive roles in regulation and responsiveness i.e. such females are highly effective to keep away the harmful effects caused by lethally mutated genes as well are able to face new immunological problems e.g. pathogenic contaminations [14] [15]. However Y-linked SRY gene acts to form testicles and synthesize testosterone, which causes the development of masculinity while genetically inexpressive SRY leads to ovarian growth as well as development of femininity. Previous experiment of 'Four Core Genotypes' using mice showed that effectiveness of sex chromosomes alongwith gonads on phenotypic expressions and to determine the activity of SRY gene.

Deletion of SRY (SRY $^{-}$) :- Y-linked SRY deletion resulting XY^{-} FCG mice having ovaries i.e. gonadal females .

Insertion of SRY (SRY^{+}) :- If SRY transgene is inserted into the autosome of XX SRY or XY^{-} SRY FCG mice through somatic cell gene therapy, results in testes bearing male mice.

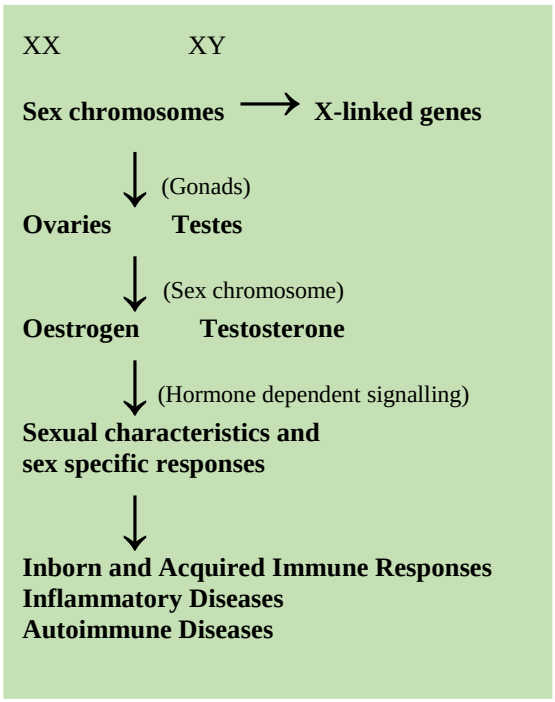

Figure 3. Sex chromosomal and sex steroidal effects on Immune Responses in Mammals. X linked genes, SRY gene on Y chromosome & sex steroids together affect the sex-differential immunity

Thus, in experimental FCG mice gonadectomy leads to depletion of gonadal steroidal hormones that disclose sex chromosomal activities, which include proneness to autoimmunity and infectious diseases (proneness to autoimmune diseases—XX>XY). Two human genetic inherited disorders related to sex chromosome aberrations include Klienfelter and Turner's syndromes further justify the impacts of X chromosome on Immunity. Males with Klienfelter syndrome having one more X chromosome, as a consequence, there are decreased maleness (reduced androgenic concentrations) , enhanced gonadotrophic levels as well as high estradiol concentrations. Thereby Klienfelter males respond immunologically, more feminine like, with enhanced antibody concentrations, T_H cell counts, T_H/T_C cell proportions and B cell counts in compared to normal healthy males . Testosterone therapy may modify the immunologic effects of Klienfelter syndrome, that again elaborates sex chromosomal as well as sex steroidal effects on immunological responsiveness. In contradiction, Turner's syndrome affected females contain single X (X 0) or majority of the X chromosome is deleted, bear reduced immunoglobulin concentrations as well as decreased T cell and B cell counts in comparison with normal healthy females [16]. Klienfelter males and Turner females together show a tendency to develop autoimmune diseases increasingly, from this point of view it has been seen that X chromosome greatly influence the susceptibility to autoimmune diseases (Figure 3).

