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# Long non-coding RNA Xist contribution in systemic lupus erythematosus and rheumatoid arthritis

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## Abstract

Growing evidence points towards the role of the long non-coding (lnc)-RNA Xist expressed in female cells as a predominant key actor for the sex bias observed in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Indeed, in female cells, lnc-Xist controls transcription directly by spreading across the inactivated X chromosome (Xi) and indirectly by sequestering miRNAs as a sponge. The inactivation process at Xi is altered in lymphocytes from SLE women and associated with important variations in ribonucleoproteins (RNP) associated with lnc-Xist. In fibroblast-like synoviocytes (FLS) and osteoclasts from RA women, proinflammatory and proliferative pathways are upregulated due to the sequestration effect exerted by lnc-Xist overexpression on miRNAs. The key role played by lnc-Xist in SLE and RA is further supported by its knock down that recapitulates the SLE B cell extrafollicular profile and controls RA associated FLS proinflammatory cytokine production and proliferation.

**Key words:** long non-coding RNA Xist, X chromosome, systemic lupus erythematosus, rheumatoid arthritis, interferon pathway

### Highlights:

- Lnc-Xist controls X chromosome inactivation and miRNAs in females.
- Lnc-Xist and RNP expression are dysregulated in autoimmune diseases.
- Lnc-Xist dependent type I interferon and extrafollicular B cell pathways are defective in SLE.
- Fibroblast-like synoviocyte (FLS) capacities in RA are controlled by lnc-Xist.

## 1. Introduction

Females are more resilient to certain infections as compared to males, but such an advantage is counterbalanced by an increased susceptibility to systemic autoimmune diseases (SAD) (Youness et al., 2021). As a consequence, the reported sex difference is nine females per male in systemic lupus erythematosus (SLE), and three females per male in rheumatoid arthritis (RA) (Krasselt and Baerwald, 2019). In contrast, males are more likely to be sensitive to infectious diseases, parasitic diseases, and they have a greater risk of non-reproductive cancers (Klein and Flanagan, 2016).

Initially, research was focused on the role of sex hormones in SAD, which is outside the purpose of this review (Moulton, 2018). However, growing evidence points towards the number of X chromosomes and, in turn, X-gene dysregulation to explain the sex bias in SAD. Cytogenetic arguments support such an assertion through the observations that men (46,XY) and women with Turner's syndrome (45,X0) are at lower risk for developing SLE (Cooney et al., 2009) as compared to males with an additional X chromosome (47,XXY; Klinefelter's syndrome) and women (46,XX) who have 10-15 fold higher risk for developing SLE (Sawalha et al., 2009). As a consequence, an over-representation of Klinefelter's syndrome is seen among men with SLE (2.5%), which can be suspected when considering fertility and gynecomastia. In women, polysomy X (47,XXX; 48,XXXX...) also contributes an increased risk of SLE up to 25-30 fold. Some SLE patients show partial acquired mosaic X chromosome losses or gains. Among them a double mosaic with monosomy (45,X0; 46,XX) is not associated with an increased SLE risk, while the detection of triple mosaic including X polysomy (45,X0; 46,XX; 47,XXX) increases the SLE risk (Svyryd et al., 2012) (Slae et al., 2014)(Iwamoto et al., 2019). Such observations are not restricted to SLE as similar observations occur in RA and Sjögren's or sicca syndrome (SjS) (Martin et al., 2019) (Harris et al., 2016). Altogether this has led to the notion that an increase in expression of the immune X-linked genes contributes to the sex bias in SAD, which was further validated through transcriptomic approaches and, in mice, using different strains and by overcoming the sex-related background expression (Sasidhar et al., 2012) (Hewagama et al., 2013) (Harris et al., 2019).

## 2. X chromosome inactivation, Inc-Xist, and nuclear co-factors

With regards to the X and Y chromosomes (Figure 1), they were both derived from the same autosome but with the particularity that the X chromosome has about 1146 genes, including a high density of immune-related genes (15%, n=172) (<http://atlasgeneticsoncology.org>). On the other hand, the Y chromosome is one third the size of the X chromosome and contains 113 genes, predominantly implicated in sex determination (i.e. the sex-determining region Y gene, *SRY*, located at Yp11.2) and spermatogenesis. The X and Y chromosomes share two homologous pseudo-autosomal regions (PAR), which lie at the tips of the two arms. The human X chromosome is submetacentric with approximately 155Mb, containing a short arm (“p” for “petit” in French that means “small”) and a long arm (“q” for “queue” that means “tail”) with the arms separated by a centromere present in the middle (position 60.6Mb). It should be noted that, although the human and mouse X chromosomes are approximately 95% similar in the genes they contain, the genes are in different order along the X chromosome, the mouse X chromosome is longer at 161 Mb, and has a telocentric structure (i.e., appearing like only a long arm with a centromere close to one end) (Boyd et al., 2000). In addition, there are some potentially important differences in the gene content, such as the fact that the human X chromosome has a high concentration of Alu elements in PAR1 (at the end of the X short arm) whereas the mouse genome contains little Alu content. These differences between the human and mouse X chromosome content and structure may have differing effects on chromosome dynamics and stability (e.g., maintenance of gene silencing), gene regulation, raising questions with regards to the carryover of mouse model studies to our understanding of human autoimmune diseases (Fali et al., 2014)(Le Dantec et al., 2015)(Garaud et al., 2009).

Outside PAR, X-linked gene regulation is equalized between males and females to manage a potentially lethal problem that could arise from overexpression due to duplicate copies of active X-linked genes in females. To this end mammalian female cells have established a random X chromosome inactivation (XCI) process in order to silence one of their two X chromosomes (Lyon, 1961). The choice between the paternal or the maternal X chromosome is random, initiated during early embryogenesis, and maintained during development through subsequent cell cycles making female cells functionally haploid mosaics when considering X-linked genes. To this end, X

chromosome inactivation (Xi) is initiated by a gene, named X-inactive specific transcript (*Xist*), located in the middle of the X chromosome at Xq13.2 (position 73Mb). At the onset of XCI, the gene *Xist* expresses, on the future Xi, a long non-coding (lnc)-RNA (17 kb long in humans) that spreads along contiguous chromatin of the Xi from which it is transcribed, and contributes to the deposition and maintenance of epigenetic modifications to finally trigger a *cis* silencing cascade. To this end, lnc-*Xist* contains several functional modules that are a series of conserved repetitive motifs from A to F, modules that can specifically bind and recruit nuclear co-factors (>200) to form extensive ribonucleoprotein complexes (RNPs) (Chu et al., 2015). Lnc-*Xist* capacity to recruit RNPs requires adenosine methylation (m6A), which is mediated by the m6A writer methyltransferase-like 3 (METTL3) (Patil et al., 2016). Lnc-*Xist*-dependent co-factors at module A are responsible for epigenetic silencing that contributes to the heterochromatic state of Xi (e.g., DNA methylation, methylation of lysine 27 on histone H3 or H3K27me3, macroH2 variants), repeat B is necessary for recruitment of the polycomb repressive complex 2 (PRC2), and repeat E controls nuclear matrix anchoring that is crucial for restricting the Xi (aka, the Barr body) to the nuclear periphery where it appears as a dense heterochromatic body under DNA staining (e.g., DAPI stain). Thus, the Xi and the Xa (the active X) harbor distinct epigenetic patterns and modifications. It should also be noted that before the Xi was determined to be a sex chromosome, the Xi was originally called the “nucleolar satellite” since it is frequently found in close association with a nucleolus, even being part of the nucleolar heterochromatic shell. This suggests that the nucleolus may have a role in maintaining XCI (Brooks and Renaudineau, 2015) (Brooks, 2017).

