Cytokine and Growth Factor Reviews 49 (2019) 42–58

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Retrotransposons shuttling genetic and epigenetic information from the nuclear to the mitochondrial compartment: Do they play a pathogenetic role in scleroderma?

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ARTICLE INFO

Keywords:
Endogenous retroelements
Retrotransposons
Viruses
Systemic sclerosis
Autoimmune diseases
Pathogenesis

ABSTRACT

Endogenous retroelements are a class of ancient defective viral insertions contained in the genome of host cells, where they account for up to 40% of all DNA. Centuries of co-existence in host genome have led to the development of immunotolerance to endogenous retroelements, most of which are defective and unable to replicate or transcribe functional proteins. However, given their capacity to move across the nuclear and mitochondrial genome and recombine, they could mix phenotypes and give rise to infections that may trigger innate and adaptive immune responses by sensing receptors capable of recognising foreign nucleic acids and proteins. It has recently been suggested that they play a role in the pathogenesis of autoimmune diseases on the grounds of their partial reactivation or the epigenetic control of host gene transcription. A number of studies have confirmed their contribution to the development of rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, but there is still a lack of data concerning systemic sclerosis (SSc). Their role in the pathogenesis of SSc can be hypothesised on the basis of mitochondrial and nuclear chromatinic damage, and hyperactivation of the immune pathway involved in antiviral defense. SSc is characterised by genetic and immunological evidence of a viral infection but, as no viral agent has yet been isolated from SSc patients, the hypothesis that partial reactivation of endogenous retroviruses may trigger the disease cannot be excluded and deserves further investigation.

1. Introduction

Viruses are the most elemental infective agents containing nucleic acids that need to invade and replicate inside a host cell: their extremely simplified structure owns the minimum equipment necessary for extra-cellular survival, infection and reproduction, and exploits the cellular environment and energy for the sole purpose of replication [1]. Viruses can give rise to latent infection and enter the host genome, thus modifying a cell's epigenetic machinery in favor of survival [2], and viral infections have been considered pathogenetic triggers of many autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS), Fig. 1. If a latent viral infection develops inside a cell belonging to the immune system, as in the case of Epstein Barr virus (EBV)-infected B lymphocytes, it may lead to an unwanted immune response. In addition, viral proteins may share cross-domains with self proteins and foment autoimmunity by means of molecular mimicry: for example, EBV protein BamHI Z EBV replication activator (ZEBRA) shares homology with the transcription factors activator protein-1 (AP-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and the EB nuclear antigen-1 (EBNA-1) protein has similarity with the Smith auto-antigen in SLE [3,4].

Viral genome may consist of DNA or RNA: RNA viruses have the oldest origin according to the RNA world hypothesis and have been replaced in modern times by viruses with a DNA genome [5]. However, in the evolutionary scenario of viruses and cells, there may have been duplex of DNA and RNA [6], and this inter-changeability is currently reflected by retroviruses, which consist of RNA viruses that integrate themselves into host cell genome through a template of DNA that is subsequently retro-transcribed to a new RNA filament. During evolution, thousands of viral and retroviral infections have invaded the eukaryotic and prokaryotic nuclear and mitochondrial genome, and thus

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https://doi.org/10.1016/j.cytogfr.2019.10.001
Received 11 July 2019; Received in revised form 9 October 2019; Accepted 10 October 2019
Available online 18 October 2019
1359-6101/

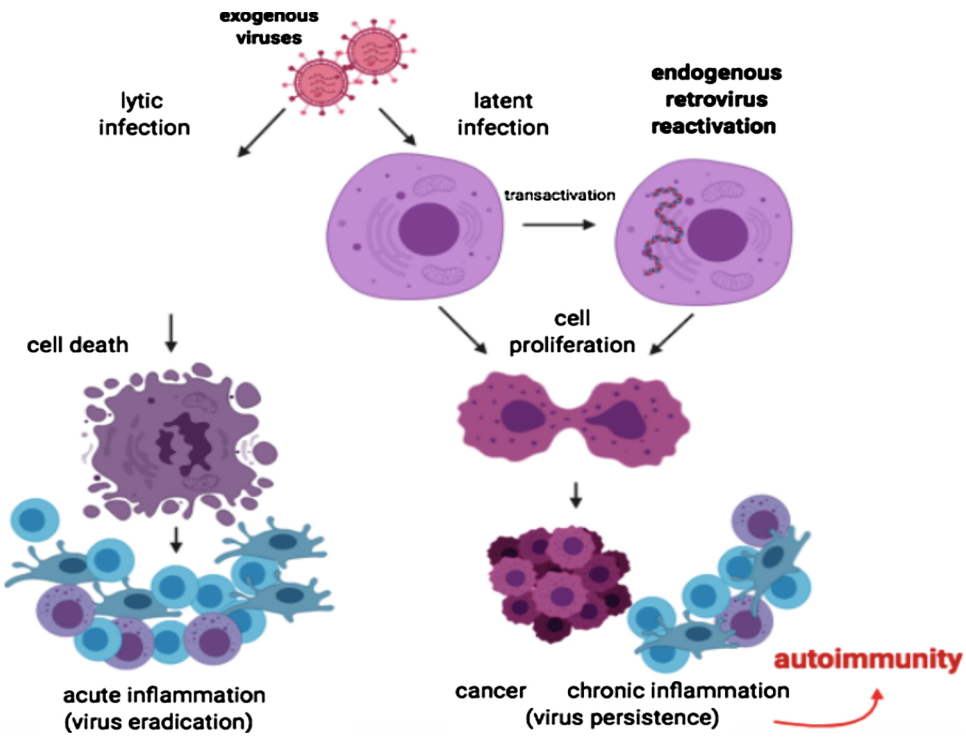

Fig. 1. Cell fate following the infection of exogenous viruses or the reactivation of endogenous retroviruses.
Exogenous viruses can establish lytic or latent infections. In the first case, host cells are destroyed soon after the release of virions. This induces an acute immune response that can eradicate the infection through the killing of infected cells. In the second case, viruses insert their genetic material into host cell genome, where it can epigenetically modify gene transcription in favor of cell survival and proliferation. As a consequence, a low viral load and the periodic release of viral antigens can elicit a chronic immune response, which, however, fails in definitely counteracting the infection. The final result can be cancer or autoimmunity. Shifting from latent to lytic infections is possible in immune-compromised individuals. The re-emergence of endogenous retroviruses resembles the latent cycle of exogenous viruses and its shift towards a lytic phase.

contributed to generating nearly half of all of the genetic material stored in vegetal and animal cells [7]. These foreign insertions or endogenous retroelements have been progressively tolerated and ignored by the host, partly because the mutational burden acquired over time prevents their transcription and replication. However, given the highly dynamic nature of cellular genome, which can generate fragments that are able to move from the nuclear to the cytosolic and mitochondrial compartments, integrate in distant DNA sites and thus introduce chromatin breaks, and complement each other to form functional virions, the hypothesis that ancient retroviruses can reactivate and trigger an immune response is now considered confirmed.

Endogenous retroelements can be divided into those that can replicate and those that cannot replicate but retain the capacity to transcribe some of their genes. Most retroelements have a defective open reading frame (ORF) and consequently impaired gene transcription but, when moving across chromatin, fragments can jump next to a functional ORF and combine with each other to become functional proviruses that express proteins and stimulate the immune system [8].

Although centuries of closeness to host genes have induced an acquired tolerance, there is evidence that the aberrant expression of endogenous retroelements can sometimes elicit an immune response or drive a cell to apoptosis in a manner that is similar to that of exogenous viral infection. RNA filaments bound to ribonucleoproteins (as well as newly synthesised *env* or *gag* proteins) can stimulate both the innate and adaptive immune systems by interacting with sensor receptors, which leads to the final assembly of the inflammasome platform and the activation of B and T lymphocytes [9,10]. A number of studies have shown a significant association between human endogenous retroviruses (HERVs) and autoimmune diseases such as RA, SLE, psoriasis and multiple sclerosis (MS) [11–13].

Systemic sclerosis (SSc) is a connective tissue disease that is characterised by the triad of autoimmunity, endothelial dysfunction and fibrosis, but the complex interplay of immune cells, vascular cells and fibroblasts still obscures its pathogenesis. Its clinical manifestations include skin and visceral fibrosis, and Raynaud's phenomenon has been described in more than 90% of patients, but their severity greatly varies from patient to patient [14].

There is still no evidence concerning the plausible role of transposable elements in the pathogenesis of SSc. A number of genome-wide association studies (GWAS) have shown that the disease has an altered genetic landscape that consists of both coding and non-coding sequences [15], and it is known that its pathogenesis is characterised by a redox imbalance that leads to the production of the reactive oxygen species (ROS) that are ultimately responsible for microvascular damage and fibrosis [16]. The generation of ROS may be due to mitochondrial dysfunction as some SSc animal studies have shown that damaged mitochondrial DNA (mtDNA) may underlie the redox imbalance and lung tissue matrix deposition [17]. Interestingly, it has been reported that cytosolic and mtDNA can be imported into the nucleus by means of energy-dependent transporters such as importin 7 [18], and deficient transfer may lead to the activation of the interferon-type I (IFN-I) response involved in the pathogenesis of many autoimmune diseases, including SSc [19]. It is known that nucleic acid fragments can stimulate cytosolic pattern recognition receptors to mount an immune response, but there is a lack of pre-clinical and clinical studies of how this mechanism may work in SSc; furthermore, the possible role of endogenous retroelements shuttling between the nuclear and mitochondrial compartments is still only hypothetical.

The aim of this narrative review is to summarise the current evidence concerning transposable retroelements and their involvement in autoimmune diseases, particularly SSc. Results can be divided into three groups: 1) description of genomic transposable elements and their role in cell nuclei and mitochondria; 2) discussion of the evidence relating genomic transposable elements to autoimmunity; and 3) the development of a hypothesis concerning the possible role of genomic transposable elements in the pathogenesis of SSc.

