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The X chromosome and immune associated genes

Ilaria Bianchi [a], Ana Lleo [a,b], M. Eric Gershwin [c], Pietro Invernizzi [a,c,*]

[a] Center for Autoimmune Liver Diseases, Department of Medicine, IRCCS Istituto Clinico Humanitas, Rozzano, Italy
[b] Department of Translational Medicine, Università degli Studi di Milano, Rozzano, Italy
[c] Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, CA, USA

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ABSTRACT

The X chromosome is known to contain the largest number of immune-related genes of the whole human genome. For this reason, X chromosome has recently become subject of great interest and attention and numerous studies have been aimed at understanding the role of genes on the X chromosome in triggering and maintaining the autoimmune aggression. Autoimmune diseases are indeed a growing heath burden affecting cumulatively up to 10% of the general population. It is intriguing that most X-linked primary immune deficiencies carry significant autoimmune manifestations, thus illustrating the critical role played by products of single gene located on the X chromosome in the onset, function and homeostasis of the immune system. Again, the plethora of autoimmune stigmata observed in patients with Turner syndrome, a disease due to the lack of one X chromosome or the presence of major X chromosome deletions, indicate that X-linked genes play a unique and major role in autoimmunity. There have been several reports on a role of X chromosome gene dosage through inactivation or duplication in women with autoimmune diseases, for example through a higher rate of circulating cells with a single X chromosome (i.e. with X monosomy). Finally, a challenge for researchers in the coming years will be to dissect the role for the large number of X-linked microRNAs from the perspective of autoimmune disease development. Taken together, X chromosome might well constitute the common trait of the susceptibility to autoimmune diseases, other than to explain the female preponderance of these conditions. This review will focus on the available evidence on X chromosome changes and discuss their potential implications and limitations.

1. Introduction

In the last few years we witnessed a rapid progress in the field of human genetics with an explosion of new information about the genetics of AID [1]. A major contribution has come from the genome-wide association studies (GWAS), but important hints derived also from studies focusing on X chromosome changes, such as abnormal X chromosome gene dosage [2–4]. This review does not aim at summarizing our current knowledge of the genetics of AID, but will mainly focus on the recent associations of autoimmunity with X chromosome defects, and on how these data are changing the genetic landscape of the most common AID. Recent discoveries within X-linked genes which provide clues to novel pathogenic pathways for autoimmunity will be showed and critically discussed.

2. Autoimmune diseases (AID): Lessons from epidemiology

AID is an heterogeneous collection of disorders in terms of epidemiologic profile, clinical manifestations and management, and healthcare burden. On the contrary, AID are commonly characterized by tissue-specific or systemic damage due to an abnormal immune response and the breakdown of tolerance to self-antigens. For these reasons, to consider a particular disease as an AID a well-established criteria must be satisfied. First, an indirect evidence based on the reproduction of the AID in disease-specific animal models. Second, a direct evidence of the AID by transferring pathogenic antibody or pathogenic immune cells (mainly T and B cells). Finally, circumstantial evidence from a clinical point of view [5]. AID can develop at any age and, although they are considered as rare conditions, they are relatively frequent when taken altogether

Abbreviations: AID, autoimmune diseases; GWAS, genome-wide association study; PBC, primary biliary cirrhosis; MHC, major histocompatibility complex; PID, primary immunodeficiency syndromes; XCI, X chromosome inactivation; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; AITD, autoimmune thyroid disease; HIGM, X-linked hyper-IgM syndrome; IPEX, Polyendocrinopathy, and enteropathy, X-linked syndrome; WAS, Wiskott-Aldrich syndrome.

* Corresponding author. Center for Autoimmune Liver Diseases, Department of Medicine, IRCCS Istituto Clinico Humanitas, Via A. Manzoni 113, 20089 Rozzano, Italy. Tel.: +39 02 82245128; fax: +39 02 82245191.
E-mail address: pietro.invernizzi@humanitas.it (P. Invernizzi).

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and are a leading cause of morbidity and mortality worldwide because of their chronic and often severe nature. Indeed, it is estimated that up to 10% of the general population are affected by one or more AID [6,7]. It is of interest that the vast majority of AID have a striking female preponderance with a female to male ratio as high as 10:1 [2,6,7]. Although it is well possible that AID are less frequent in men, we cannot exclude that they are only less diagnosed in men than in women in view of the fact that the majority of published data is based on case–control studies. Intriguingly, several recent screening studies and epidemiological studies based on administrative data from national health systems reported a less marked female to male ratio. The case of primary biliary cirrhosis (PBC) is paradigmatic because the female to male ratio is about 10:1 based on case–control studies, but 5:1 considering epidemiologic studies based on administrative data [8], and even less (ratio 2:1 - 3:1) when screening studies are considered [9].