In somatic female cells, lnc-*Xist* expression, expression of associated nuclear co-factors, and epigenetic modifications at Xi are usually maintained throughout the cell cycle and after cell division. However, exceptions exist as some genes on the Xi escape from epigenetic silencing in female cells, a process referred to as allelic escape (AE). Between Xi and Xa in female cells, AE can be tested by coupling RNA sequencing or amplification with parental single nucleotide polymorphism (SNP) data and then measuring the degree of allelic-specific expression from heterozygous sites. Tested in 29 tissues from 449 healthy controls (Tukiainen et al., 2017), the X chromosome inactivation (XCI) process accounts for at least 153/683 (23%) of the X-linked genes studied and among

them sex-biased expression is observed for 60 X-linked genes including 13 immune-related genes (e.g., ACE2, IL3RA, and CD99). Important XCI variations are reported between tissues in individuals as well as within cell types to explain the overlap but not the equality between XCI and transcript analysis. Genes that have escaped XCI are further characterized by an enrichment in epigenetic markers for activation at promoters and/or at enhancers (e.g., DNA demethylation and H3K27Ac are epigenetic markers for activation). Gender-specific epigenetic changes occur preferentially in areas adjacent to transcription factor binding sites as revealed when conducting ATAC-Seq (assay of transposase accessible chromatin with sequencing) assays (Qu et al., 2015). A defective XCI process is observed in SADs (Souyris et al., 2018) (Y. Zhang et al., 2020) and sex differences in the human peripheral blood transcriptome overlap with X-linked genes associated with SAD (Jansen et al., 2014).

### **3. Lnc-Xist, nuclear co-factors and miRNAs in immune cells**

Using a single cell imaging approach to follow lnc-Xist binding on the Xi in T and B cells, it was first observed that co-localization of lnc-Xist and the silencing epigenetic marker H3K27me3 starts to disappear from the Xi when the antigen receptor is acquired at the progenitor lymphoid cell stage in bone marrow (Wang et al., 2016) (Syrett et al., 2017). Next, lnc-Xist is missing in peripheral blood circulating mature T and B cells, but eventually is restored following activation in secondary lymphoid organs. The authors have further established that lnc-Xist expression, lnc-Xist recruitment at Xi, and lnc-Xist colocalization with the heterochromatin marker H3K27me3 in activated T and B cells can be reproduced *in vitro* following Toll-like receptor (TLR)4/9 engagement, and to a lesser extent, after B cell receptor (BCR) stimulation in B cells. Regarding activated B cells, lnc-Xist RNA binding on the Xi is maximal in follicular B cells and intermediate in germinal center B cells, plasma cells and memory B cells (Syrett et al., 2017). With regards to innate cell bone marrow progenitors, lnc-Xist is normally expressed and located at the Xi, while absent from the Xi in natural killer (NK) cells, macrophages, lymphoid and myeloid dendritic cells (DC) (Syrett et al., 2018).

XCI maintenance in lymphocyte cells is dependent on Xist-RNP complexes involving lnc-Xist and RNP co-factors as demonstrated in B cells for the X-linked immune gene *Tlr7*

that requires to be inactivated the formation of silencing complexes involving at least lnc-Xist, PTEN (phosphatase and tensin homolog, an ubiquitous RNP co-factor) and Trim28 (tripartite motif-containing 28, a tissue specific RNP co-factor) (Yu et al., 2021). Trim28 (also known as KAP1 and TIF1- $\beta$ ) interacts with zinc finger transcription factors like Yin Yang1 (YY1) (Lee et al., 2018). It has been further shown, in both activated T and B cells, that YY1 has a dual function to upregulate Xist RNA expression, on one hand, and to promote, on the other hand, lnc-Xist RNA binding on Xi and X-linked gene silencing by controlling XCI maintenance (Syrett et al., 2019) (Syrett et al., 2017).

Another characteristic of lnc-Xist (Figure 2), when not bound to Xi and present in the cytoplasm, is by sequestering miRNAs as a sponge leading to the release of RNA transcripts normally targeted by active miRNAs which, in turn, can affect cellular signaling pathways (Chen et al., 2016) (Q. Liu et al., 2020) (W. Liu et al., 2021) (Sun et al., 2021)(Renaudineau et al., 2021).

## **4. Xist in autoimmune diseases**

### **1. Anti-Barr body autoantibodies**

lnc-Xist and/or its RNP co-factors are suspected of being dysregulated in SAD and the first evidence came from reports of SLE patients or SLE-related autoimmune patients who have developed anti-nuclear antibodies directed against the Barr body (Hong et al., 2001) (Brooks et al., 2002). Anti-Barr body autoantibodies isolated from one patient were effective in recognizing an unknown 39 kDa RNP co-factor that co-localizes with lnc-Xist at Xi.

### **2. lnc-Xist/RNP localization and XCI**

As compared to controls, lnc-Xist and the marker of epigenetic repression, H3K27me<sub>3</sub>, are abnormally lost from the Xi in pediatric and adult SLE female B cells, as well as in late-stage T and B cells from female mice (NZB/W)F1. This lupus prone mouse strain is generated as F1 hybrids from NZW and NZB mice (Syrett et al., 2020) (Pyfrom et al., 2021). An upregulation of lnc-Xist has been reported in female SLE T and B cells, which suggests that the defect is not quantitative but qualitative and related to the nuclear factors or m<sup>6</sup>A implicated in the Xist-RNP complex (Y. Zhang et al., 2020). To address this question, the lnc-Xist interactome was further explored between healthy and SLE



lymphocytes showing at the transcriptional level important variations and a predominant down-regulation of the nuclear factors implicated in the Xist-RNP complex in both T (60%) and B cells (74%) from female SLE patients (Syrett et al., 2019) (Pyfrom et al., 2021). The mRNA level of the m6A writer METTL3 is also significantly decreased in PBMC from SLE patients, while upregulated in fibroblast-like synoviocytes (FLS) from RA patients (Luo et al., 2020) (Shi et al., 2021).