2. Genomic transposable elements in cell nuclei and mitochondria

2.1. Classification and biologic properties of nuclear genomic transposable elements

In 2003, the completion of the Human Genome Project led to the surprising discovery that the human genome has more non-coding than coding DNA and that, although it contains about 30,000 genes, only 2% of nuclear DNA is committed to protein synthesis [20]. The parallel

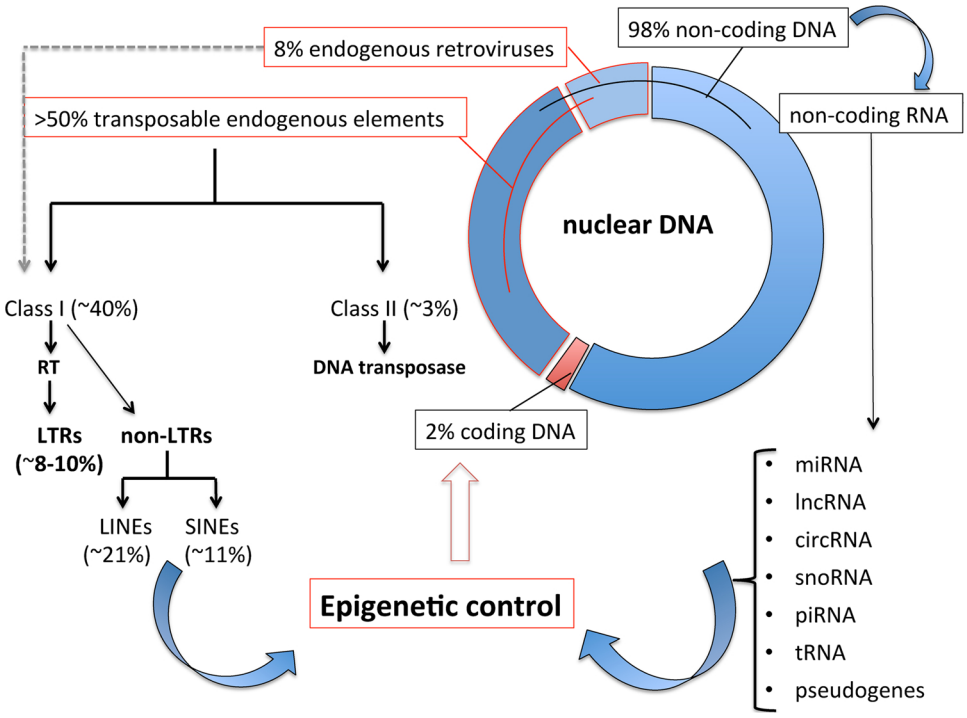

Fig. 2. Schematic representation of human nuclear coding and non-coding DNA.
Nuclear genome mostly consists of non-coding DNA sequences, which are partly transcribed into the non-coding RNA. In addition, more than 40% of the non-coding DNA is made of transposable elements, in turn subdivided into class I retrotransposons, also known as endogenous retroelements, and class II DNA transposons. Endogenous retroelements use reverse transcriptase and include endogenous retroviruses, while DNA transposons encode a DNA transposase. Class I retroelements are further classified into LTRs and non-LTRs. The main role of non-coding DNA, either as non-coding RNA either as transposable elements, is the epigenetic control of coding genes.
Abbreviations: RT, reverse transcriptase; LTRs, long terminal repeat elements; LINE, long interspersed nuclear elements; SINE, short interspersed nuclear elements; miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; snoRNA, small nucleolar RNA; piRNA, piwi-interacting RNA; tRNA, transfer RNA.

Encyclopedia of DNA Elements (ENCODE) project showed that the function of non-coding DNA seems to be mainly regulatory, as it can be transcribed into the non-coding RNA involved in controlling the transcription of coding genes. In addition, more than half of the human genome consists of movable elements (transposons), about 40% of which are endogenous retroelements [21]. The mobile DNA elements are divided into class I retrotransposons (also known as endogenous retroelements) and class II DNA transposons, which represent 3% of the human genome and encode a transposase that allows them to be cut and pasted into other DNA regions, Fig. 2.

Like exogenous retroviruses, class I retrotransposons use reverse transcriptases to catalyse the reverse transcription of DNA and insert it into host cell genome but, unlike retroviruses, cannot infect new cells or individuals, and simply replicate inside the same cell and are then inherited as a genetic trait during meiosis and mitosis [22].

Since the first experiments by McClintock using vegetable transposable retroelements [23], the classification of these genomic movable fragments has changed over time depending on the biological context. The first attempts in botany attributed endogenous transposable retroelements to the class of *Retroelementopside* in accordance with the classification of Hanson and Herslop-Harrison [24], which was further divided into the orders of *Retrovirales* that can replicate and transcribe their genes, and *Retrales* that cannot. Endogenous retroelements were later also detected in animal genomes and single prokaryotic or eukaryotic cells, and their currently most widely accepted human classification separates long terminal repeat elements (LTRs), including HERVs and mammalian apparent LTR retrotransposons (MALRs), and non-LTR elements, which include long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs) [25].

LTRs account for about 8–10% of human genome [26]: there are more than 200 families in the *repbase* database of eukaryotic repetitive elements [27], which Medstrand et al. have grouped into six superfamilies [28]. They usually contain genes encoding endonucleases and reverse transcriptases, and HERVs (which account for 8% of the human genome and are phylogenetically related to β-retroviruses) retain the genes encoding the viral proteins *gag*, *pro*, *pol* and *env* but, as they have dysfunctional ORFs, cannot reactivate [29]. However, by transposing over chromatin, various HERVs can insert themselves near to functional genes and recombine to form complete and functional proviruses through a process known as phenotypic mixing, although healthy cells can usually epigenetically control the mixing and prevent their re-emergence. This mechanism seems to be tissue-specific and has been described in germinal and embryonic cells and in cancer tissues. It is known that endogenous retroelements can have different tasks in germinal and somatic cells and, as they are inherited, may favour placental development and immune tolerance towards the offspring. Animal experiments have shown that proteins such as replication timing regulatory factor 1 (RIF-1) and Krab-associated protein-1 (KAP-1) are essential during embryogenesis as they prevent endogenous retroelement reactivation by epigenetically modifying chromatin status [30,31]. It is worth noting that RIF-1 is a telomere-associated protein whose main function is to protect DNA integrity. On the contrary, the reactivation of retroelements in somatic cells could give rise to an unwanted immunological response [8]. In addition, by transposing near to coding genes, proto-oncogenes or onco-suppressors, HERV promoter and enhancer sequences may induce their transcription *in cis*, thus favoring the development of genetic diseases or cancer [32,33].

LINEs and SINEs respectively account for about 21% and 11% of human DNA as there are very many copies in the genome. LINEs may produce the proteins ORFp1 (an RNA-binding protein) and ORFp2 (an endonuclease), but SINE sequences lack ORFs and exploit LINE machinery to duplicate [8,34]. The ORF elements in LINEs are in the 5′untraslated region, and may regulate downstream gene translation [35]. SINEs, which contain *Alu* sequences and a variable number of tandem repeats (VNTRs), can transpose near an ORF element by exploiting the *in cis* promoting effect of LTRs or other autonomous elements.

Given their tendency to duplicate, non-LTR sequences seem to have contributed to the development of telomeres during eukaryotic evolution. Telomeres are short repetitive sequences that are rich in guanine and end in 3′ as a single strand. They are synthesized by means of a telomere-specific reverse transcriptase (or telomerase) whose mechanism of action is very similar to that of viral reverse transcriptase [36,37]. The length of telomeres has been associated with cell aging and aging-related morbidity [38] and, given the close interconnection between telomeres and non-LTRs, this suggests that LINEs and SINEs

are central to the pathogenesis of many diseases. For example, SINE-VNTR-*Alu* (SVA) sequences correlate with human brain evolution and genetic diseases [39], and a deficit in telomerase activity has been associated with autoimmunity and premature immune aging [40].

2.2. Genetic transposable elements and mitochondria

In eukaryotic cells, mtDNA consists of a circular, double-stranded genome containing 37 genes, 13 encoding proteins and 24 encoding RNA. Each strand has a different guanine-cytosine (GC) composition, thus allowing its differentiation into heavy (H)-strand and light (L)-strand mtDNA [41]. MtDNA may vary among ethnic groups and can harbor single nucleotide polymorphisms (SNPs) that allow haplogroups to be distinguished. Five mtDNA haplogroups (H, J, K, T and U) have been described in Caucasians, and their association with the risk of certain human diseases is still debated. Some haplogroups may be associated with accelerated aging, inflammation, oxidative stress and vascularisation. The use of H mt and J mt cybrids (cells with identical nuclear DNA but different mtDNA) has shown that the J haplogroup shows less ROS production and electron transport, and an altered expression of nuclear genes encoding complement, apoptosis and inflammation mediators [42]. In addition, subjects carrying a J haplogroup produce less adenosine triphosphate (ATP) and more lactate due to an increase in the glycolytic pathway, and show impaired inactivation of the complement cascade because of the under-expression of complement factor H inhibitor, complement decay-accelerating factor (DAF) and B-cell lymphoma (BCL)2-like13. They also express less retinoic acid receptor alpha (RARα), a protein that increases the production of vascular endothelial growth factor (VEGF), and show reduced angiogenesis.

It is worth noting that an experiment involving human retinal cell cybrids showed that mtDNA SNPs can influence the transcription of nuclear genes involved in inflammation and angiogenesis (such as NF-kB2 and VEGFA) by controlling the methylation of chromatin and the acetylation of histones [43]. This observation is very important because mitochondria have a less efficient DNA repair machinery and mitochondrial somatic mutations (some of which occur in non-coding genes) seem to influence the expression of nuclear genes involved in survival pathways and are, therefore, related to cancer pathogenesis [44,45]. In addition to mtDNA control over nuclear epigenetics, carcinogenesis studies have shown that mitochondrial genome can transpose copies into the nuclear genome [46]. These nuclear mtDNA segments/sequences or NUMTs may be inherited or generated *de novo* (somatic mutations), and thus drive genomic instability in cancer, Fig. 3 [47]. Copies of the entire mtDNA or fragments can be transferred into nuclear DNA and contribute to disease progression in several ways [48]. This seems to occur in the early stage of neoplastic transformation with a frequency that depends on the type of cancer. It is interesting to note that cancer cells have fewer NUMT copies in their nuclear genome, whereas striated muscle and heart have more copies, which may be related to differences in oxidative metabolism [49]. In mitochondria, some movable mtDNA fragments rich in GC content can alter the transcription of mitochondrial genes as described in the yeasts *Magnusiomyces capitatus* and *Saccharomyces cerevisiae*. These elements, which roughly resemble the *hop* elements in bacteriophages, form hairpin loops in their nucleotide sequences and thus induce a translational bypass [50]. In addition, the existence of mitochondria-associated non-coding RNA, known as mito-miRNA, has been described. Likewise nuclear micro-RNA (miRNA), mito-miRNA seems to preside to the epigenetic control of mitochondrial gene transcription [51]. However, given the difficulties in experimentally proving the existence of a miRNA machinery in mitochondria and the complementarity of mito-miRNA with nuclear genome sequences, the origin of mito-miRNA is still unclear. In this light, mito-miRNA may represent a fair example of a shuttling of non-coding genetic sequences from nuclear to mitochondrial compartments.

