NIH Public Access
Author Manuscript
Autoimmun Rev. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:
Autoimmun Rev. 2013 September ; 12(11): 1046–1051. doi:10.1016/j.autrev.2013.04.004.

POTENTIAL ROLE OF HUMAN-SPECIFIC GENES, HUMAN-SPECIFIC MICRORNAS AND HUMAN-SPECIFIC NON-CODING REGULATORY RNAS IN THE PATHOGENESIS OF SYSTEMIC SCLEROSIS AND SJÖGREN'S SYNDROME

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Abstract

The etiology and pathogenesis of human autoimmune diseases remain unknown despite intensive investigations. Although remarkable progress has been accomplished through genome wide association studies in the identification of genetic factors that may predispose to their occurrence or modify their clinical presentation to date no specific gene abnormalities have been conclusively demonstrated to be responsible for these diseases. The completion of the human and chimpanzee genome sequencing has opened up novel opportunities to examine the possible contribution of human specific genes and other regulatory elements unique to the human genome, such as microRNAs and non-coding RNAs, towards the pathogenesis of a variety of human disorders. Thus, it is likely that these human specific genes and non-coding regulatory elements may be involved in the development or the pathogenesis of various disorders that do not occur in non-human primates including certain autoimmune diseases such as Systemic Sclerosis and Primary Sjögren's Syndrome. Here, we discuss recent evidence supporting the notion that human specific genes or human specific microRNA and other non-coding RNA regulatory elements unique to the human genome may participate in the development or in the pathogenesis of Systemic Sclerosis and Primary Sjögren's Syndrome.

Keywords

Human specific genes; microRNAs; Non-coding RNA; Autoimmune diseases; Systemic Sclerosis; Sjögren's Syndrome

1. Introduction

The etiology and pathogenesis of human autoimmune diseases remain unknown despite intensive investigations. The extensive genome-wide association studies conducted in the last decade have led to the identification of numerous genetic factors that may predispose to their occurrence or modify their clinical presentation. However, to date no specific gene abnormalities have been conclusively demonstrated to be responsible. One of the most

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remarkable consequences of the extensive DNA sequencing studies accomplished in the last two decades was the realization of the extremely high conservation of coding gene sequences among various species. Indeed, comparison of the human and chimpanzee genomes indicated that these two species differ by less than 2% in the complement of expressed genes [1] and it has been reported that there are less than 200 genes in humans that are not present in chimpanzees, our closest evolutionary relative [1,2]. The completion of the human and chimpanzee genome sequencing has opened up novel opportunities to examine the role of human-specific genes in human development as well as the possible contribution of human-specific genes and other regulatory elements unique to the human genome towards the pathogenesis of a variety of human disorders. Thus, in addition to being responsible for human specific traits, such as bipedalism, highly enlarged brain cortex, and human language, it is likely that human specific genes and other regulatory elements unique to the human genome may be involved in the development of various disorders that do not occur in non-human primates including certain autoimmune diseases such as Systemic Sclerosis (SSc) and Primary Sjögren's Syndrome (SS). This remarkable observation allows to raise the possibility that certain human diseases, such as SSc or SS, that do not have a counterpart in chimpanzees or in other non-human primates may occur or may develop owing to either structural alterations in human-specific genes. Alternatively, these disorders may be caused by functional derangement of other human-specific regulatory elements, such as microRNAs (miRNA) or non-coding RNAs (ncRNA), or may be the result of functional abnormalities caused by deletions of genes or regulatory elements from the chimpanzee genome that have been lost during recent evolutionary events and are absent from the human genome. Here, recent evidence supporting the notion that human specific genes or human specific microRNA and other human-specific regulatory elements may participate in the development or in the pathogenesis of SSc and SS will be discussed.

2. Human specific genes

The identification of human specific genes and other regulatory elements unique to the human genome has accelerated the study of recent evolutionary events in human development and has provided novel pathways to the study of the pathogenesis of a variety of human disorders. Numerous observations have already been described documenting the important role of human specific genes particularly in relation to brain and brain cortex development [3–8]. Notable examples include the identification of the *FOXP2* gene which encodes an essential homeodomain protein required for human speech [5], the demonstration that the *AHI1* gene regulates axon guidance [2], and the discovery that genes encoding ASPM and microcephalin are essential for normal cerebral cortical growth and may be responsible for the substantial increase in brain cortex size in humans [8]. However, as pointed out by Stahl and collaborators [9,10], human specific genes rather than creating new signaling pathways are more likely to be involved in modulation or evolutionary regulation of previously developed and highly conserved pathways. Thus, in addition to being responsible for human specific traits, such as bipedalism, highly enlarged brain cortex, and human language, it is likely that human specific genes and other regulatory elements unique to the human genome may be involved in important regulatory roles including the regulation of important immunological functional pathways.