4.2. Micro RNA and long non coding RNA

Micro RNAs (mi RNAs), a class of small (18- 25 nucleotides) single-stranded non-coding RNAs which downregulate genetic activities either by repress translation or by degrade mRNA. Molecular biology studies reveal that mammalian mi RNAs may regulate approx 25% and above genes that encode molecules. In addition these can also regulate nearly every cellular functions. Even a single mi RNA is believed to trigger many of such genes and expression can be specific to the cell. Generally mi RNAs are evolutionary conserved, indicating these miRNAs face stronger natural selection and play crucial roles in the development and disease progression. As male and female organisms ranging from invertebrates to higher vertebrates express mi RNAs differentially, so it can be say that mi RNAs have some specific roles in developing immune related diseases in both male and female. The percentage of human X-miRNAs is of about ten percent out of the total 750+ genomic mi RNAs and up to date study reveals that Y chromosome contains only 2 mi RNAs. Such higher percentages of mammalian X-mi RNAs indicate they play X biased roles that affecting sex-differential immunity [17] (Table 1).

Table 1. Some Important Mammalian X-miRNAs and their respective roles

X linked Micro RNAs (X-mi RNAs)	Function(s)	Ref.
miR-221,miR-222	Cancer onset and progression	[29]
miR-223,miR-106a ,miR-424	Immune regulation	[30,31,32]
miR-18 ,miR-19	Sex differences in immune responses	[17]

As well as females are hyper responsive due to high X– mi RNAs that help to get away X inactivation, as a result they are more prone to develop some immune related diseases. Long non-coding RNAs (lnc RNAs) are RNA molecules that also take part to regulate transcription during innate and adaptive immunity.

4.3. Genetic Polymorphisms

Sex chromosomal genes and autosomal genes are different from each other in encoding immunological proteins that's why sex differential immune responses occur. For instance, HLA allelomorphs and genes encoding few interleukins and IL-12R in both males and females, each of these are important and regulate sex-dimorphic antibody responses after being vaccinated against measles, mumps, rubella ,tetanus, diphtheria etc. in the age groups of 5 to 60 years [10].

5. Impact of Hormonal Factors on Sex Differential Immunity

5.1. Oestradiol

Oestradiol (e g., 17beta oestradiol or E2) or estrogen, a sex steroid hormone synthesized and released by ovaries and adrenal medulla, the level of which vary throughout the period of menstruation. Women those are conceived show uplifted estrogenic levels but decrement occurs after 45 to 50 years of age. Several immune cells (lymphoid tissue cells) like lymphocytes, and other professional APCs contain estrogen receptors (ERs) . Between two subtypes of ERs for classical ER signalling, ER alpha (a subtype) is more expressive in T lymphocytes whereas ER beta(another subtype)is more expressive in B lymphocytes . Another form of ER signal transduction pathway held in these lymphoid cells where estrogen receptors interact with estrogen response element-free transcriptional factors such as NF-kB , SP1, AP1 .

E2 impacts on Innate Immunity

E2 impacts on innate immunity from many aspects like functionality of immunocytes. Experiments on both human and mice reveal that neutrophil counts may increase in blood and lungs, respectively through the treatment with E2 . In vitro treatment of NK cells with E2 shows that IFN gamma production and overall cytotoxicity both have to be enhance but some markers that activate natural killer cells and the FAS L are expressed negatively as well reduced the secretion of granzyme B in mice. Dual effects of E2 on human monocyte and macrophages have been recognised — low E2 causes higher generation of cytokines that up-regulate inflammation (e g. IL-6, TNF) but they are produced in reduction when E2 concentrations are large.

Estradiol may increase the expressiveness of PAMP-recognising receptors, such as Toll-like receptor 4 in mice peritoneum . E2 exposed dendritic cells increase the synthesis of CXCL 8 and CCL 2 as well estrogen also promotes DC differentiation. Differentiated CD 11c+ DCs produce high amounts of pro inflammatory cytokines in ovariectomized mice after treatment with physiological doses of E2. GM CSF (a colony stimulating factor) exposed E2 promotes monocytic differentiation to form dendritic cells that are able to cause inflammation, exhibiting high generation of IFN alpha and inflammation up-regulatory cytokines, enhanced TLR 9 signalling, greater internalisation as well presentation of antigens to naive T cells . In vitro E2 exposure of neutrophils leads to high degranulation and elastase release whereas eosinophil counts may be reduced when exposed to E2.