The trafficking of genetic material inside and outside nuclei and mitochondria is ensured by endonucleases that cleave and rearrange genomic strands and importins that mediate cytosolic transfer [18]. At least 18 importins and six exportins have been described in humans, each of which recognises specific protein motifs and is involved in cell differentiation [52]. One group of researchers has discovered that genetic material can be transported from mitochondria to nucleus by importin-7 [18], a nucleo-cytoplasmic protein that belongs to the importin-β family of nuclear transport receptors. It transfers a number of nucleic acid-binding proteins, including ribosomal proteins and glucocorticoid receptors by means of a RAs-related Nuclear protein (RAN) guanosine triphosphate (GTP)-dependent mechanism, but it is still unclear whether importins are involved in the pathogenesis of autoimmune diseases.

2.3. Genomic transposable elements and non-coding RNA

Non-coding RNA originates from non-coding DNA and is currently divided into miRNA, long non-coding RNA (lncRNA), circular RNA (circRNA), small nucleolar RNA (snoRNA), pseudogenes, piwi-interacting RNA (piRNA) and transfer RNA (tRNA); Fig. 2 [53]. Transposable elements and non-coding RNA are strictly inter-related. Short non-coding retroelements with a nucleotide length of less than 200 bases have recently been included in the classification of non-coding RNA elements by Garofalo et al., which suggests that the two may have a common origin [54]. Many of the non-coding sequences of the genome are due to the ancient transposition of endogenous retroelements: it has been suggested that piRNAs may be remnants of transposons, and *Alu* sequences may be part of cirRNA (in which they contribute to the circularisation of the filament) and lncRNAs. Globally, up to 80% of human lncRNA and miRNA sequences overlap those of transposable elements. Nucleotide complementariness is also indicated by the fact that many non-coding RNAs, such as piRNAs, can base pair with endogenous retroelements in order to control their stability or prevent their expression. More specifically, piRNAs (which are mainly expressed by germinal cells) represent a sort of “genetic immune system” and can counteract the insertion of invasive transposons into host DNA [55]. This interplay is further complicated by the mutual influence of nuclear and mitochondrial non-coding sequences. Nuclear miRNAs, in fact, can epigenetically control the transcription of mito-miRNAs [56].

3. Genomic transposable elements in autoimmunity and systemic sclerosis

3.1. Background

The rationale underlying the hypothesis that endogenous retroelements play a central role in the pathogenesis of autoimmune diseases is based on the fact that many of the viruses sustaining a latent infection, such as hepatitis C virus (HCV) and EBV, chronically activate innate and acquired immune cells, and contribute to the development of the tertiary lymphoid organs that are a hallmark of both infectious and autoimmune diseases [57]. Infections sustained by EBV, cytomegalovirus (CMV) or parvovirus B19 can induce autoimmunity and an IFN-I signature in SLE patients by means of molecular mimicry, epitope spreading, or bystander activation [58]. Moreover, clinical manifestations of autoimmune diseases ranging from arthromyalgia and fatigue to skin rashes often overlap those of infectious viral diseases.

No microbial candidate has yet been found to be a direct inducer of autoimmune diseases, but it is widely accepted that the most likely pathogenetic mechanism is an interaction between a genetically favorable background and a microbial trigger, which may be an external infection or dysbiosis [59].

SSc is a chronic autoimmune chronic disease that more frequently affects women (female:male ratio 6:1) and has a worldwide prevalence

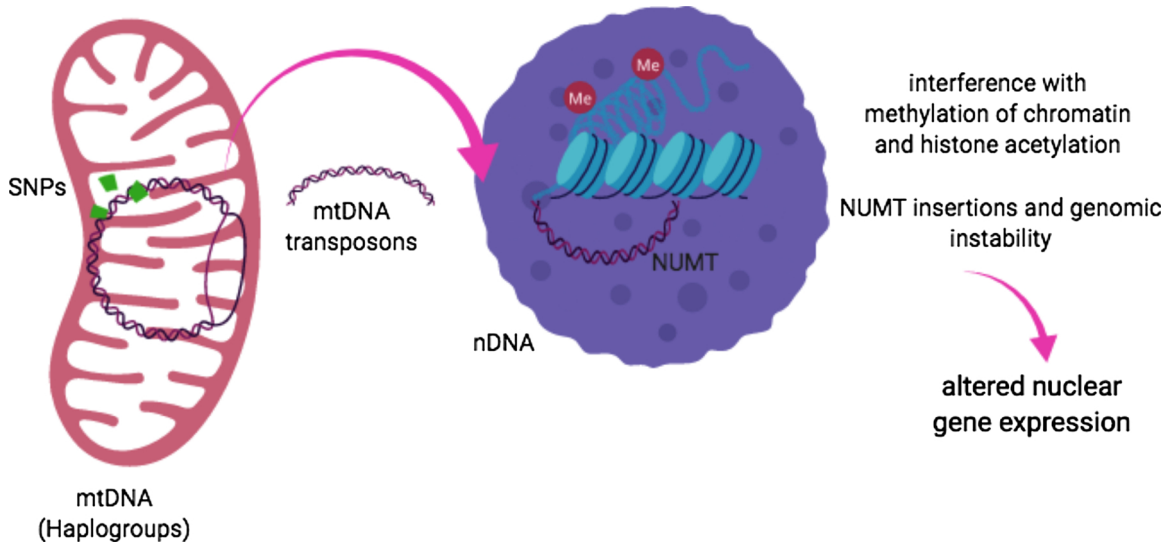

Fig. 3. Mitochondrial and nuclear communication pathways.
Mitochondrial DNA can epigenetically control the transcription of nuclear genes by altering the methylation status of chromatin or influencing the acetylation of histones. In addition, mitochondrial DNA can transpose copies into nuclear genome and drive genomic instability. Abbreviations: SNPs, single nucleotide polymorphisms; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; NUMT, nuclear mitochondrial DNA segments/sequences.

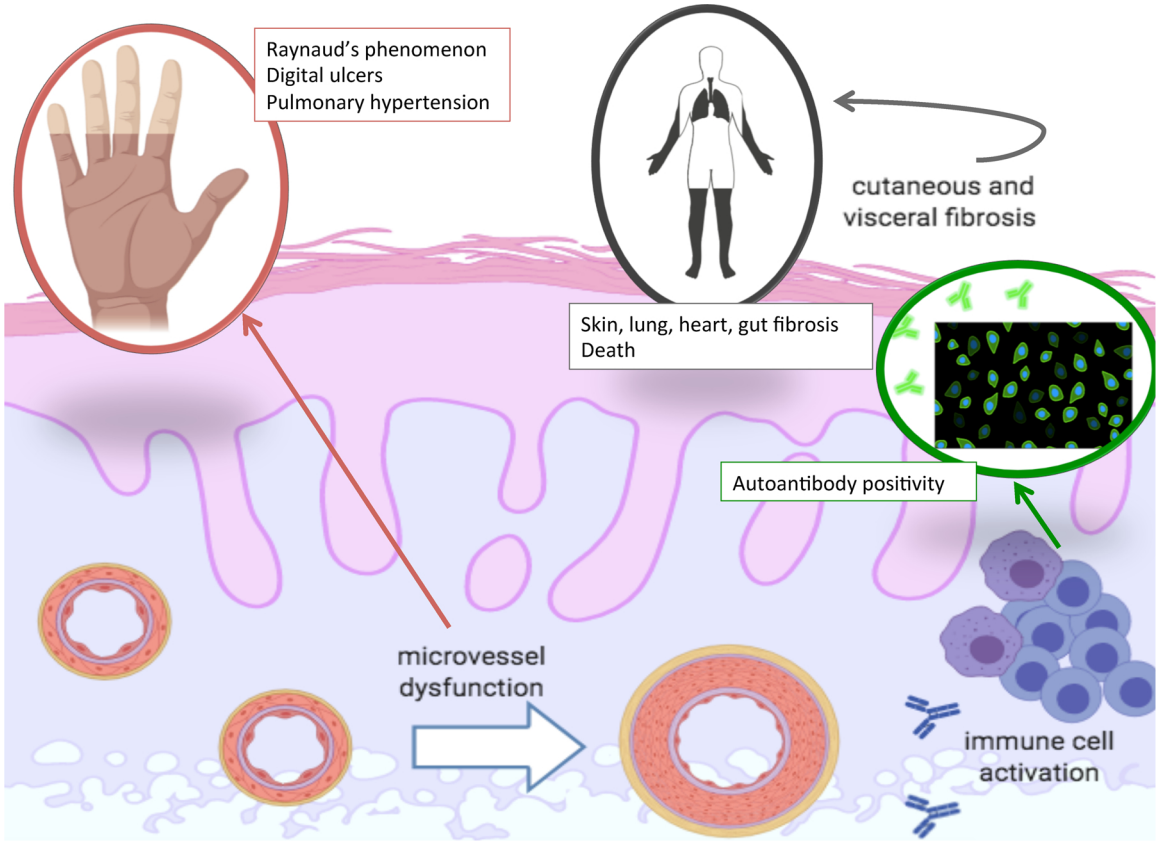

Fig. 4. The pathological hallmarks of systemic sclerosis.
Systemic sclerosis is characterised by skin and visceral fibrosis, endothelial dysfunction and myofibroblast proliferation (finally leading to the obliteration of small vessels), and activation of the immune system, mirrored by the production of autoantibodies.

of 150–300 cases per million [60,61]. Germinal transmission has been hypothesised on the basis that first-degree relatives and siblings are 15 times more likely to develop the disease [62]. SSc has a broad spectrum of clinical manifestations, with Raynaud's phenomenon occurring in nearly 95% of cases and usually preceding the onset of other symptoms. The two hallmarks that differentiate SSc from other autoimmune connective tissue diseases are irreversible microvascular modifications leading to the final obliteration of small vessels, and aberrant connective tissue fibrosis, which can affect every organ from the lungs to the heart and digestive tract, Fig. 4. Patients may therefore develop cutaneous, gastrointestinal, lung and heart fibrosis when fibroblastic hyper-activation is prevalent, or digital ulcers, pulmonary hypertension

and a renal crisis when microvascular damage predominates. The disease has limited and diffuse forms, depending on the extent of skin fibrosis, but even the limited form, which is usually characterised by a higher risk of digital ulcers, esophagopathy, calcinosis and pulmonary hypertension, may also have a variable rate of visceral fibrosis.

Diagnosis is usually based on a complex algorithm that includes typical signs and symptoms, capillaroscopic anomalies or autoantibody positivity, which has been designed in order to identify early forms of the disease [63,64]. The European and American SSc classification criteria take into account its pleiotropic expression and provide eight domains that include peculiar symptoms or instrumental and laboratory findings [65]. Given the complexity of its clinical presentation and the concomitant involvement of immune, endothelial and fibroblastic cells, it is still hard to define a unique pathogenetic starting point. SSc patients have a hyper-activated immune system, and are positive for serum autoantibodies reacting against centromere (ACAs), topoisomerase I (anti-SCL70), RNA-polymerase III and other ribonucleoproteins. Positivity for a specific class of autoantibodies can dictate the disease phenotype: the presence of anti-SCL70 is associated with the diffuse cutaneous form, lung fibrosis and a poor prognosis, whereas the detection of ACAs is usually associated with the limited form, pulmonary hypertension and esophageal dysmotility [66]. As in other connective tissue diseases, autoantibodies react against nuclear antigens, although autoantibodies against angiotensin II type I and endothelin-1 type A receptors have been described [67].