3. Pathologic conditions associated with human specific genes

Despite the potential importance of the study of human specific genes to human biology and pathology, only a few of these genes have been extensively studied in human disorders. Among these are genes encoded by the neuroblastoma breakpoint family (NBPF) which are associated with the development of neuroblastoma in humans [11,12], the nuclear pore complex-interacting protein (NPIP) which has been reported to be overexpressed in retinal tissues of patients affected with macular degeneration [13], and *TBC1D3*, an oncogene overexpressed in breast and prostate cancers that encodes a protein with a specific domain capable of modulating growth factor receptor signaling [10]. There is, however, extensive recent interest in the possible role of human-specific genes and human-specific genomic regulatory elements in the development of complex human diseases including certain autoimmune diseases [14].

4. Human diseases not described in chimpanzees

Although many human diseases have homologues in various animal species including quite distant evolutionary species, such as the mouse and other rodents, there are certain human disorders that have not been described in the closest human evolutionary relatives such as apes and chimpanzees. A very extensive search was performed recently by our group to document the presence of either SSc or SS in chimpanzees. This included a detailed review of the available published medical and veterinary literature, as well as, inquiries to the Office of Comparative Pathology at the National Institutes of Health (S. Jimenez; unpublished). From these extensive search and inquiries, it became apparent that these two diseases have not been described or encountered in chimpanzees.

Although the etiology of SSc and SS is unknown and the complex pathogenesis of both disorders has not been fully elucidated, it is generally recognized that immunological abnormalities play a crucial role [15–20]. Indeed, both SSc and SS are characterized by T and B cell hyperactivity [15–20] as well as by the participation of monocytes and tissue macrophages, particularly during the initial or early stages of SSc [21,22]. These prominent immunological abnormalities include alterations in innate immunity with expression of the type I interferon signature, infiltration of affected tissues with oligoclonally expanded T cell populations, production of specific autoantibodies, and numerous alterations in T and B cell subpopulations [23–30]. It is also of importance that both SSc and SS are characterized by B cell hyperactivity and development of tertiary lymphoid organs and/or B cell infiltration of affected tissues, decreased switched and unswitched peripheral memory cells in SS and increased CD19 expression indicative of B cell activation in SSc.

5. Relative over-reactivity of human lymphocytes compared to lymphocytes from chimpanzees

Despite the remarkable sequence conservation between the genomes of humans and chimpanzees [1,2], it has become well recognized that some immune responses capable of mediating strong immunological events in humans occur at a much less intense level in chimpanzees. Thus, it appears that immunologic reactivity to certain immune stimuli is muted or absent in chimpanzees compared to humans. For example, it has been described that HIV infection is much less severe in chimpanzees and there is no progression to full blown AIDS with a maintenance of substantially higher levels of CD4 T cells in the chimpanzees in comparison to humans [31,32]. There is also evidence to suggest that there are remarkable differences in the pathological responses between humans and chimpanzees to infection with hepatitis C virus (HCV). For example, the development of antibodies to HCV viral envelope proteins is less frequent and substantially muted in chimpanzees compared to humans, and the severe complications of HCV infections, including fibrosis of the liver, cirrhosis, and terminal liver failure are much less common in chimpanzees than in humans [33,34]. Other evidence to indicate that the immunological responses of chimpanzees are muted compared to those of humans are the development of milder reactions to varicella infections in chimpanzees [35] and their very low, if any, susceptibility to infections with major human pathogens such as Epstein-Barr virus and mycoplasma pneumoniae [36].

A remarkable and catastrophic event further pointed out the substantial differences in the immune responses between humans and non-human primates. This event was a Phase 1 clinical trial of TGN1412, a humanized monoclonal anti-CD28 receptor antibody [37]. This biological agent had been developed and tested extensively in *Cynomolgus macaques* who tolerated its administration without side effects. A clinical trial in 2006 administered an extremely low dose of this antibody, equivalent to 1/500th of the highest dose that had been tested in *Cynomolgus macaques* to six human volunteers with highly deleterious consequences, including the development of a severe cytokine storm which led to massive multiple organ failure and nearly death in the recipients [37]. Although the mechanisms responsible for this catastrophic event have not been fully elucidated as discussed recently [38,41], numerous studies have demonstrated remarkable differences in the immune response between lymphocytes from chimpanzees and humans, and have uncovered a striking over-reactivity of human lymphocytes to a variety of T cell stimuli [42–44]. These studies demonstrated that human lymphocytes manifest a generalized over-reactivity in comparison to lymphocytes from chimpanzees and that this over-reactivity was probably responsible for the catastrophic events of the anti-CD28 antibody clinical trial.