E2 impacts on Adaptive Immunity

E2 effects on adaptive immunity adversely by enhancing both cellular and humoral immune responses. E2 in low concentration promotes T_H1 type immune responses thereby mediating cellular immunity , while E2 in high concentration promotes T_H 2 type responses that stimulate B cells to produce antibodies in various organisms alongwith cultured cells [18] . Low dose of estradiol also positively regulate transcription factors such as MAPK and recognise micro RNAs thereby occurs enhanced synthesis of IFN gamma from T lymphocytes in murine studies .

Transcriptional analyses showed that NF-kB induce inflammation up-regulatory responses that are regulated by E2 and transcriptional repressive interactivity of NF-kB [18]. In vivo, the number of T_{reg} cell populations are increased by the action of E2 in females and ex vivo, this hormone also enhances regulatory T cell counts produced by peripheral lymphocytes and/or macrophages. In experimental mice, T_H17 cells synthesize interleukin-17 , the levels of which are decreased when high dosage of E2 and may be increased at low E2 concentration, hence ovariectomized female mice show high T_H17 sub populations and IL-17 production . Aforementioned that E2 also stimulates feminine humoral immune responses by enhancing plasma B cell counts as well as IgG and IgM concentrations at pre ovulation period .

5.2. Progesterone

Progesterone is synthesized and released by ovaries at the period of menstruation but placental release become raised in case of pregnant mothers. Progesterone signalling occurs mainly through progesterone receptors (PRs) whereas glucocorticotrophic and mineralocorticotrophic receptors play minor roles, however, PRs can be expressed on several immunocytes of those are mainly professional APCs. The hormone is effective in anti-inflammation; treatment of macrophages and dendritic cells with P4 (abbreviated term of this hormone) leads to reduced activity and production of interleukin-1beta , TNF as well as IFN gamma than normal cells . P4 exposed mice macrophages induce the expression of markers that are possibly activate macrophages, viz., FIZZ1 and YM1 and decrease generation of NO and iNOS . Due to activity of P4, both TLR and NF-kB pathways become affected (TLR 3 and TLR7 are expressed in low levels and NF-kB pathway associated factors show lower state of activation). When natural killer cells exposed to progesterone , it declines the activity and productivity of IFN gamma via apoptotic pathway causing anti inflammation. In addition NK cell numbers and the rate of caspase dependent apoptosis both are enhanced.

On the effect of P4, T_H2 cells are expressed more than T_H1 cells, causing higher synthesis of B cell activating anti-inflammatory cytokines that eventually raise up immunoglobulin concentrations, thereby total antibody concentration become increased . P4 treated — eosinophils are raised in numbers; T_{reg} cell frequencies are enhanced; T_H17 cell frequencies are decreased.

5.3. Androgens

These include dihydrotestosterone (DHT) and testosterone, present at high levels after masculine puberty and gradually masks the immunocytic activities . For example, testosterone decline NK cell activity in mice in vivo. In vivo and ex vivo studies reveal that TLR4 expressions on macrophages are also decreased by the hormonal action, following raised proneness to infectious diseases. Testosterone reduced the production of nitric oxide and tumor necrosis factors from macrophages whereas increased the synthesis of IL-10 and TGF beta, causing enhanced inflammation-inhibitory responsiveness through androgen receptor (AR) signal transduction pathway [19]. Testosterone has suppressive effects on pro-inflammation and decline neutrophilic synthesis of kinases and LTs. Men with low testosterone levels or androgen deficiencies are more prone to develop inflammatory diseases because of raised levels of cytokines those are responsible to induce inflammation (such as., interleukin-1beta , interleukin-2, TNF) than men with normal androgen concentrations. Beside these, they have high antibody concentrations and T_H/ T_C cell proportions like women . Low testosterone level is also induced by the treatment with gonadotrophin releasing hormone (GnRH) antagonist that reduces the number of regulatory T cells and raised the number of natural killer cells. Testosterone at physiological concentrations suppress T_H1 cell responsiveness by reduced IFN gamma productivity as well as T_H2 type response by declining IL-4 and IL-5 productivity whereas T_H17 cells produce higher IL-17. In response to androgens, both number and activity of CD 8+ T cells are lowered.
Hence, all these studies elaborate the regulatory effects of sex steroidal hormones in sex differential immunity.