Being genetic sequences and retaining some characteristics of their ancient origin as retroviruses, endogenous retroelements could represent the unifying pathogenetic scenario of autoimmune diseases, linking genetics to environmental triggers, such as viral infections. In SSc, a disease in which the pathogenesis is further complicated by ROS production and fibrosis, retroelements shuttling inside and outside mitochondria could perhaps disturb mitochondrial functions and drive oxidative stress. The following subparagraphs aim to describe the interconnection between retrotransposons and the immune system and to speculate on this hypothetical pathway.

3.2. Genomic transposable elements in the development of the immune system

The development and maturation of the immune system is strictly interconnected with the infections occurring during an individual's lifetime. More than 500 million years ago, the appearance of endogenous retroviruses in fish was paralleled by the development of a primordial adaptive immune system [68], Fig. 5. Different groups of endogenous retroviruses can mix in unrelated phylogenetic species and this may spread their immunogenicity. It was once believed that each group was species-specific, with γ-retroviruses solely found in mice, α-retroviruses in birds, ε-retroviruses in fish, and β-retroviruses in primates and mammals, but examples of inter-species sharing have been reported. Endogenous retroviruses can switch from one host to another individual, perhaps by means of body fluid exchange [69].

The enrichment of human DNA with foreign sequences retained from the past generations protects against future external viral exposure by competing for the receptors or molecules that are involved in viral life-cycle mechanisms. A low viral RNA and viral protein load is crucial for tonic immune cell responses: for example, it has been shown that measles virus RNA can persist in lymphoid organs for at least six months after infection and strengthen immune responses [70]. T lymphocytes mature early in the thymus and later in peripheral organs, where medullary thymus epithelial cells and dendritic cells present antigens to nascent T cells in a major histocompatibility complex (MHC)-restricted or unrestricted manner [71]. Autoreactive cells in the thymus are deleted or converted into regulatory cells by means of a complex epigenetic mechanism that also characterises dendritic cells themselves [72]. B cells mature in the bone marrow and lymph nodes and, although require T cells for their maturation and activation, a part of B immune responses develops in the absence of T lymphocytes. The reactivation of endogenous retroelements in the early phase of B and T cell development, and the subsequent production of retroviral proteins, may contribute to finally shaping the immune response.

One real-time polymerase chain reaction (RT-PCR) study of mice has revealed the tissue-specific expression of some endogenous retroelements (*Mus dunni* endogenous virus) and the retention of intact *gag*, *pol* and *env* gene sequences prevalently in the thymus, spleen and lung [73]. The thymus may be the first organ in which endogenous retroviruses and their products contribute to the development of the immune system. It is possible that a number of endogenous retroelement proteins may not be presented to nascent lymphocytes during embryogenesis because of epigenetic silencing, and that the later reactivation of these retroelements (perhaps by means of the transactivation by an unrelated infection) generates an immune response that paves the way for the development of autoimmune diseases.

However, the proteins of endogenous retroelements can elicit different immune responses, and are also capable of stimulating immune tolerance: for example, the *env* protein of HERV-W contains an immune suppressive domain that is similar to that found in syncytin and is fundamental for the development of cytotrophoblasts as it confers immune tolerance to human and primate fetal and placental tissues. One experimental animal study has found that the mRNA of the *env* protein of ovine beta retroviruses (enJSRV) that is associated with ovine pulmonary adenocarcinoma is over-expressed in the thymus, spleen and lymphatic organs of ovine fetuses, and this may silence the production of specific antibodies by inducing central immune tolerance [74]. Accordingly, cancer cells may mask themselves by expressing *env* proteins of endogenous retroelements that are usually ignored by the immune system.

DNA transposable elements have also been found to be involved in the recombination of variable (V), diversity (D) and joining (J) domains of immunoglobulins, an evolutionary step in vertebrate immunology [75]. The variable expression of endogenous retroelements in different cell-types and times of cell lifecycle denotes their biologic importance and is presumably under an epigenetic control. Cells have developed a series of mechanisms constraining endogenous retrovirus reactivation, one of which is the mammalian synthesis of tripartite motif-containing protein 5 (TRIM5α), which has anti-retroviral activity. Polymorphisms in the gene encoding this molecule have been associated with the prognosis of patients with human immunodeficiency virus (HIV) infection [76], but there are no data concerning a possible association between TRIM5α and autoimmunity.

3.3. Epigenetics and re-emergence of retrotransposons

Epigenetic is a crucial means of controlling the re-emergence of retrotransposons. Changes in methylome and histone acetylation, as well as interactions with regulatory proteins, may constrain or promote the expression of transposable elements [21]. Similarly, epigenetics also plays a fundamental role in controlling non-coding RNA [77], which is strictly related to movable genetic elements. Methylation of the cytosine-phosphate-guanine (CpG) islands that are abundantly expressed in endogenous retroelements may be an attempt to counteract the reactivation of transposons and retroviruses [78], and a reduction in the methylation of transposable repetitive elements such as *Alu*, LINE-1 and LTRs has been described during aging. Autoimmune diseases are characterised by cell modifications that resemble accelerated aging, including short telomeres, immune-senescence, impaired autophagy, or mitochondrial dysfunction [79–81]. A recent study on patients with Behçet's disease found different patterns of methylation in the *Alu* sequences obtained from peripheral blood mononuclear cells (PBMCs) and neutrophils, with more pronounced under-methylation in patients than controls and a significant association with disease activity [82], and the reduced methylation of LINEs has been found in the lymphocytes and neutrophils of patients with SLE [83]. Interestingly, the

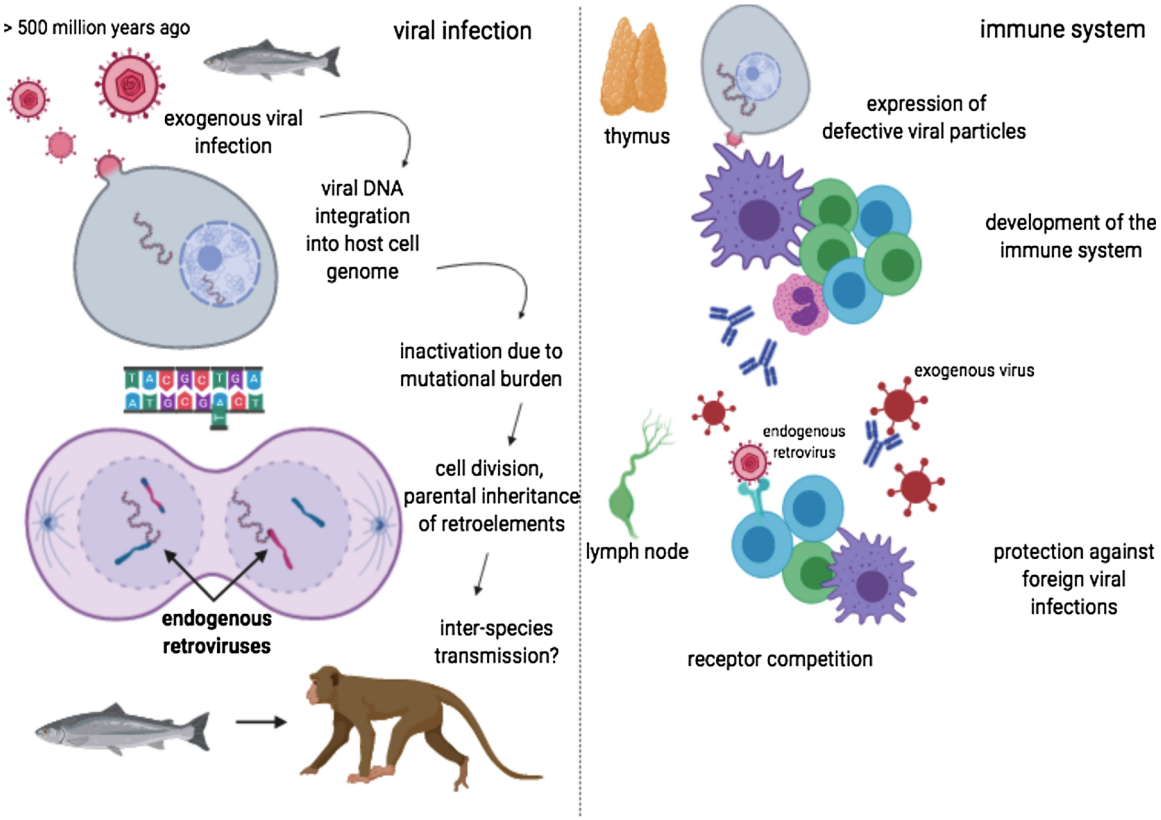

Fig. 5. Viral infections and the development of the immune system.
More than 500 million years ago, some exogenous viruses establishing a latent infection and progressively tolerated by the host due to inactivating mutations, gave rise to the appearance of endogenous retroviruses in fish. This phenomenon led to the parallel development of a primordial adaptive immune system. Endogenous retroviruses can combine and spread from species to species, thus increasing their immunogenicity and refining the repertoire of antigens recognized by immune cells. A low load of endogenous retroviral antigens is supposed to be useful in maintaining a tonic immune response and in preventing exogenous viral infections through receptor competition.

under-methylated LINE-1 sequences could control *in cis* the transcription of other genes involved in cell apoptosis and immune responses.

Finally, autoimmune diseases are characterised by the aberrant expression of non-coding RNA. Research into miRNA has shown that they are dysregulated in the blood and other biologic fluids of patients with many immune-mediated diseases (including RA, SS, and SLE) of which they are now considered biomarkers [84–86], and recent studies have highlighted the involvement of other non-coding RNAs in autoimmunity [87]. Given their sequence homology, the aberrant production of miRNAs and other non-coding RNAs could be an attempt to counteract the increased expression of endogenous retroelements [88] as non-coding RNA may have an early surveillance function that leads to the rapid sequestration of transcribed copies of retrotransposons.

3.4. Genomic transposable elements activating the immune system: when nucleic acids are enemies

When epigenetic mechanisms are inefficient or saturated, nucleic acid fragments of endogenous retroelements may elicit an immune response by interacting with Toll-like receptors (TLRs), Figs. 6 and 7.