6. Regulation of gene expression by non-coding genomic elements

The last decade has witnessed a remarkable revolution in the understanding of the fine regulatory mechanisms controlling the patterns of gene expression of the complement of genes encoding translated proteins [45,46]. Indeed, numerous RNA regulatory elements that are not translated into proteins and that are capable of exerting a remarkable modulation of gene expression, collectively referred to as non-coding RNAs (ncRNAs), have been identified in the human genome [47–49]. These elements include miRNAs, long-intergenic non-coding RNAs (lincRNAs), and several other regulatory RNA species [50–58], including the recently identified circular RNAs [59–61]. It should be emphasized that the function of these novel RNA species is just beginning to be characterized. The most extensively studied ncRNA regulatory species are miRNAs [53–58]. MicroRNAs comprise a large family of small (21–23 nt) RNAs that exhibit a high degree of structural and functional conservation throughout species and their biogenesis is quite complex [62–64]. Binding of miRNA to the 3' untranslated regions (3'UTRs) of target genes is highly-specific and as a result of such sequence-specific binding miRNAs are capable of repressing the translation of target genes and/or inducing the degradation of target gene translated mRNA [65–68]. Binding to target mRNAs with perfect or near perfect complementarity induces mRNA degradation, whereas imperfect complementarity often induces translational repression. A 7–8 nt sequence in the 5' end of miRNAs, referred to as the “seed sequence”, is critical for efficient targeting. To date approximately 1,000 miRNAs encoded in the human genome have been identified and it has been shown that they are expressed in a tissue-specific and cell-type-specific manner. Individual miRNAs can target numerous mRNAs and individual mRNAs can be targeted by multiple miRNAs, providing a remarkably vast regulatory potential [59–64]. Although substantial progress has already been accomplished in the understanding of miRNA biogenesis and in the functional characterization of numerous miRNAs, the role of lincRNAs and other non-coding RNA species remains for the most part uncharacterized, except for notable progress with some of them such as HOTAIR [69–71]. Another level of complexity has recently been introduced regarding the regulatory role of non-coding RNA species with the identification of a new species of RNA, circular RNA. This novel species of RNA may play a crucial role in the regulation of miRNA function as they may act as reservoirs of large amounts of miRNAs and have numerous binding sites for specific miRNAs, a property that allows them to act as a miRNA sponge, effectively preventing the binding of miRNA to their specific targets [59–61].

Although the role of these regulatory RNA species is just beginning to become clarified, it has already become apparent that they may play crucial roles during normal development, as well as, in the pathogenesis of various genetically determined and, more importantly, acquired disorders. Furthermore, the existence of an organism-specific miRNA regulation for important protein-coding genes is very likely. Indeed, differential expression of certain miRNA has been described in the brains of human, chimpanzee, and macaques employing microarrays [72,73]. Moveover, of direct relevance to the topic discussed here, was the identification of miR-941 a human-specific miRNA which emerged *de novo* in the human lineage [74]. This human-specific miRNA is highly expressed in pluripotent cells and preferentially targets genes in the hedgehog and insulin-receptor pathways, pathways that have received recent attention for their possible involvement in the pathogenesis of SSc [75,76].

7. Other regulatory human-specific genomic changes

On the other hand, it is also likely that some important regulatory elements present in the chimpanzee genome may have been deleted and lost during evolution. Indeed, recent studies identified molecular events most likely to cause significant regulatory alterations in humans [3,77,78]. These alterations involved complete deletions of sequences highly conserved between chimpanzees and other mammals. These deletions occurred almost exclusively in non-coding regions of the human genome and, interestingly, were enriched in proximity to genes involved in steroid hormone signaling such as the androgen receptor and in various neural functions including elements involved in expression of specific brain regions in humans.

8. Role of ncRNA in the pathogenesis of autoimmune diseases

Numerous recent studies have examined the role of miRNAs in the pathogenesis of various autoimmune [79–89] and fibrotic disorders including SSc [90–100]. Furthermore, the involvement of human-specific miRNAs in the regulation of the phenotypic conversion of epithelial and endothelial cells into activated myofibroblasts has also been recently described [101–105]. Thus, the role of RNA regulatory species in the pathogenesis of these autoimmune diseases deserves attention and should be intrusively investigated as they may provide novel targets for therapeutic interventions.