Analysis of the AE profiles that characterize a defective XCI process by lnc-Xist/RNP between SLE females and healthy controls have further revealed that abnormal Xi maintenance starts early in T cell embryogenesis as the SLE-associated AE pattern was similar in all T cell subsets analyzed (T naive, T memory, TH1 and TH17), while the SLE-associated AE pattern increases during B cell maturation from transitional to naive B cells (Y. Zhang et al., 2020). SLE-associated AE-linked genes are retrieved in females with inactive or active disease, broadly distributed on the two arms of chromosome X, and associated with DNA demethylation at the promoters. In RA patients, a higher AE profile is retrieved among those presenting RA-susceptibility alleles coding for the “shared epitope” (Kanaan et al., 2016).

### **3. lnc-Xist overexpression and sponge for miRNAs**

As presented in table 1 and when comparing miRNAs sponged by lnc-Xist in tumor cells and those associated with RA and SLE, up to 25 miRNAs may be suspected of being sponged by lnc-Xist in autoimmune diseases (Table 1). Among them, the lnc-Xist capacity to act as a sponge for miRNAs was explored in osteoblasts and FLS from RA patients (W. Liu et al., 2021) (Z.-Q. Wang et al., 2020) (Cheng et al., 2021). In osteoblasts from RA patients, lnc-Xist overexpression exerts a negative effect on the miRNA Let-7c through direct binding, and as a consequence STAT3 (signal transducer and activator of transcription 3), the target of the miRNA Let-7c, is upregulated. As STAT3 is implicated in both osteoclast differentiation and pro-inflammatory cytokine production (IL-6, TNF- $\alpha$ ), lnc-Xist knock-down and Let-2C upregulation could suppress inflammation and promote osteoclast differentiation and proliferation. Another miRNA affected by the sponge activity of lnc-Xist in FLS from RA patients is miR-126-3p. As a consequence, the inhibitory effect of miR-126-3p on the NF-KappaB signaling pathway is defective thus promoting in turn FLS proliferation, synovial tissue hyperplasia and inflammation resulting in joint swelling, stiffness, loss of function and pain. The interaction between lnc-XIST and miR-485 was recently described in FLS from RA patients (Sun et al., 2021).

The lnc-Xist sponge effect on miRNAs may be also suspected in other SAD as lnc-Xist is overexpressed in lymphocytes of SLE women, as stated previously, and in lymphocytes and salivary glands of SjS women (Mougeot et al., 2019).

## 5. Xist deregulation and consequences

### 1. Extrafollicular B cell pathway

B cells in SLE patients are hyperactive and display a variety of abnormalities that result from a preferential differentiation into the non-canonical extrafollicular (EF) pathway instead of the canonical follicular pathway. Normally present in all individuals, an EF B cell expansion is observed in the peripheral blood of SAD patients (>10% of B cells), including SLE, and retrieved in other pathological conditions such as innate or acquired immunodeficiency and in severe COVID19 disease cases (Woodruff et al., 2020) (Rakhmanov et al., 2010). EF B cells are defined by an unusual phenotype (Figure 3A), which has been referred to as age/autoimmunity associated B cells (ABC), atypical memory B cells, double-negative B cells, tissue-like memory B cells, CD21<sup>low</sup> B cells, or CD11c<sup>+</sup> B cells among other names. Driven in response to a TLR7 dependent type I interferon stimulation and by the T cell cytokines IL-21 and IFN- $\gamma$  (Fillatreau et al., 2021) (Soni et al., 2020) (Grasseau et al., 2020), EF B cells migrate to the tissues, where they provide a T-cell dependent primary wave of early antibodies that play a critical role in host defense but can also contribute to a deleterious autoimmune response as long-standing autoreactive B cell clones improperly negatively selected can be produced outside lymphoid germinal centers (Figure 3A).

Yu, et al. (Yu et al., 2021) have proposed that the lnc-Xist/RNP complex controls EF B cell expansion, which was first suspected by comparing transcriptional profiles of human B cells with lnc-Xist knock-down, and expanded EF memory B cells from SLE and RA patients. In order to test this hypothesis, authors have further stimulated B cells with lnc-Xist knock-down, through the co-stimulation of the BCR and TLR7 for 5 days, and found that EF memory B cells (CD11c<sup>+</sup> T-bet<sup>+</sup>) were expanded. The capacity of the lnc-Xist/RNP complex to drive EF B cell development is in line with the observation that Xist-silenced B cells showed an increased expression of 118 X-linked genes including *TLR7* (Xp22.2), *Cxorf21/TASL* (Xp21.2) an adaptor protein for TLR7/IFN type I signaling

and *CXCR3* (Xq13.1) that drives EF B cell migration to the tissues (Heinz et al., 2020). Such an observation is in line with the report of an increased expression of IFN-stimulated genes including *TLR7* and *CXCR3* in EF B cells from pre-adult and adult-onset SLE patients (Nehar-Belaid et al., 2020). In addition, lnc-Xist-dependent Xi genes, such as *TLR7* and *CXORF21/TASL*, have been characterized as showing a shift from a repressive profile (repressive epigenetic marker H3K27me3, methylated DNA) to an active profile (active epigenetic marker H3K27Ac at (super)enhancers and lower DNA CpG content) when there is lnc-Xist knock-down. Altogether, this supports the concept that, in activated lymphocytes, the lnc-Xist/RNP complex substitutes active epigenetic markers (DNA demethylation at promoters and H3K27Ac at enhancers) for silencing a set of Xi immune-related genes.

## 2. Interferon type I pathway

The TLR endosomal pathway involves 5 X-linked genes (*TLR7*, *TLR8*, *cxorf21/TASL*, *IRAK1*, and *IRF7*) acting as master genes through the report of genetic associations in SLE and RA (Elkon and Briggs, 2020) (Arleevskaya et al., 2020) (Bettacchioli et al., 2021). As reported in Figure 4, endosomal TLR signaling leads to the activation of two dual signalling pathways including the type I interferon pathway that can be prevented by hydroxychloroquine, used as first line of treatment in RA and SLE, and effective to prevent endosomal acidification and in turn TLR activation (Cenac et al., 2021). The key role played by *TLR7* is further supported by the observation that translocation of the *TLR7/8* locus located at the telomeric end of the X chromosome onto the Y chromosome leads to the Y-linked autoimmune acceleration (Yaa) phenotype in male mice (Subramanian et al., 2006). The Yaa strain develops lupus-like phenotypes with elevated autoantibodies and glomerulonephritis, phenotypes that could be reversed when a *TLR7* null mutation is introduced on the X chromosome (Santiago-Raber et al., 2008). Animal models have also revealed that *TLR8*-deficiency in monocytes and *TLR9*-deficiency in B cells and neutrophils control the *TLR7* capacity to mediate lupus (Desnues et al., 2014) (Umiker et al., 2014). The negative effect of *TLR9* was confirmed in subsequent studies showing that *TLR9* knock-down in the lupus-prone mice MRL/Lpr abrogated the production of anti-dsDNA and anti-chromatin antibodies (Tilstra et al., 2020).