Ten TLRs have been described so far [9], of which TLRs 3, 7, 8 and 9 are located on endosomes and recognise DNA or RNA fragments [89]: TLR3 recognises double-stranded RNA; TLR7 and TLR8 recognise single-stranded RNA; and TLR9 recognises unmethylated CpG DNA. These receptors seem to play a prominent role in pathogenesis of SLE, which is characterised by impaired apoptosis and nuclear debris clearance, and the production of anti-nuclear and anti-DNA autoantibodies [90]. The engagement of nucleic acids with TLRs triggers a conformational change in the N-terminus of the receptors, the further recruitment of adaptor proteins such as myeloid differentiation primary response 88 (MYD88) or TIR-domain-containing adapter-inducing interferon-β (TRIF), and the final activation of transcriptional factors such as AP-1 and NF-kB (Fig. 8).

TLR7 is encoded on chromosome X, which may explain the higher prevalence of autoimmune diseases among women. It has been hypothesised that nucleic acid fragments bound to the nuclear proteins of dying cells mimic viral particles and elicit an immune response. In the absence of cell damage, the aberrant replication of endogenous retroelements or DNA transposons may generate copies of nucleic material capable of moving from the nucleus to the cytosol and sensing TLRs. In support of this, the ribonuclear protein Ro60 bound to *Alu* sequences forms a self-antigen that is recognised by autoantibodies in SLE and SS patients. In this case, Ro60 could play a protective role by sequestering the *Alu* sequences and preventing them from engaging with TLR7. A group of researchers has recently reported the over-expression of LINE-1 transcripts in kidney samples of SLE patients and minor salivary gland sections of SS patients [91], which could elicit an IFN-I response by stimulating TLR7 and TLR8 in plasmocytoid dendritic cells. The same authors have also demonstrated that LINE-1 transcripts are epigenetically repressed in minor salivary gland biopsies of SS patients with concomitant B-cell lymphoma, whereas they are over-expressed in patients with uncomplicated SS [92].

Cytosolic ribonucleotide fragments may also activate other immune pathways by means of the sensing proteins retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and cyclic GMP-AMP synthase (cGAS), Fig. 8. Some of these pathways are strong inducers of an IFN-I response, which is common to many autoimmune diseases. After oligomerisation, these receptors may induce the

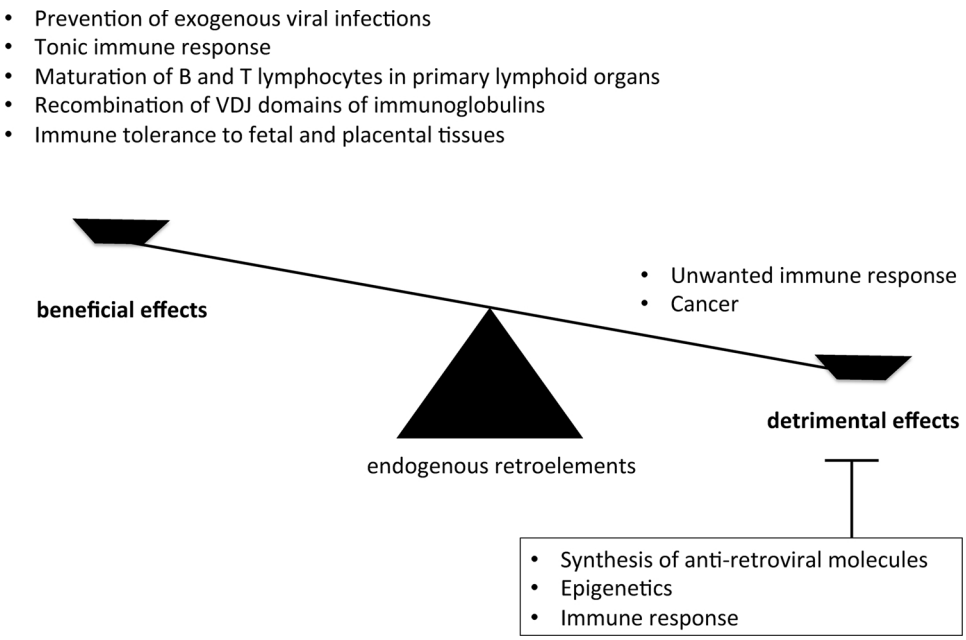

Fig. 6. Beneficial and detrimental effects of endogenous retroelements.
Endogenous retroelements preside over many physiologic processes: they tune the immune response, contrast exogenous viral infections and favor the fusion of syncytiotrophoblast. However, the aberrant expression of endogenous retroelements can also be at the basis of autoimmunity, autoinflammation and cancer. Cells prevent the detrimental reemergence of endogenous retroelements through the synthesis of anti-retroviral molecules, epigenetics and, eventually, the setting of an immune response.

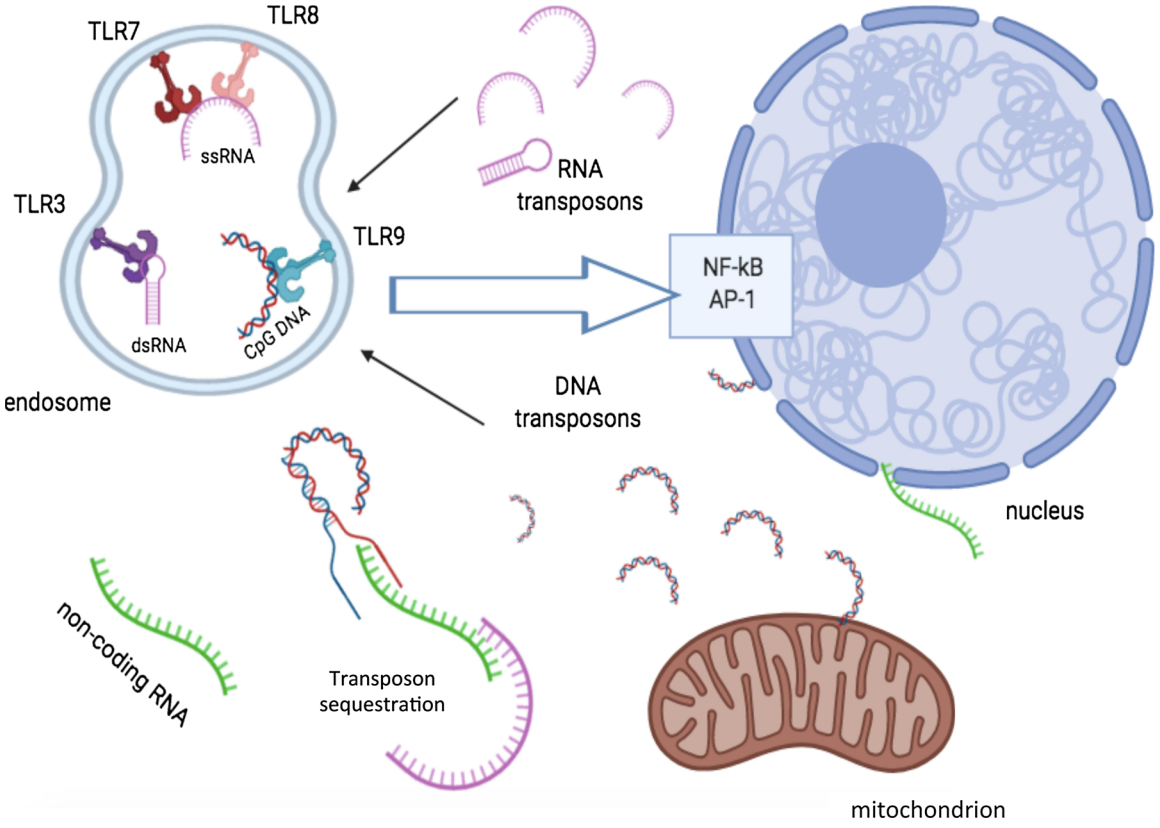

Fig. 7. Activation of the immune system by nucleic acids.
The *primum movens* of the inflammatory cascade induced by exogenous and endogenous nucleic acids is represented by the engagement of RNA or DNA filaments to TLRs expressed on endo-lysosomes. TLR3 recognises dsRNA, TLR7 and TLR8 ssRNA and TLR9 unmethylated CpG DNA. TLRs are usually able to discriminate between foreign and endogenous nucleic acids, however, post-transcriptional modifications, such as oxidation, or ancestral motifs like those harbored by mtDNA, can stimulate these receptors to induce the NF-kB and AP-1-mediated transcription of pro-inflammatory genes. Non-coding RNA filaments, like miRNAs, can prevent this pathway by base-pairing and sequestering nucleic acids in cytosol.
Abbreviations: TLR, toll-like receptor; ssRNA, single-stranded RNA, dsRNA, double-stranded RNA; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein-1.

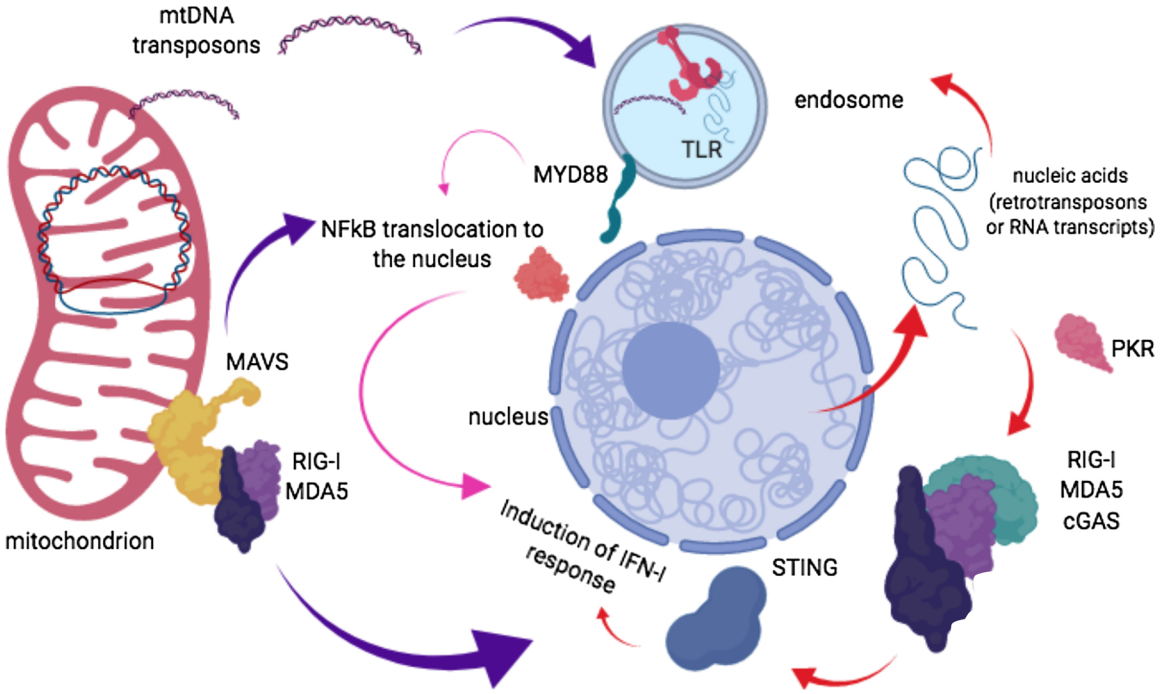

Fig. 8. Activation of type I interferon response by transposable retroelements.
Nuclear DNA and RNA free sequences derived from retrotransposons or their transcripts can be exported in cytosol and endosomes, where they interact with TLR3, TLR7, TLR8 and TLR9, and trigger a downstream signaling cascade involving MYD88 and NF-kB. Alternatively, nuclear or mitochondrial transposons can induce the assembly of a molecular platform formed by RIG-I, MDA5 and cGAS, or stimulate PKR. Both the two pathways finally converge on the STING-mediated transcription of IFN-I genes. Mitochondria harbor on their membrane the sensor proteins MAVS, able to interact with RIG-I and MDA5. This mechanism can further amplify the IFN-I signature.
Abbreviations: mtDNA, mitochondrial DNA; TLR, toll-like receptor; MYD88, myeloid differentiation primary response 88; NFkB, nuclear factor kappa-light-chain enhancer of activated B cells; PKR, double stranded RNA-dependent protein kinase; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated protein 5; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; IFN-I, interferon-type I; MAVS, mitochondrial antiviral signaling proteins.