3. Genetic influences in AID

Lost of tolerance has been one of the major enigmas of immunologists although it is largely accepted that pathogenesis of AID is multifactorial, with environmental and genetic factors interplaying to determine disease onset and progression [9–11]. Nevertheless, while the quantification of environmental factors is extremely difficult, a plethora of evidences indicate that genetics has a major role in AID susceptibility and progression [3,4,12]. Among others, the hypothesis that common genes underlie multiple AID, and that several diseases share common pathogenic pathways is strongly suggested by the observation that individual AID often coexist within family members. This concept is also supported by the consistently higher concordance rate in monozygotic twins than in dizygotic twins and, again, by the numerous epidemiological evidences showing a worldwide marked geographical variability in the prevalence of AID. Finally, it has been reported a large number of associations between AID and genetic major histocompatibility complex (MHC) and non-MHC variants [3,4,13–18]. It is clear that very few of AID are due to a single gene mutations, such as autoimmune lymphoproliferative syndrome and the syndrome of autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dysplasia (APECED) [19]. AID are indeed multigenic disorders and their predisposition represents the net effect of protective and enhancing genes.

Since the completion of the human genome sequence in 2005, there has been a significant progress in our understanding of human genetics and also of genetics of AID [4,20–24]. In particular, significant technical advances allowed to evaluate the entire human genome for common variants (i.e. those present in more than 5% of the general population) and to identify a number of new genes involved in autoimmunity [25]. Among them, genes encoding MHC antigens, genes encoding immunoglobulins, T cell receptors for antigen, and the molecules that control immune activation, as well as genes affecting antigen processing and presentation, lymphocyte proliferation and differentiation [17,18,26]. In parallel, we also witnessed the accumulation of evidences indicating that autoimmunity may occur in patients affected by primary immune-deficiency (PID), with a progressive understanding of the underlying molecular and cellular mechanisms that interconnect these conditions [27–30]. Finally, recent studies indicate that genes located on the X chromosome play a major and unique role in autoimmunity [2].

4. The unique biology of X and Y chromosomes

Females carry two X chromosomes, one from each parent, whereas males carry an X chromosome inherited from the mother and one Y chromosome from the father. The X chromosome contains about 1000 genes spanning about 155 million base pairs with an equal dosage between female and male obtained by inactivation of one of the two X chromosomes in female that forms a heterochromatin body (named Barr body) within the nucleus [31]. The inactivation of X Chromosome (XCI) is indeed a pivotal epigenetic mechanism involved in the dosage compensation of X-linked genes between females and males. In any cell, the process of XCI in early female embryonic development is thought to be progressive, random across alleles, and clonally maintained once established, and results in females being a functional mosaics for the active X chromosome. In particular, the silencing of the inactive X chromosome is due to packaging into transcriptional inactive heterochromatin, irrespectively to the parental origin of X chromosome. The XCI is a multistep process. First, there is a mechanism of counting and choice of the chromosome that will start XCI. The entire course of action is directed by the X inactivation center (Xic), a nuclear complex constituted by many of non-coding DNA elements and genes (Tsix, Xist, etc). Mosaicism of female cells is a great advantage in case of deleterious mutations of X chromosome genes, as ensures increased diversity to immune responses.

On pseudoautosomal regions of X chromosome there are a number of genes which have homologous genes also on the Y counterpart and achieve dosage compensation between males and females thanks to an XCI escaping mechanism that allows these genes transcription on both X chromosomes. This mechanism can well explain those major human defects due to abnormal numbers of the X chromosome, such as 45,X0 or 47,XXY. Paradigmatic in this regard are male patients with Klinefelter's syndrome (47,XXY), who have similar risk to develop systemic lupus erythematosus (SLE) compared to females (46,XX) thus indicating a role for X-linked genes dosage in the pathogenesis and this female preponderance disease [32].

5. X chromosome and AID: when the number is the problem

The number of X chromosomes, and the consequent altered X-linked genes dosage, is critical for the maintenance or the loss of the immune tolerance [33]. Paradigmatic is that the lack of one X chromosome (45,X0) or the presence of major defects of X chromosome (i.e., micro- or macro-deletions) cause premature ovarian failure [34,35] and Turner's syndrome [36–38], two conditions often associated with AID and with many autoimmune features. It is to note that X chromosomes (or part of them) can be progressively lost with a consequent haploinsufficiency of some X-linked genes and a detrimental effect on the immune system homeostasis [2]. Autoreactive T cells, but also B cells and other immune-related cells, cannot be tolerized by self-antigens encoded by one of the two X chromosomes, thus triggering an autoimmune response in target tissues.

On this regard, our group showed an enhanced X monosomy rate in the peripheral blood mononuclear cells (PBMC) from women with systemic (systemic sclerosis (SSC)) and organ-specific (PBC and autoimmune thyroiditis (AITD)) AID [39–42]. Nevertheless, it is possible that this is not true for any AID as we failed to confirm the finding in women suffering for SLE [43,44]. In one of this AID, PBC, we have also demonstrated that X chromosome is preferentially lost, thus ruling out the possibility that a specific haplotype on X chromosome could trigger AID in a predisposed subject. At this point, we still need to determine the parental origin of the remaining chromosome mainly because the disease is characterized by a relatively old mean age at diagnosis with consequent difficulty in obtaining DNA from parents [43]. We believe that the progressively acquired haploinsufficiency for genes on X chromosome in immune-related cells is a mechanism for immunosenescence, the state of altered immune function of the