## 3. Other pathways

The over representation of the X-linked genes in SLE women is not restricted to the interferon type I pathway as revealed from the analysis of lymphocytes from SAD

women when conducting genome-wide association studies (GWAS), methylome-wide association studies (EWAS), and transcriptomic analysis (Arvaniti et al., 2020). Indeed, other immune X-linked genes affected are CD40L (T cell signal for B cells), CXCR3 (extrafollicular and tissular chemotaxis), OGT (O-GlcNacylation enzyme; lymphocyte activation), FoxP3 (Tregs), BTK (B cell activation), MECP2 (lymphocyte growth), ACE2 (immune regulator), and several immune related micro-RNAs (miR7f-2, miR188-3p, miR-421, and miR-503) (Hewagama et al., 2013). Although limited as compared to SAD patients, a sex expression signature characterizes women when comparing peripheral blood mononuclear cells and tissues between healthy males and females across different age groups and from different continents (Oliva et al., 2020). Of note in SLE men, TNF-related factors predominate as compared to the interferon signature retrieved in SLE women (Hui-Yuen et al., 2016).

### **Conclusion:**

Sex-specific effects contribute to SAD development and woman have a higher risk over males. The X chromosome contains multiple immune-related genes as well as the *Xist* coding gene for an lnc-RNA that regulates XCI in female cells when associated with RNPs. As the field has progressed toward characterizing lnc-Xist as an important player in SAD, new challenges have started to open up. From the basic point of view, how dysregulations reported at lnc-Xist/m6A/RNPs/miRNAs in SAD affect the immune response needs to be further explored as the possibility to reverse this process exists. To this end and as presented in Figure 5, we can already propose several options in order to pave the way for future therapeutic options through the modulation of (i) lnc-Xist expression; (ii) METTL3 and m6A deposition on lnc-Xist to control RNP binding, the role of m6A on binding with miRNAs may also be suspected; (iii) RNP expression; and (iv) the control of the sponge effect on miRNAs.

**Table 1: Suspected miRNAs sponged by Inc-Xist in systemic autoimmune diseases.** In order to establish this list, a pubmed search (January 2022) was conducted first using as key words “Xist”, “miRNA”, “sponge”, and “human”, and next the list was compared to the HMDD v3.2 database using as key words “SLE” and “RA” (<http://www.cuilab.cn/hmdd>)

<b>miRNA (hsa)</b>	<b>Cell type</b>	<b>Target genes</b>	<b>Pathway(s)</b>	<b>SLE, RA</b>	<b>Reference</b>
Mir-let-7	GC, urine	AURKB	cytokines	RA	(Wang et al., 2020) (Han et al., 2020)
mir-101-3p	NSCLC, GC, RB	EZH2, ZEB	Glycolysis, cell growth, MAPK	SLE	(Hua et al., 2021) (Chen et al., 2016) (Cheng et al., 2019) (Yang et al., 2013)
mir-106a	LUAD, ovarian cancer, plasma, PBMC	MDM4	Cell growth, TGF- $\beta$ 1	SLE, RA	(Marshall et al., 2019) (Guo et al., 2021) (Carlsen et al., 2013)
mir-106b-5p	RCC	p21	G0/G1 cell arrest	Unknown	(Sun et al., 2019)
Mir-122	Kidney, plasma	PFKFB2	AMPK pathway	RA	(Cheng and Wang, 2020) (Wang et al., 2015)
Mir-125b-5p	LSCC, PBMC, serum, FLS	TRIB2, ETS1, STAT3	cytokines	SLE, RA	(C. Liu et al., 2020) (Luo et al., 2013)
mir-1254	LUAD	MAPK8IP3		Unknown	(Marshall et al., 2019)
Mir-126	GC, PBMC, CD4+ T cells, FLS	IRS1, PIK3R2, DNMT1	cytokines, epigenetics	SLE, RA	(Cheng et al., 2020) (Zhao et al., 2011) (Yang et al., 2015) (W. Liu et al., 2021)
Mir-129-5p	ESCC	CCND1	Cell growth	Unknown	(Wang et al., 2021)
mir-1301	LUAD	EWSR1, CENPT		Unknown	(Marshall et al., 2019)
mir-137	NSCLC, PC	PXN, TGF- $\beta$ 1, NOTCH1	Cell viability	Unknown	(Jiang et al., 2018) (Liu et al., 2019)
Mir-142-5p	Kidney, RB, CD4+	PDCD4	Cell growth, T and	SLE	(Tang et al., 2020)

	T cells		B cell activation		(Xu and Tian, 2020) (Ding et al., 2012)
Mir-153	OS	SNAI1	Oxydative stress	Unknown	(Wen et al., 2020)
Mir-155	HCC, PBMC, urine, serum, SF, monocytes	Sox6, PTEN, CREB, SOCS1, CASP10, APAF-1	apoptosis, cytokines	SLE, RA	(Lin et al., 2018) (Lashine et al., 2015) (Rajasekhar et al., 2017) (Li et al., 2013)
Mir-17	Aortic tissues, PBMC	PTEN, E2F1, cMyc, TRAF2, cIAP1	Cell growth, IFN signature, cytokines	SLE, RA	(X. Zhang et al., 2020) (Sarhan et al., 2015) (Akhtar et al., 2016)
Mir-181a	HCC, pDC, PBMC	PTEN	Cell growth, IFN signature	SLE	(van den Hoogen et al., 2018) (Lashine et al., 2011)
Mir-185	GC, kidney	TGF- $\beta$ 1	Cytokines	SLE	(Q. Zhang et al., 2018)
mir-200b-3p	HCC, serum	ZEB	metastasis	SLE	(L. Liu et al., 2021) (Liu and Xu, 2019) (Wang et al., 2011)
Mir-200c	BCSC, BCC, kidney	ANLN	Cell growth	SLE	(M. Zhang et al., 2020) (Dai et al., 2009)
mir-20a	LUAD, BC, T cells	PARP6, TF	Coagulation, cytokines	SLE, RA	(Marshall et al., 2019) (Teruel et al., 2011) (Guggino et al., 2018)
Mir-204	RB, HUVEC, T cells	TLR4	Cell growth	RA	(Yao et al., 2020) (Lai et al., 2017)
Mir-21	OS, urine, T and B cells	PDCD4, TLR8, MaR1	Cytokines, chemokines	SLE, RA	(Zhang and Xia, 2017) (Tangtanatakul et al., 2019) (Young et al., 2017) (Jin et al., 2018)
Mir-212-3p	Kidney, T cells	ASF1A/BRWD1	cytokines	Unknown	(Cheng and Wang, 2020)
Mir-214-3p	EOC, PDLSC		ALP activity	RA	(Wang et al., 2018) (Lai et al., 2017)
Mir-23a	Melanoma, kidney,	GINS2, IKK $\alpha$	Cytokines	SLE, RA	(Hao et al., 2021)