activation of tumor necrosis factor (TNF) receptor-associated factor (TRAF) family proteins and the final activation of transcriptional factors. RIG-I and MDA5 can recognise 5′-triphosphate RNA filaments, which are usually of viral origin, whereas the cell RNAs undergoing the removal of the triphosphate group are usually ignored; however, endogenous retroelements may interact with these receptors in B lymphocytes and cancerous cells [9]. Foreign or cellular RNA fragments can also interact with double-stranded RNA-dependent protein kinase (PKR), which has anti-viral properties. Globally, the stimulation of all these receptors converges on the protein stimulator of IFN genes (STING), and therefore leads to an IFN-I response. This pathway is of crucial importance in autoimmune diseases dominated by an IFN-I signature, like SLE. In a case control study on 64 SLE patients, 31 subjects affected by other autoimmune diseases and 35 healthy controls, Kato et al. showed that the production of IFN-I, notably increased in SLE patients, depends on the activation of the STING cascade [93]. A further clue lies in the occurrence of familial chilblain lupus and other diseases having a lupus-like phenotype in individuals with genetic variants of the *STING* gene [94]. An experiment on female C57BL/6 mice, a murine model of SS, showed that the STING pathway could be involved also in the development of SS disease, as it correlates with salivary gland infiltration and autoantibody production [95]. According to these data, STING could represent an ideal therapeutic target in autoimmunity; on the other hand, it is considered an oncosuppressor, thus arising a dilemma concerning the risk of carcinogenesis due to STING antagonism [96].

Nuclear DNA or mtDNA may respectively activate the absent in melanoma 2 (AIM2) and nucleotide-binding oligomerisation domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasomes [97]. The role of NLRP3 inflammasome is well know in the pathogenesis of autoinflammatory syndromes, a group of genetically inherited immune-mediated diseases characterised by episodic attacks of fever and other systemic or organ-specific manifestations [98]. There is sufficient evidence proving that autoimmune diseases, including SLE and RA, can be also considered as the result of the hyper-activation of the inflammasome platforms [99–101]. The activation of NLRP3 inflammasome has been supposed also in SSc, where it may be associated to fibrosis and production of interleukin (IL)-1 [102]. It seems that the activation of the inflammasome pathway is required for the differentiation of fibroblasts, as the inhibition of caspase-1 typically prevents the production of collagen-1 in fibroblasts of patients with fibrotic diseases [103].

3.5. Genomic transposable elements activating the immune system: the role of mitochondria

Mitochondria and their genome are now considered to be involved in the pathogenesis of some autoimmune diseases, including RA and SLE [104]. Evolving from an ancient endosymbiont, these organelles can retain a certain degree of immunogenicity. MtDNA has a different pattern of methylation and oxidation that may confer unique characteristics favoring recognition by TLRs and the activation of innate immune cells [105,106]. So far, during mitochondrial stress, the release of mtDNA and formyl peptides can activate an immune response in a way that is similar to bacterial infections [107]. MtDNA fragments are able to induce the maturation of plasmocytoid dendritic cells and the secretion of IFN-α, following the engagement of TLR9 [108]. An interesting experiment, conducted on SSc cutaneous biopsy samples, explanted skin fibroblasts and murine models, found that mtDNA CpG-rich fragments activate TLR9 in SSc myofibroblasts and induce the final production of transforming growth factor (TGF)-β, thus fomenting fibrosis [109]. This process could be blocked by bortezomib, a selective

Table 1
Summary of the results of the main studies linking endogenous retroelements to autoimmunity.

Author, year	Model	Disease	Sample type	Technology Employed	Results	Reference
Bergallo M et al., 2018	Human	PSO	PBMCs	RT-PCR	Lower HERV-E expression in samples of PSO patients than controls	[12]
Yuksel S et al., 2016	Human	Behçet's disease	PBMCs and neutrophils	Combined bisulfite restriction analysis (COBRA) of interspersed repetitive sequences	Hypomethylation of the *Alu* sequences in patients and significant association with disease activity	[82]
Sukapan P et al., 2014	Human	SLE	PBMCs	COBRALINE-1 and COBRAAlu	Hypomethylation of LINE-1 sequences in SLE patients	[83]
Mavragani CP et al., 2016	Human	SLE and SS	Kidney and minor salivary gland sections	Polymerase chain reaction, Western blotting, immunohistochemistry	Increased expression of LINE-1 in patients' samples and correlation with IFN-I response	[91]
Mavragani CP et al., 2018	Human	SS	Minor salivary gland sections	Bisulphite pyrosequencing	Epigenetic repression of LINE-1 expression in SS patients with concomitant B-cell lymphoma	[92]
Mameli G et al., 2017	Human	RA	Serum	Indirect ELISA	Serum from RA patients reacting against HERV-K *env*-su19-37 peptide	[126]
Nelson PN et al., 2014	Human	RA	Serum	Indirect ELISA	IgG antibodies against HERV-K10 Gag matrix peptide in RA patients *vs.* controls	[127]
Wang X et al., 2019	Human	SLE	CD4 + T cells	qRT-PCR	Increased expression of HERV-E clone 4-1, whose 3' LTRs can work as a sponge for miR-302d, resulting in the maturation of Th17 lymphocytes and increased IRF9 pathway activation	[128]
Kowalczyk MJ et al., 2012	Human	Localised scleroderma	Skin biopsies and PBMCs	Real-time polymerase chain reaction	Reduced expression of HERV-E *pol* and increased expression of HERV-K *env*, HERV-R *pol-env*, and HERV-W *env* in PBMCs of patients *vs.* controls. Up-regulation of HERV-K *env* in skin biopsies of patients *vs.* controls	[129]
Nexo BA et al., 2016	Human	RA, type I DM, MS	PBMCs	PCR and mass-spectrometry-based Sequenom platform	SNPs within or near 51 HERVs predictive of a specific disease	[130]
Laska MJ et al., 2017	Human	SLE, RA	PBMCs	Real-time reverse transcription-polymerase chain reaction analysis	Immune suppressive effect of the *env*59 domain of HERV-H mirrored by reduced expression of TLR7 and IL-6	[131]
Pascual M et al., 2001	Human, cell lines	RA	Peripheral blood and B cell lines	PCR and direct sequencing	LTR3 positivity associated with DQB1 alleles, *0302, *0402, *0601, *0202, and *0305; significant difference in LTR3-positive DQB1*0302 allele among patients and controls	[134]
Messemaker TC et al., 2018	Human	SSc	Skin biopsies	Ion-torrent and DEseq2	676 deregulated long non-coding genes in SSc patients, most of which involved in B cell proliferation and skin homeostasis	[138]

Abbreviations: SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; RA, rheumatoid arthritis; DM, diabetes mellitus; MS, multiple sclerosis; PSO, psoriasis; SSc, systemic sclerosis; PBMCs, peripheral blood mononuclear cells; CD, cluster of differentiation; IFN-I, type I interferon; COBRA, combined bisulfite restriction analysis; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; qRT, quantitative reverse transcription; LINE, long interspersed nuclear elements; HERVs, human endogenous retroviruses; SNP, single nucleotide polymorphism; TLR, toll-like receptor; IL, interleukin; LTRs, long terminal repeats; Th, T helper; IRF, interferon regulatory factor; miR, microRNA.

inhibitor of the 26S proteasome currently used in multiple myeloma, which prevents the post-translational modifications of TLR9 in the endo-lysosomes.

Additionally, mitochondria may also act as pathogen scavengers and set biological pathways aimed at cell protection: for example, the mtDNA released by eosinophils in the extra-cellular environment following stimulation with IFN-γ in response to Gram-negative bacteria can act as a pathogen trap [110].

It has also been shown that mitochondria harbor sensor molecules on their membrane that trigger antiviral responses [111]. One of these is mitochondrial anti-viral signaling protein (MAVS, also known as IPS-1), which is involved in RIG-1 and MDA5 signaling and associated with the production of IFN-I [112]. MAVS acts upstream of NF-κB and interferon regulatory factor (IRF) 3 phosphorylation [113], and its overexpression promotes an aberrant IFN-β response, Fig. 8.