6. Impact of External Factors on Sex Differential Immunity

6.1. Nutrition

Nutrition of the fetus bring about sex differential immune responses in future. Previous studies include Gambian – placebo controlled study reveals that micronutrient supplement consumption of mother during pregnancy affects sex differential CpG methylation of genes (e g , genes encode for CD4, defensins and IFN signalling associated genes) engaged in immunity and defence against infection , and female fetuses are more affected under supplementations than male fetuses under the same . This analysis illustrates the sex differential development of fetuses begin within uterus and continued below 1 years of age, which indicate that nutrition may epigenetically influenced for prolonged time at the gestational period . Another studies reported that breast milk feeding of infants greatly affects their immune system — infant females are more immunologically benefited than infant males. For example, infant females have reduced risk of neonatal respiratory tract infection after breastfeeding whereas male infants not. Interestingly, micronutrients itself act differentially in males and females. For instance, human trial on Tanzanian mothers infected with HIV reveals that micronutrient supplementation (such as vitamin B, C and E supplements) at perinatal and postnatal conditions reduces the mortality rate upto 32% among females than males [20] .

Along with this study, several studies also reported that if mothers are supplemented with such nutrients that will play more beneficiary roles on feminine growth and development as compared to males. Vitamin A supplements have differential immunogenic effects on both sexes — it decreased leukocyte counts in males whereas enhanced leukocyte counts and higher IFN gamma production occur in females (children of 6—23 months of age , after measles vaccination when supplemented with vitamin A show this result).

6.2. Microbiota

Host microbiome perform significant roles in several disease onset and progression like inflammatory diseases and lifestyle diseases whereas sex affects the host microbiome. During pre puberty, sex specific influence on microbiome does not occur and it was established after thorough study on pre-pubertal mice where sex doesn't affect microbiota. Several studies on mice reveal that sex differential expressiveness of host genes within the GI tract occur during pre-pubescence, which indicate such sex-differential genes may be effective even in insufficient sex steroidal concentrations. *Bacteroidetes sp*. are more frequent in male mice as compared to females during post puberty . Previous experiment on mice demonstrates that the intestinal microbes perform hormone dependent regulation of autoimmunity (changes in sex steroidal concentrations, that may secure males from insulin dependent diabetes mellitus (IDDM). Feminines can also get protection from IDDM if such male microbes are transferred to them).
Similarly *Bacteriodetes* spp. are more frequent in men as compared to women [21]. Previous study based on the sexual interactivity with diet in Pisces and mammals strongly revealed that diet affects sex-differential intestinal microbiota in 2 species of fish, influences human *Fusobacterium* spp. frequencies, while gut microbiota in experimental mice doesn't affected. Dietary ineffectiveness on gut microbiota of both male and female mice may caused by high consumption of highly simplified diets and experimental circumstances where they reared. Diet affects intestinal microbiota in *Homo sapiens* in such a way that causes several autoimmune diseases like ulcerative colitis and Crohn's disease may develop in sexually dimorphic manner, associated with dysbiosis.

7. Age and Reproductive Condition affects Sex Differential Immunity

Every living organisms have a biological processes of aging and reproduction that may affects sex-differential immunity. Sex differential immune responses occur at different life stages—

In uterus : Environment influence on fetus thereby they become epigenetically adapted which may causes lifelong alternations of genetic expression e.g activities of immune

components. Female fetuses are more adapted to maintain stresses within the uterus in compared to males. Prematurity of male fetuses (whose birth is before 8 months of gestational period) leads to their chronic placental inflammation, which is relatively high in case of them, contributing males have less stable cardiovasculature and increased cytokine levels that may reduce their life expectancy whereas opposite diagrams are found in case of females. Male fetuses are able to secrete androgens from their testes from 2.5 months of pregnancy that causes androgenic effects on sex-differential immune responses may develop from the prenatal stages. Masculine fetal umbilical cord blood (UCB) is more IgE-rich by maternal IgE levels than females that may leads to the development of atopy (Table 2).