	cartilage				(Dai et al., 2009) (Hu et al., 2017)
Mir-27b-3p	SMSC, OSCC	ADAMTS-5		Unknown	(Zhu et al., 2021)
mir-29b	LUAD, HSF	CRIPAK, PAN2, COL1A1, FN1, DNMT1	Cell growth, epigenetics	SLE	(Marshall et al., 2019) (Cao and Feng, 2019) (Qin et al., 2013)
Mir-29c	NPC, LSMC, B cells	H2AX	Cell growth	SLE	(Han et al., 2017) (Duroux-Richard et al., 2015)
Mir-30b	WI-38 cells	CCL16	LPS inflammatory	Unknown	(Xu et al., 2021)
mir-30c	LUAD	ING5		Unknown	(Marshall et al., 2019)
miR-320	HUVEC	NOD2		Unknown	(Xu et al., 2018)
Mir-329	glioma	CREB1	Cell growth	Unknown	(Y.-P. Wang et al., 2020)
Mir-335	NSCLC, BC, B cells	SOD2	ROS	SLE	(Liu et al., 2019) (Chen et al., 2020) (Duroux-Richard et al., 2015)
miR-34a	NPC, CC, TC, PC, T cells, FLS	E2F3, Wnt1, YAP, XIAP	Wnt/ $\beta$ -catenin, EGFR/TGF- $\beta$ 1, inflammation, apoptosis	SLE, RA	(Song et al., 2016) (Sun et al., 2018) (Liu et al., 2018) (Zou et al., 2020) (Claßen et al., 2017) (Niederer et al., 2012)
mir-361	LUAD, RB, pDC	MAPK8IP3, PZBTB40, STX7	IFN signature	SLE	(Marshall et al., 2019) (Yang et al., 2020) (van den Hoogen et al., 2018)
mir-424	Pituitary gland, DPC		Hedgehog pathway	Unknown	(Cuthbert and Lipsky, 1986) (Lin et al., 2020)
mir-429	PC, serum, urine	ZEB1	Cell migration	SLE	(Shen et al., 2019) (Wang et al., 2011)
mir-449	NSCLC	Bcl-2	apoptosis	Unknown	(Zhang et al., 2017)
miR-485	FLS		cytokines	RA	(Sun et al., 2021)
miR-491-5p	NPC			Unknown	(Cheng et al., 2018)

miR-494	EC, kidney	CDK6	Jak2/STAT3 axis	SLE	(Chen et al., 2019) (Dai et al., 2009)
mir-520	NSCLC	BAX	apoptosis	Unknown	(T.-T. Liu et al., 2021)
Mir-653	Chondrocytes	SIRT1	Inflammation	Unknown	(Lian and Xi, 2020)
mir-660	LUAD	CCDC57		Unknown	(Marshall et al., 2019)
mir-93	LUAD, B cells, plasma	LPIN3		SLE	(Marshall et al., 2019) (H. Zhang et al., 2018)

**Abbreviations:** LUAD: lung adenocarcinoma; NSCL: non-small-cell-lung carcinoma; WI-38 cells: lung fibroblast cell line; NPC: nasopharyngeal carcinoma; HCC: hepatocellular carcinoma; OS: osteosarcoma; GC: gastric cancer; BCSC: bladder cancer stem cell; CC: colon cancer; HUVEC: human umbilical vein endothelial cells; EOC: epithelial ovarian cancer; TC: thyroid cancer; RB: retinoblastoma; EC: esophageal cancer; RCC: renal cell carcinoma; PC: pancreatic cancer; HSF: human skin fibroblasts; ROS: reactive oxygen species; PDLSC: periodontal ligament stem cell; LSCC: laryngeal squamous cell carcinoma; BC: Breast/bladder cancer; ANLN.; DP: dermal papilla cells; LSMC: leiomyoma smooth muscle cells; SMSC: synovium-derived mesenchymal stem cells; OSCC: oral squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma; PBMC: peripheral blood mononuclear cells; pDC: plasmacytoid dendritic cells; FLS: fibroblast-like synoviocytes; SF: synovial fluids; RA: rheumatoid arthritis



## Figures

**Figure 1: Schematic map of the Y and X chromosomes.** The short (p) arm, the long (q) arm, the pseudo-autosomal regions (PAR)1 and 2, and the X inactivation specific transcript (*Xist*) locus are indicated. Comparative location of X genes (n=1146), X immune-related genes (n=172) and X-linked genes dysregulated in peripheral blood between women and men with systemic lupus erythematosus (SLE) (Hewagama et al., 2013).

**Figure 2: Long non-coding (lnc)-Xist RNA dysregulation and consequences in women with systemic autoimmune diseases (SADs).** Lnc-Xist, when coupled with ribonucleoproteins (RNPs), maintains both DNA methylation (5-mC, 5'-methylcytosine) and the repressive mark H3K27me3, and then controls transcription from the inactive X chromosome in females. This dosage compensation process prevents X gene imbalance between male (XY) and female (XX) cells. In addition, lnc-Xist can positively regulate miRNAs, when lnc-Xist harbors specific miRNA target sequences, thereby decreasing the abundance of miRNAs. In women with SADs, lnc-Xist/RNP dysregulation is suspected to affect X chromosome epigenetic marks (5-mC, H3K27me3) as reported when lnc-Xist and RNPs are lost by knock-down (Yu et al., 2021); and miRNA sponging when lnc-Xist is upregulated.

**Figure 3: The non-canonical extrafollicular (EF) pathway of B cell activation is driven following TLR7 engagement and by the T cell cytokines IL-21 and IFN- $\gamma$ .** **A:** The autoreactive B cell (ABC) phenotype shared pan-EF markers (CD19+, CD21<sup>low</sup>, CD11c<sup>high</sup> and t-bet+) and differentiation markers to distinguish naïve (IgD+, CD27-), memory (IgD+/-, CD27+) from double negative type 2 (DN2, IgD-, CD27-, CXCR3+) EF B cells. **B:** Main characteristics of the non-canonical EF-pathway as compared to the canonical germinal center B cell pathway.

**Figure 4: The role of X chromosome and autosomal genetic variants associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in the host immune response.** Following ribonucleic-acid (RNA) mediated Toll-like receptor (TLR) 7/8 or deoxyribonucleic-acid (DNA) mediated TLR9 activation, a supramolecular organization complex is initiated. Two dual pathways can be activated, the pro-inflammatory Myd88/IRAK/NF-kB pathway, while following endosomal acidification

and proteolytic cleavage, TLRs interact with Slc15A4 and its adaptor (cxorf21/TASL) leading to IRF5 activation and in turn causes type I interferon gene transcription. The 5 X-linked genes (TLR7, TLR8, cxorf21/TASL, IRAK1 and IRF7) associated with SLE and/or RA.

**Figure 5:** The control exerted by lnc-Xist on the inactive X chromosome (Xi) and by sequestering miRNAs is altered in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) due to cell specific dysregulations in the expression of lnc-Xist, methyltransferase like 3 (METTL3), an adenosine methylation (m6A) writer, and ribonucleoproteins (RNPs). As a consequence, dysregulation of X genes and miRNAs are suspected of influencing the interferon pathway and the NF- $\kappa$ B/pro-inflammatory cytokine pathway, two pathways upregulated in SLE and RA.