One fascinating hypothesis considers mitochondria as the converging point of anti-microbial and cell stress responses, through the activation of inflammasomes [111]. Mitochondria are known to be involved in the integrated stress response (IRS), a cell mechanism that can be elicited by viral double-stranded RNA infections and may control protein translation [107]. Viral double-stranded RNA can interact with PKR to phosphorylate eukaryotic translation initiation factor 2A (eIF2A), which inhibits protein translation and leads to the restoration of cell homeostasis or (in the case of failure) apoptosis. It has been shown that PKR can recognise 23 mitochondrial proteins in animal models [114]. An up-regulated IRS has been reported in experimental murine models of autoimmune encephalomyelitis and in the tissues of patients with MS [115]. As HERVs are hypothetical triggers of MS, they may induce the activation of IRS in order to protect oligodendrocytes from stress. Using different human cell types, including epithelial cells and fibroblasts, Kim et al. have demonstrated that endogenous double-stranded RNA (mainly represented by non-coding transposable elements such as *Alu*, LINEs, LTRs, and centromeric a-satellite RNA sequences) interact with PKR and elicit an IRS [116]. They also found that, in addition to endogenous RNA filaments, most of the nuclear material associated with PKR was mtDNA paired with endogenous RNA. Polymorphic variants of mtDNA could further alter its nucleotide sequence and this, in turn, could favor the aberrant binding of mtDNA to PKR. A support to this view comes from a study on Caucasian patients with MS, showing that some mtDNA haplogroups are significantly associated with the risk of developing the disease [117]. Instead, there is no evidence concerning the involvement of mtDNA haplogroups in rheumatic diseases. However, these findings provide an interesting insight into the pathogenic scenario of autoimmune diseases such as SSc, and strengthen the idea of a nuclear-mitochondrial genetic interchange. It has been shown that cell nuclei and mitochondria can communicate and share information in an anterograde (from nucleus to mitochondria) or retrograde (from mitochondria to nucleus) manner [107]. This interchange is highly important because mitochondria are unable to encode proteins belonging to complex II of the electron transport chain (which are therefore of nuclear origin) and have many stress-sensor proteins that can trigger specific intra-nuclear signaling. For example, the aberrant production of ROS can activate the NF-kB pathway and drive cell survival, proliferation and inflammation [118]. In addition, mitochondria are the source of ATP and acetyl-CoA that play a crucial role in epigenetics. ATP is, in fact, essential in regulating the function of the methyl donor S-adenosylmethionine (SAM) and the enzyme methionine adenosyltransferase (MAT), both involved in the process of chromatin methylation. Acetyl-CoA is, instead, necessary for histone acetylation. Depletion in ATP due to a mitochondrial dysfunction has been reported in lymphocytes of SLE patients [119], and the impairment in mitochondrial energetic processes can epigenetically influence the transcription of pro-inflammatory genes [120]. In a Sequenom MassARRAY study on 523 MS patients and 97 SLE patients, Vyshkina et al. found that the mtDNA K* haplotype, having the variants at nts 9055, 10,398 and 14,798, was strongly associated with MS, while the variant at nt9055 in the ATP6 or F0F1- ATPase gene was found in SLE patients, where it could be at the basis of the low ATP production observed in SLE lymphocytes [121].

3.6. Genomic transposable elements synthesizing proteins: HERVs

Apart from duplicating and engulfing the cell environment with nucleotide copies, some endogenous retroelements can translate functional proteins. Some HERVs have an intact ORF and their proteins can activate the immune system by stimulating the T cell receptors (TCRs) on naïve T cells or B cell receptors (BCRs) on B cells. It seems that HERV *env* protein inhibits T and B lymphocyte functions, whereas *gag* may have opposite effects [122]. However, the *env* protein of some HERVs can activate the immune system: the *env* protein of the HERV-W family has been associated with the development of MS, demyelinating lesions and neuroinflammation as a result of the stimulation of TLR4 [123,124]. Consequently, it has been used as a therapeutic target in patients MS, and a monoclonal antibody antagonising its effects is currently being tested in clinical trials [125]. Several reports, summarized in Table 1, described the association between HERVs and autoimmune diseases, including RA, psoriasis, SLE and scleroderma [126–129]. One interesting study of 710 patients with RA, 1183 with type-1 diabetes mellitus, and 350 with MS identified several SNPs within or near 51 HERVs that may be predictive of a specific disease [130]: for example, it was found that the SNPs rs993426 near HERV-K and rs2096537 near HERV-H (both on chromosome 22, and respectively encoding *in frame gag* and *pol*, and *pol*) significantly associate with RA. Noteworthy, the same authors described that HERV-H family owns a motif in the *env* sequence, namely the *env59* gene or immunosuppressive domain (ISU), which contrasts inflammation in SLE and RA [131].

LTRs, flanking HERVs' coding sequence at the 5′UTR and 3′UTR, work as promoter and enhancer sequences. When transposed next to genes of crucial importance in the activation of the immune system, they can modulate their transcription, thus triggering genomic instability, cancer and autoimmunity. Despite a plenty of data linking LTRs to cancer, few studies have investigated the role of LTRs in autoimmunity. LTRs are usually epigenetically silenced; however, external bacterial or viral infections can rescue their inactive status and trigger the transcription of genes involved in proliferative or inflammatory pathways [132,133]. For instance, the flanking sequences LTR3, LTR5, and LTR13 can insert near the DQB1 locus where they seem to contribute to the genetic susceptibility to rheumatic diseases such as RA. A Spanish study on 145 RA subjects showed an association between LTR3 and the DQB1 alleles *0302, *0402, *0601, *0202 and *0305, with a significant difference between controls and patients according to LTR3-positive DQB1*0302 allele [134]. Polymorphic variants in human leukocyte antigen (HLA) genes are of crucial importance in setting autoimmunity, as they can improperly drive the activation of auto-reactive immune cells. In RA pathogenesis a great importance has been attributed to polymorphic alleles of HLA-DRB1 locus, especially the HLA-DRB1*04 allele, coding a 5 amino acid shared epitope, which is supposed to be involved in the presentation of arthritogenic peptides or in the selection of autoreactive lymphocytes [135]. However, it is unknown whether LTRs can transpose near HLA-DRB1 and influence RA risk.

3.7. Genomic transposable elements and systemic sclerosis

3.7.1. Current pathogenetic view of systemic sclerosis

The initial trigger of SSc is still unknown. According to the current view of SSc pathogenesis, genetics, epigenetics and environmental

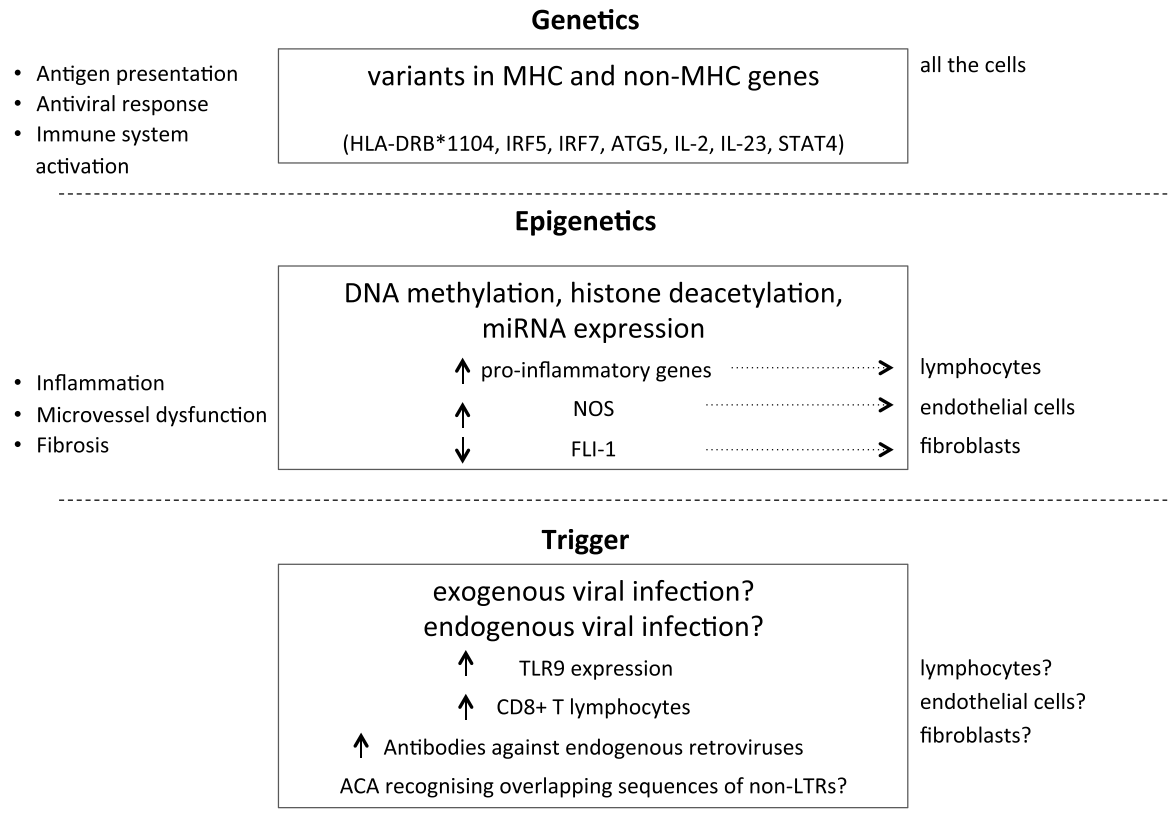

Fig. 9. Pathogenetic steps of systemic sclerosis.
The pathogenesis of systemic sclerosis is currently considered as the result of the combination of a favorable genetic and epigenetic background with an environmental trigger. Although the hypothesis is still speculative, triggers may be represented by infections sustained by both exogenous and endogenous viruses, able to establish a latent phase. The activation of an antiviral response is in support of this view.
Abbreviations: MHC, major histocompatibility complex; HLA, human leukocyte antigen, IRF, interferon regulatory factor; ATG, autophagy protein; IL, interleukin, STAT, signal transducer and activator of transcription; NOS, nitric oxide synthase; FLI-1, Friend leukemia integration 1 transcription factor; TLR, toll-like receptor; CD, cluster of differentiation; ACA, anti-centromere antibodies; LTRs, long terminal repeats.

triggers contribute altogether to the development of the disease, Fig. 9. GWAS have revealed significant associations with MHC and non-MHC genes. In the case of Caucasian subjects, it has been reported that HLA-DRB*1104 is associated with the risk and severity of the disease, with widespread skin fibrosis being the most frequent manifestation in patients carrying this genotype [136]. The non-MHC polymorphic genes include those encoding molecules involved in antiviral defense, such as IRF5 and IRF7, autophagy protein-5 (ATG-5), the IL-2 and IL-23 pathway, and the signal transducer and activator of transcription (STAT4) [137]. These molecules are involved in the IFN-I response and the differentiation of T helper 1 lymphocytes that are capable of counteracting intracellular microorganism invasion.

Epigenetics may also play a role in the pathogenesis of SSc. It has been reported that microvascular endothelial cells, lymphocytes and fibroblasts respectively show different rates of DNA methylation, histone deacetylation, and miRNA expression. The pro-inflammatory genes encoding cluster of differentiation (CD)40 L and CD70 are over-expressed in lymphocytes because of decreased gene methylation; nitric oxide synthase is over-expressed in endothelial cells as a result of increased histone acetylation of the promoter sequence of the gene; and the gene coding for Friend leukemia integration 1 transcription factor (FLI-1), which is involved in extracellular matrix deposition, is under-expressed in fibroblasts because of over-methylation [137]. Some studies of skin samples and sera have detected a specific miRNA signature, with miRNA-21 being over-expressed, and miRNA-196a, miRNA-145 and miRNA-29a under-expressed; all of these miRNAs are involved in controlling fibrosis and collagen synthesis. Given the interplay between non-coding RNA and endogenous retroelements and their overlapping sequences (some of which may have an antisense orientation), it is possible that this epigenetic signature represents an attempt to constrain endogenous retroelement reactivation by means of base-pairing neutralisation. In a recent study of RNAs in skin samples of 14 patients with early SSc and six healthy controls, the use of Ion-Torrent and DEseq2 revealed 676 deregulated long non-coding genes, of which 257 were antisense genes controlling the transcription of paired sense genes [138]. The most deregulated were the antisense RNA transcripts *CTBP1-AS2, OTUD6B-AS1* and *AGAP2-AS1*, which are involved in B cell proliferation and skin homeostasis. It is not yet known why this mechanism occurs in specific cell types or whether the variations in expression condition the final phenotype.