Pre puberty/ Childhood: During birth, fetus faces new environment and multiple new antigens rather than maternal environment. Previous studies investigate immune responses in newborns using UCB sample because of the availablity of enormous amount of blood; nevertheless, sex specific investigation is somehow limited. A study on both premature (whose birth is before 8 months of gestational period) and mature babies reveals that cells having single nucleus present in the UCB react with Toll-like receptor agonists and these reactions are not affected by sex in both groups [22]. Another study on infant cord blood suggesting that female cord blood have higher frequencies of T_H cells, elevated T_H/T_C cell ratios and lower NK and T_C cell populations as compared to male cord blood. Whatever, male babies show greater frequencies of basophils and NK cells upto age of 13 months as well as they also exhibit higher inflammation up-regulatory responses as compared to females after activation by lipopolysaccharide or mitogen. Hence male infants have better natal immunity than female infants. B cell numbers are also variable in both sexes at childhood . Experiments on neonatal rodents indicate that the thymic development is influenced by neonatal sex steroid hormones that leads to sex-differential T_H/T_C cell ratios (↑female ↓male), NK T cells (↓female ↑male) and CD 4+CD 25+FOXP3+ regulatory T cell numbers (↓female ↑male) [23] (Table 2).

Puberty : During puberty, sex steroids affect immune system greatly. Male infants show higher inflammatory responses than females early in life, but after puberty females are persistently more inflamed than males. Genetic study on post pubescent mice reveals that acquired immunity related gene expression (e.g Ig and *Bcr* genes) is uplifted in females, while males exhibit increased gene expression related to innate immune responses (e.g *SAA*, haptoglobin, *PAI2* , *Ccl 9* and *Ccr 1*)[24]. In pubertal females, fluctuations in hormonal levels occur during menstrual cycle and at the same time sex steroidal levels also fluctuate thereby cyclic changes in immune functions occur i.e changes in immunocyte counts and functions, including high regulatory T cell frequencies when estradiol levels remain in superior during pre ovulatory period (Table 2).

Old age : As age increases, feminine sex steroid concentrations diminish quickly but masculine sex steroidal levels show normal diminishment, similarly decreased functionality of the immune system in both sexes also continued . Although both aged male and females have declined immune functions, yet aged females are more immune privileged than aged males may be due to X chromosome diploidy , but this scenario may occur in the presence of diminished sex steroidal concentrations after completion of menstruation. Immunosenescence is characterized by — progressive downgradation of pro-inflammation (rate: females > males) ; increment of NK cell numbers (rate: females > males) [25] ; decrement of counts of B cells as well as CD 4+ T cell sub populations (rate: males > females) ; decreased activation of T cells (males > females); even antigen re-exposure induce very little upliftment of CD 4+ memory T cell numbers in aged males than aged females [25]. "Age associated B cells " (populations of B cells) have been declined rapidly in aged males, that's why males have increased chances to develop diseases caused by autoimmunity than aged females(Table 2).

Table 2. Changes in Innate and Adaptive Immunity in both Sexes of Human at Different Life Stages

Different life stages	Innate Immunity	Adaptive immunity	Ref.
In utero	↑Inflammation (males)	↑ IgE levels in males	[33]
Pre-puberty /Childhood	↑ Inflammatory responses (males) ↑ Natural killer cell counts (males)	T_H/T_C cell proportions and T_H cell counts same T_C cell counts same IgA conc.: males ≥ females IgM conc.: males ≥ females IgG conc.: same B cell counts same Regulatory T cell counts: males ≥ female	[22,23]
Post-puberty/ Adulthood	↑Inflammatory responses (females) ↑ NK cell counts (males)	T_H/T_C cell proportions and T_H cell counts ↑ (females) T_C cell counts ↑ (males) Proliferated T cells ↑ (females) Regulatory T cell counts ↑ (males) B cell counts ↑ (females) Antibody levels ↑ (females)	[24,34]
Old age	↑Inflammatory responses (males) ↑ IL-10 (females) ↑ Natural killer cell counts (females)	T_H/T_C cell proportions and T_H cell counts ↑ (females) T_C cell counts ↑ (males)	[16]

		Proliferated T cells ↑ (females) Regulatory T cell counts ↑ (males) B cell counts ↑ (females) Antibody levels ↑ (females)	