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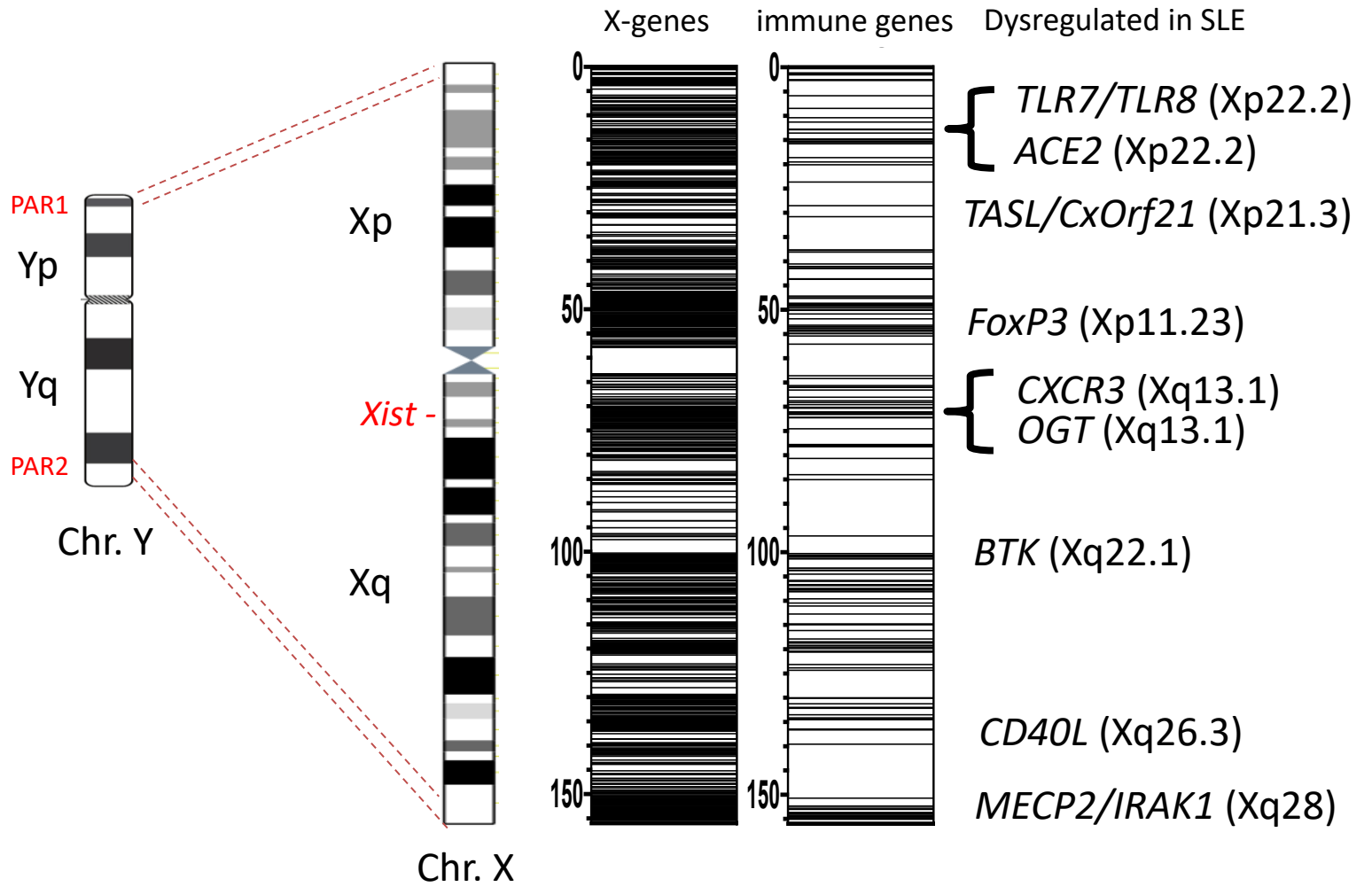
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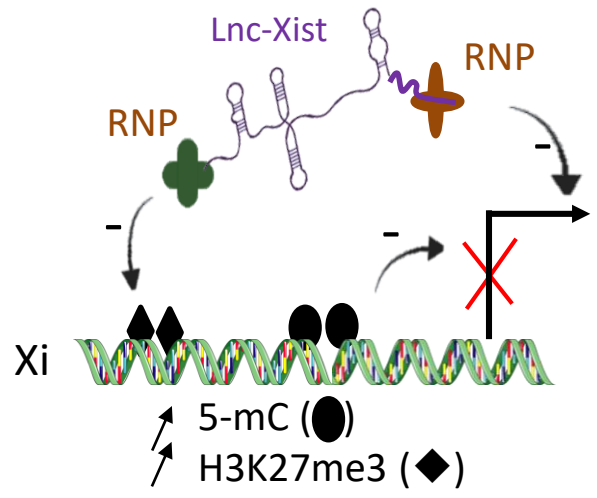
Figure 1