Unlike SLE and SS, no infective agent has been found that is clearly involved in the pathogenesis of SSc. A group of researchers investigating the role of CMV in SSc have recently reported an increased CD8+ lymphocyte response against the virus in 20 SSc patients in comparison with 18 controls, and this was significantly related to disease duration and the degree of cutaneous fibrosis as measured using the modified Rodnan skin score [139]. Another study of a cohort of 42 patients with SSc, 18 with primary biliary cirrhosis, and 52 healthy controls detected increased levels of antibodies against intra-cisternal A-type particle endogenous retrovirus proteins in the serum of 55.5% of the patients with primary biliary cirrhosis and 66.0% of the SSc patients, whereas there weren't positive findings among the controls

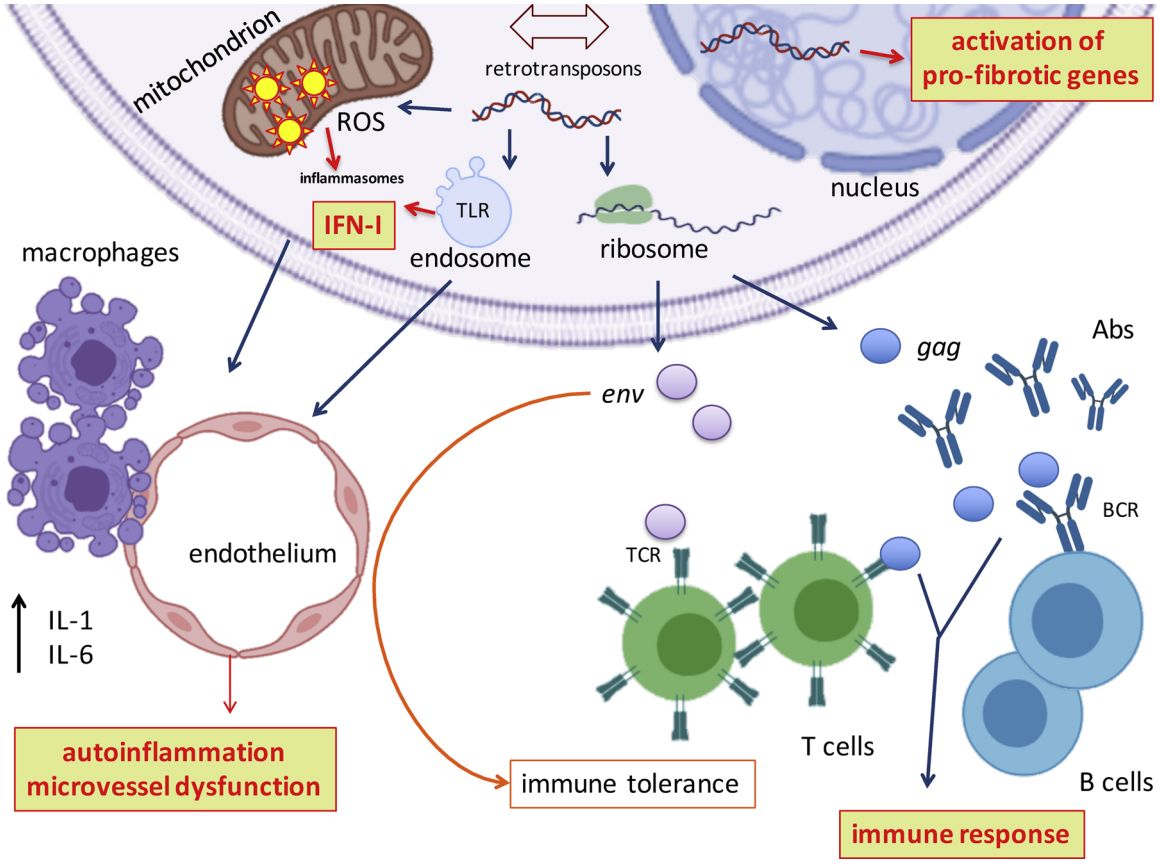

Fig. 10. The role of endogenous retroelements in the pathogenesis of systemic sclerosis.
Systemic sclerosis is characterised by autoimmunity, fibrosis and microvessel dysfunction. The aberrant expression of endogenous retroelements could unify these pathogenic scenarios. Endogenous retroelements can, in fact, stimulate the immune system in several ways. When moving from nucleus or mitochondria to cytosol, nucleic acids can interact with TLRs, placed on endosomes and trigger autoinflammation and an IFN-I response. This cascade is of utmost importance in macrophages and culminates in the release of pro-inflammatory mediators, like IL-1, able to induce, in turn, endothelial dysfunction. If a further progression to protein translation occurs, the generation of viral proteins can stimulate the immune system, including both the activation (through *gag* and *env* proteins) and the inhibition (by means of *env* proteins) of the immune cells.
Transposable fragments of genomic material can be shuttled between nucleus and mitochondria through importins. Aberrant insertions of genetic sequences in both nuclear and mitochondrial genomes are at the basis of an altered transcription of genes involved in cell lifecycle and respiratory chain, respectively. The following generation of ROS, also favored by inflammation, is then responsible for DNA oxidation and further activation of inflammasome platforms.
Finally, retrotransposons could epigenetically control the transcription of pro-fibrotic genes and contribute to reshape the phenotype of fibroblasts and myofibroblasts.
Abbreviations: TLR, toll-like receptor; TCR, T cell receptor; BCR, B cell receptor; Ab, antibody; ROS, reactive oxygen species; IFN-I, interferon-type I; IL, interleukin.

[140].

Interestingly, some authors have demonstrated that TLR9 is overexpressed in fibroblasts taken from cutaneous biopsies of patients with SSc, and that TLR9 is a marker of progressive fibrosis and its levels directly correlate with those of TGF-β [109]. In the same experimental study, pre-treatment of human healthy skin fibroblasts with CpG DNA greatly stimulated TLR9 and the subsequent expression of collagen 1 and 2 mRNA, and increased fibroblast migration.

The autoantibodies ACAs, found in SSc patients, react against centromeric ribonucleoproteins, and it has been postulated that the centromeres may arise from non-LTR retrotransposon proto-telomeres [36]. As telomeric sequences widely overlap those of retrotransposons, it can be argued that ACAs may be partly directed against retrotransposons.

SSc is characterised by an aberrant production of ROS that leads to inflammation, myo-fibroblast proliferation and endothelial dysfunction. Accordingly, mitochondria play a central role in the pathogenesis of SSc as they are responsible for producing energy through the oxidative chain, although they may also be involved in controlling cell life cycles and inflammation. In SSc patients, mtDNA may acquire some somatic mutations of genes encoding respiratory chain proteins. It has been shown that the injection of bleomycin in a murine model of bleomycin-induced SSc may generate ROS capable of inducing mitochondrial genetic variants in lung fibroblasts and epithelial cells that autonomously drive fibrosis [17].

The involvement of mitochondria in the pathogenesis of SSc is also supported by the concomitant occurrence of anti-nuclear and anti-mitochondria autoantibodies in some patients [141]. A recent immunoprecipitation/Western blotting study identified four autoantigens belonging to the pyruvate dehydrogenase complex that lies in the inner membrane of mitochondria in 15% of 85 SSc patients [142]; interestingly, most of these patients were ACA positive and had a limited cutaneous form of SSc. Furthermore, some SSc patients (ranging from 1.5% to 14.3% depending on the case series) have anti-Th/To autoantibodies against a macromolecular protein–RNA complex known as the human RNase mitochondrial RNA processing (MRP) complex, an endoribonuclease capable of cleaving mitochondrial RNA [143].

3.7.2. Shuttling of retrotransposons between nucleus and mitochondria: the unifying pathogenetic scenario?

The transposition of elements jumping from nuclei to mitochondria and *vice versa* may contribute to the aberrant codification of proteins

involved in the redox chain, as demonstrated in an experimental murine model [17], and, acquired SNPs in mtDNA can influence the expression of the VEGF gene, as demonstrated in mitochondrial haplogroups. This is worth noting because SSc patients show microvascular dysfunction and the over-expression of this mediator, which is also directly associated with fibrosis [144]. It can be hypothesised that mtDNA fragments may favor the reactivation of endogenous retroelements by directly jumping near a defective sequence and providing intact ORFs, or by remotely controlling their transcription through epigenetics. The subsequent generation of many RNA copies of endogenous retroelements invading the cytosol may induce a protective response: i.e. the over-expression of non-coding RNAs capable of base pairing with their sequences and the stimulation of sensor proteins, some of which are located on mitochondria. In their turn, mitochondria may activate and generate ROS in order to counteract retrotransposons, which could damage mtDNA and further amplify the loop. However, given the extremely dynamic nature of nucleic acids, it cannot be excluded that nuclear transposable elements may anticipate mtDNA and create the basis of the disease. The hypothetical scenario outlining the role of endogenous retroelements in the pathogenesis of SSc is depicted in Fig. 10.

All in all, this profoundly different cellular scenario could explain the puzzling pathogenesis of SSc by combining genetics, epigenetics, endogenous infections, immune responses, and oxidative stress.

4. Conclusions

The nuclear genome harbors a large number of non-coding sequences, most of which are remnants of ancient viral infections. Being able to transpose themselves near to functional genes, some of these endogenous retroelements can reactivate, transcribe copies and produce proteins. Cells have complex machinery to prevent endogenous retroelement reactivation, which involves epigenetics and the activation of homeostatic pathways elicited by cytosolic and mitochondrial sensors. However, in some cases, these protective mechanisms fail and endogenous retroelements can induce an immune response, with mtDNA further contributing to their re-emergence. Many studies have confirmed the role of endogenous retroelements in the pathogenesis of autoimmune diseases. It is therefore conceivable that, in SSc patients, the aberrant reactivation of retrotransposons could simultaneously be the cause and effect of a network of intracellular cascades combining genetics, epigenetics, endogenous infections, immune responses and oxidative stress.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship

RT conceived the idea, drafted the manuscript and drew the figures; FA helped in writing the manuscript and critically revised the paper. PS and MJL critically revised the paper.

Declaration of Competing Interest

None.

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