9. Conclusion

The studies reviewed here provide strong support to the notion that human specific genes, the newly emerging classes of organism-specific ncRNAs and the existence of organism-specific aspects of mRNA-driven gene regulation, including miRNAs, long ncRNAs and other ncRNA species (Table I), may play a crucial role in the mechanisms that are responsible for the phenotypic differences between humans and chimpanzees with regard to the development of human specific autoimmune diseases. These potentially important mechanisms are illustrated diagrammatically in Figure 1. Thus, we posit that certain human autoimmune disorders including SSc and SS, which have not been described in chimpanzees, may occur exclusively in humans owing to increased or uncontrolled immunological reactivity in humans determined by either expression of human specific genes, or by alterations in regulatory networks. These alterations may be the result of the effects of human-specific genes or of differences in regulatory RNA species, such as human specific miRNAs and other short, circular, or long ncRNAs. We further posit that experimental investigations to explore this hypothesis may provide valuable information regarding the pathogenesis of these common and currently incurable systemic autoimmune disorders and may provide novel therapeutic targets for these disorders.

Acknowledgments

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health, under Award Number AM19606. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The expert assistance of Kenneth Brown is duly acknowledged.

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Take Home Points

- Human-specific genes and regulatory elements may play a role in autoimmune diseases not encountered in non-human primates such as Systemic Sclerosis (SSc) and Primary Sjögren's Syndrome (SS).
- These unique genetic elements may include human-specific genes, microRNAs, or other non-coding RNAs species capable of modulating gene expression.
- Although the etiology of SSc and SS is unknown, their exclusive occurrence in humans may result from uncontrolled immunological reactivity mediated by human-specific genes or non-coding RNA regulatory elements.

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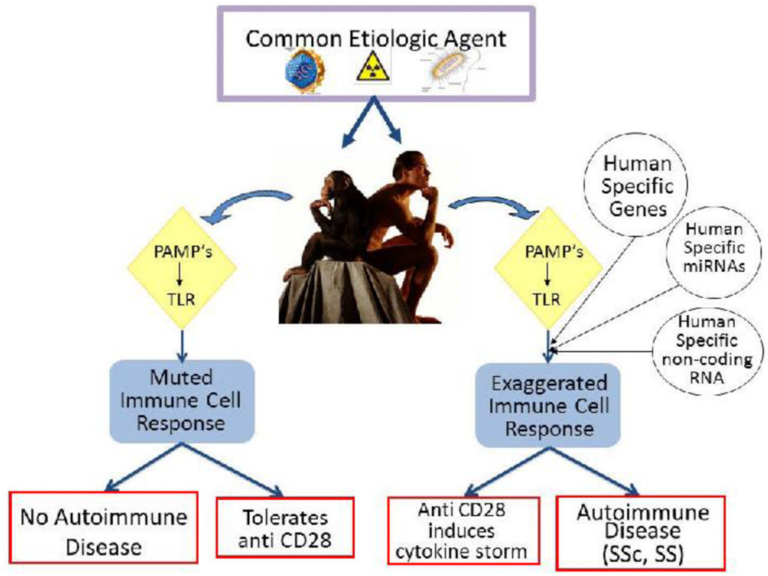

Figure 1. SCHEMATIC DIAGRAM ILLUSTRATING THE POSTULATED ROLE OF HUMAN SPECIFIC GENES AND OTHER HUMAN SPECIFIC GENOMIC REGULATORY ELEMENTS IN THE DEVELOPMENT OF AUTOIMMUNE DISEASES SUCH AS SSC AND SS

A common etiologic agent is recognized by innate immunity cells through PAMP's (pathogen-associated molecular patterns) receptors which then activate specific toll like receptor (TLR) pathways to initiate adaptive immune responses. Some of these immune responses are muted in chimpanzees as evidenced for example by tolerance to anti CD28 antibodies, and, therefore, the chimpanzees do not develop SSc or SS. In contrast, in humans the immune response is exaggerated owing to the effects of either human-specific genes or to regulatory abnormalities mediated by human-specific miRNAs or human-specific short and long ncRNAs and as a result they develop SSc or SS.

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Table 1

POTENTIAL MECHANISMS INVOLVED IN THE DEVELOPMENT OF HUMAN-SPECIFIC AUTOIMMUNE DISEASES

• Human-specific post-translational protein modifications
• Acquisition of human-specific genes:
◯ Gene duplication
◯ Gene splicing
• Loss of functional non-human primate specific genes:
◯ Deletions
◯ Mutations
• Human-specific alterations in regulatory non-coding RNA:
◯ piwi-interacting RNAs
◯ microRNA
◯ Long ncRNA
◯ Long intergenic ncRNA
◯ Circular RNA
• Human-specific mutations in long ncRNA protein-binding partners