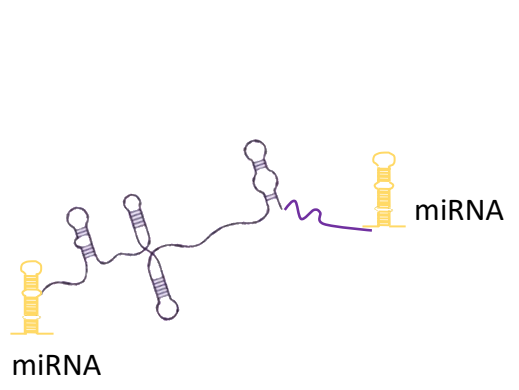
Healthy controls

Systemic autoimmune diseases

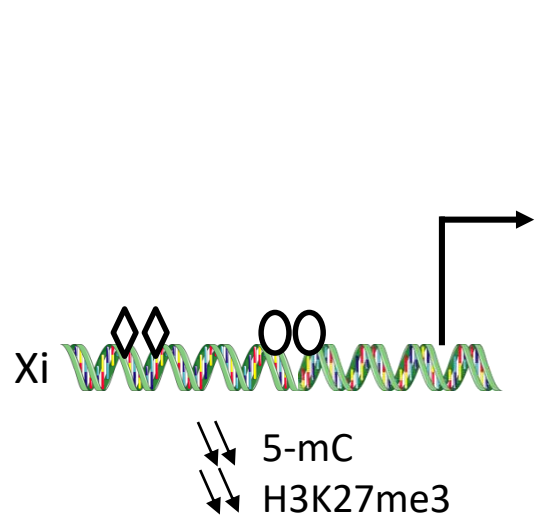
*XCI process (at Xi chromosome)*



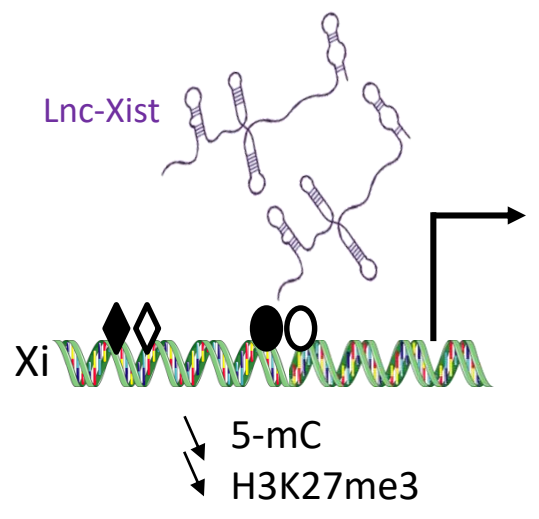
*Lnc-Xist sponge effect (cytoplasm)*



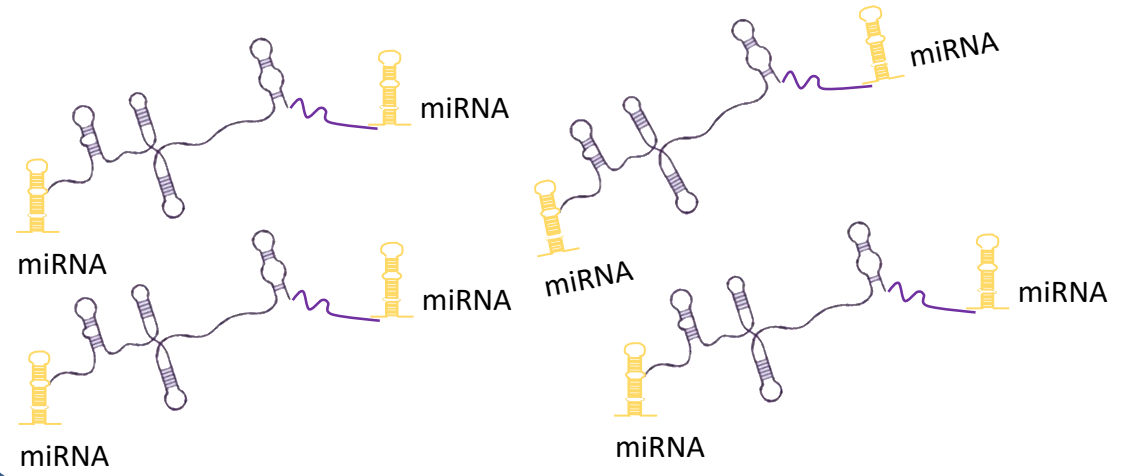
1) *Lnc-Xist loss*



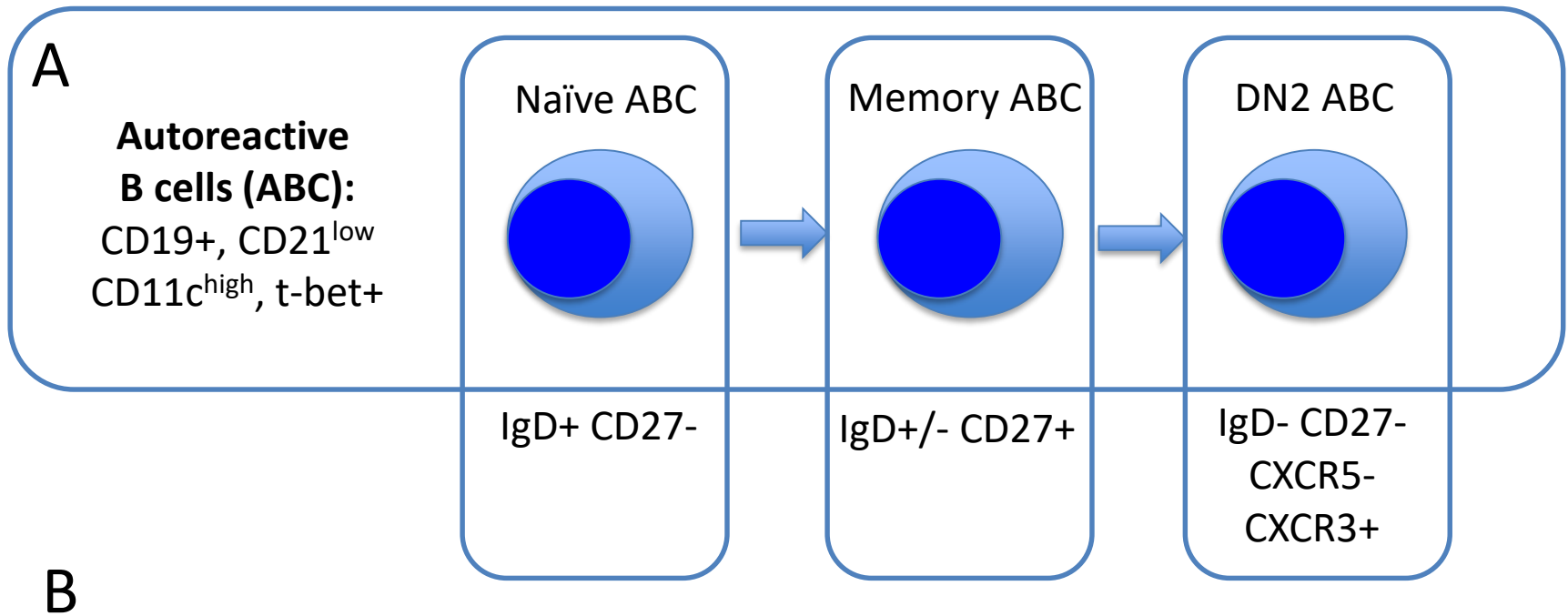
2) *RNPs loss*



3) *Lnc-Xist upregulated (strong sponge effect)*