8. Pathogenicity of Immunosuppressive Diseases affected by Sex Differences

8.1. Autoimmune diseases

Human females are highly suffered from autoimmune disorders including SLE, rheumatoid arthritis, Addison's disease etc. than males. In contrast, men show higher incidence of some autoimmune diseases, though less common, such as myocarditis and idiopathic pulmonary fibrosis, in acute phases of these autoimmune diseases they show higher T_H1 cell responses to their self antigens [26]. Experiments using experimental autoimmune encephalomyelitis (EAE) model of mice and humans with multiple sclerosis(MS) reveal that sex-differential autoimmunity occurs in which immunological alongwith hormonal factors are involved— females show higher incidence and severity than that of males. These females exhibit higher number of activated T helper 1 cells and higher IFN gamma production while males show raised T_H17 cell responses. Such females have suppressed cellular immunity by the administration of high doses of estrogens and that relieve them from disease severities . Testosterone-treated male patients with MS show slow cerebral atrophies; decreased CD4+ T cell numbers and IL- 2 synthesis from mononuclear immunocytes; enhanced NK cell counts as well as high TGF beta production from PBMCs .

8.2. Malignancy

Apart from reproductive organs, several non reproductive cancers affect both sexes, with males show increasing risk of malignancy and almost two times higher risks of death caused by malignancies as compared to females. Highest sexual discriminations in death rate occur in case of laryngeal, oesophageal and pulmonary cancers. Various factors affecting male biased mortality that are quite different from females including infections from viruses, immunological functions, regulation of hormones, genetic expressions, sex chromosome complements , damages by oxidation, autophagocytosis and many more . Even cancer immunotherapies show sex differential results such as programmed death-ligand 1 (PD-L1) specific monoclonal antibodies, may treat women more efficiently than men with melanomas.

8.3. Infectious diseases

Males show higher susceptibility to infectious diseases caused by pathogens than females. These sex differences are caused by some factors such as modes of transmission of infection (e.g. human-to-human / vector borne/ blood borne/ food and water borne) , immunity status [27]. Newborn females have less vulnerability to infectious diseases than males that may reduce their mortality. In third world nations, 5–17 years old males show increased risks from falciparum malaria, Kala-azar, amoebiasis-related hepatic abscesses, schistosomiasis, toxocariasis and filariasis. Adult women show 1.6 times higher risk to develop AIDS than adult men, but they have 40% less HIV RNA load than males as well as higher activation of CD 8+ T cells have been observed in females when HIV become untreated. Although men exposed to influenza A virus more than women, but case of fatality has been reported higher in women whereas men are more prone to develop hepatocellular carcinoma and more prevalent to hepatitis B virus (HBV) infection than women.

In addition, cases of tuberculosis and clinical cryptococcosis are 2 times and 10 times higher in males than females, respectively. Recently, COVID 19 (Corona Virus Disease 2019) affect greatly men than women and the death rate due to novel coronavirus (SARS-COV-2) infection is two times higher in US men than women along with 69% of overall deaths due to COVID 19 in western Europe have been male. Similar picture have been seen elsewhere. Several sex based epidemiological studies on incidences of pneumonia suggesting that males show higher incidence than females and it increases with age in both sexes (*Streptococcus pneumoniae* — more frequent in females; *Legionella pneumoniae* and *Klebsiella pneumoniae* — more frequent in males)(Figure 4).

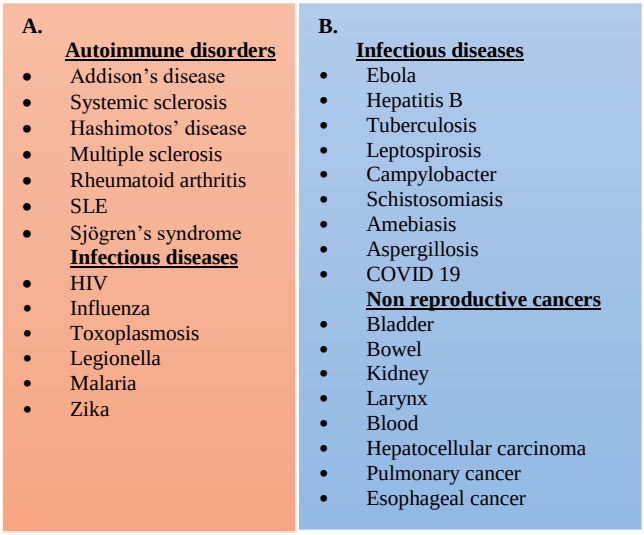

Figure 4. Sex biasness in the pathogenicity of autoimmune disorders, infectious diseases & malignancies— A. Female-biased diseases ; B. Male-biased diseases .Autoimmune diseases affect females more than males whereas incidence of infectious diseases and risk and malignancy of non reproductive cancers are higher in males than that of females

9. Vaccine Efficacy on Sex-biased Immunity

There are many vaccines like DTaP & Td/Tdap, Hep A & Hep B vaccines , flu vaccines , PPSV23 , rabies vaccines, MMR, smallpox vaccines, RTS,S vaccine , HPV vaccines are sex-differentially effective from infants to aged adults [28] . Women show greater responsiveness of antibodies following vaccination against bacteria and viruses as compared to men i.e dosage administration is significantly reduced in women than men. As an instance, adult females required only half dose of influenza vaccine to boost up antibody concentrations

but full dose vaccine may be effective to achieve equal antibody titres in males. Along with high immune responsiveness, females also exhibit frequently occurring harmful physiological reactions following vaccination (greater in younger and aged females) , may be due to higher inflammatory responses occur in females than males[10] (Table 3).

Table 3. Sex-differential immune responsiveness following vaccination in both sexes

Groups are triggered	Vaccines	Immune responsiveness	Side effects (if any) in both sexes	Age (years)	References
Children	Diphtheria	> (Females)	N/D	<2	[28]
	Pertussis	> (Females)	N/D	<2	[28]
	Malaria (RTS, S vaccine)	> (Females)	Raised (females)	<2	[28]
	Measles	≥ (Females)	Raised (females)	<3	[28]
	Human papillomavirus (HPV)	> (Females)	Raised (females)	5-17	[28]
	Pneumococcal (Vaccine: PPSV23)	> (Females)	N/D	6-9	[28]
	Rabies	> (Females)	N/D	6-9	[28]
	Hepatitis B(Hep B)	> (Females)	N/D	<12	[28]
Adults	Hepatitis B	> (Females)	Raised (females)	>18	[28]
	Genital herpes	> (Females)	N/D	>18	[28]
	Yellow fever	> (Females)	Raised (females)	>18	[28]
	Rabies	> (Females)	N/D	>18	[28]
	Small pox	> (Females)	N/D	>18	[28]
	Influenza	> (Females)	Raised (females)	18-49	[28]
Aged adults	Influenza	> (Females)	Raised (females)	>60	[28]
	Td/Tdap	> (Males)	Raised (females)	>60	[28]
	PPSV23	> (Males)	Raised (females)	>60	[28]

10. Conclusion and Future Scope

In this review, I would attempt to provide some informations and evidences regarding this, in which sex affecting both innate and adaptive (humoral and cell mediated) immunity; also influencing the pathogenesis of some immunosuppressive diseases like autoimmune diseases ,non reproductive cancers and infectious diseases and vaccine efficacy that lead to sex-specific outcomes. This study is always relevant from the aspect of immune-related diseases because of exact causative factors that may lead to such diseases are still unknown. From the evolutionary aspect of sex-differential immunity it can be say that there may also be a interrelation between sex-specific immune mediated diseases and increased survival of human beings.

Now-a-days we need cost-effective personalized treatments that have as possible as less side effects and will be helpful to all individuals suffering from immune mediated diseases. But if we treat such diseases person-specifically with prolonged treatments/therapeutic interventions/medications then it will not possible to give equal protection for both sexes. For short-term treatments it is essential to know appropriate factors affecting sex differential immunity. Further analyses are required to recognise these factors and they may possibly interact with hormonal, genetic and environmental factors.

Data Availablity

The data that helps to find out the study is freely available at PubMed , Science Direct ,Researchgate and Google scholar.

Conflict of Interest

Not applicable

Funding Source

Not applicable

Author's Contribution

The author reviewed literatures, edit and prepare the full manuscript.

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