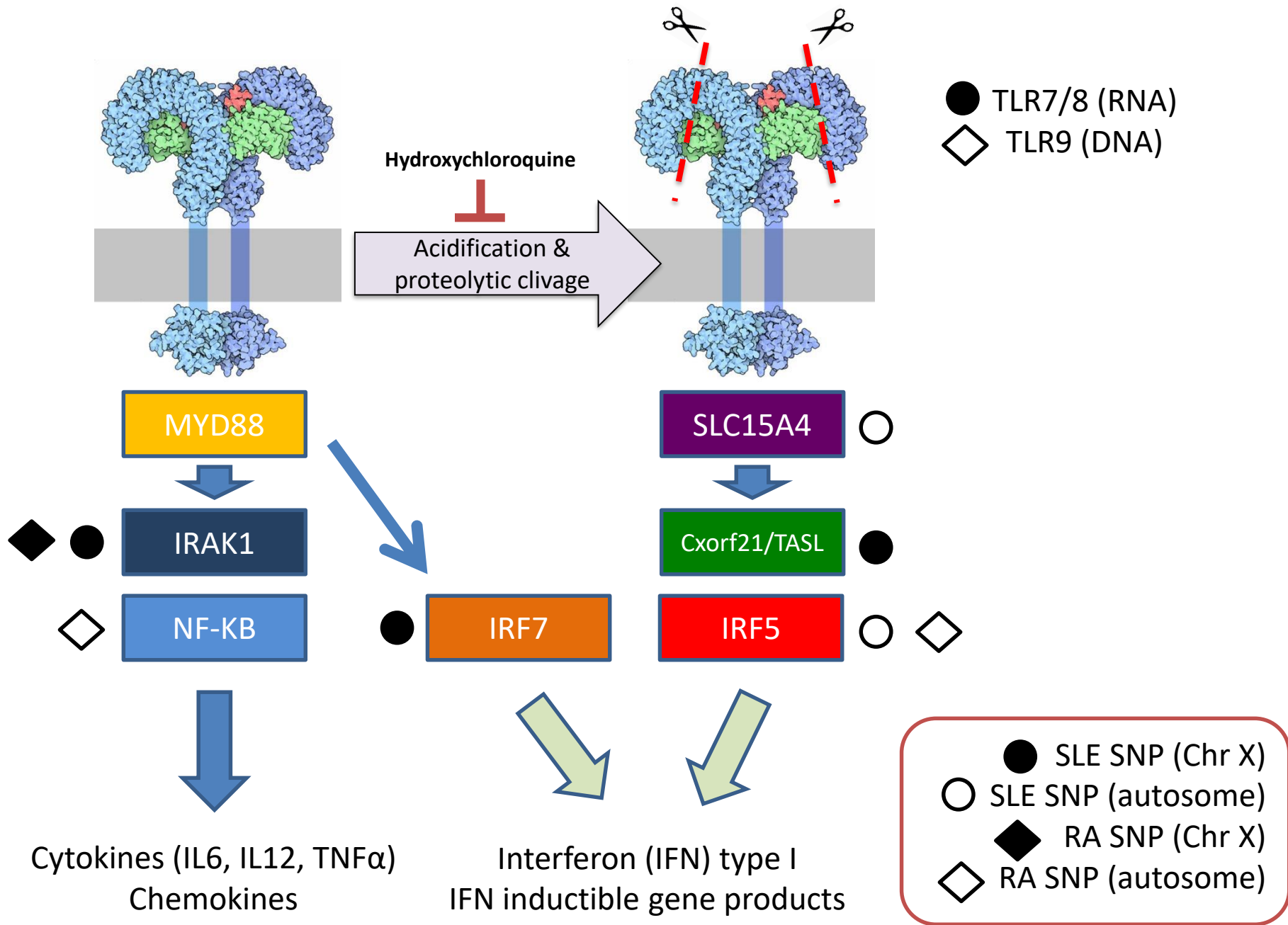


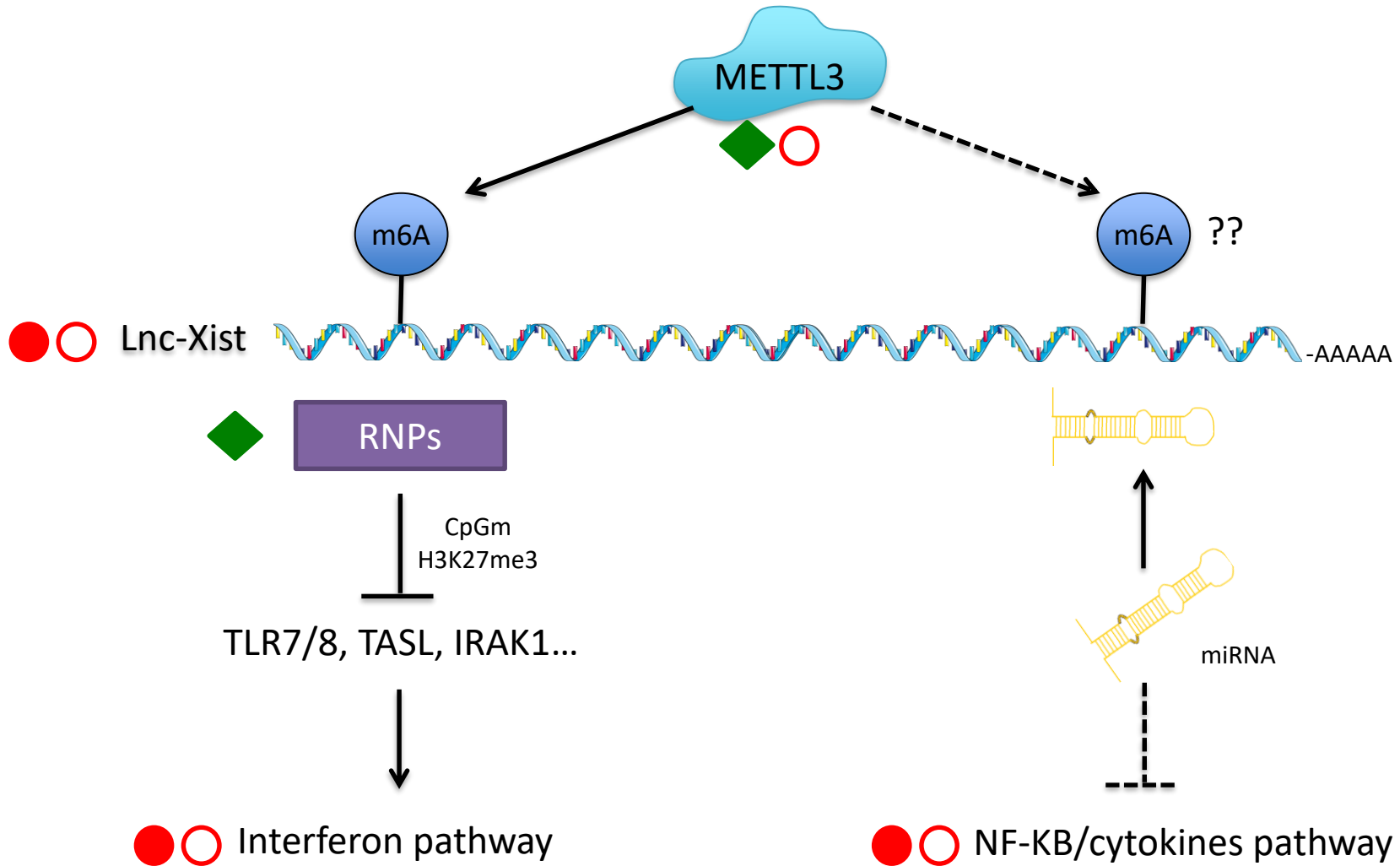




Pathway	Extrafollicular	Follicular
T cell dependence	Yes	Yes
Female bias	Yes	No
Class switch	Yes	Yes
Affinity maturation	Low	Yes
Negative selection	Low	Yes
Time to antibody	3-5 days	≥7 days

Figure 4





●	Up-regulated in SLE	◆	Down-regulated in SLE
○	Up-regulated in RA	◇	Down-regulated in RA