Book Chapter

Cross-Talk between Mitochondrial Dysfunction-Provoked Oxidative Stress and Aberrant Noncoding RNA Expression in the Pathogenesis and Pathophysiology of SLE

Chang-Youh Tsai¹*, Song-Chou Hsieh²†, Cheng-Shiun Lu²,³, Tsai-Hung Wu⁴, Hsien-Tzung Liao¹, Cheng-Han Wu²,³, Ko-Jen Li², Yu-Min Kuo²,³, Hui-Ting Lee⁵, Chieh-Yu Shen²,³ and Chia-Li Yu²*

¹Division of Allergy, Immunology & Rheumatology, Taipei Veterans General Hospital & National Yang-Ming University, Taiwan
²Department of Internal Medicine, National Taiwan University Hospital, Taiwan
³Institute of Clinical Medicine, National Taiwan University College of Medicine, Taiwan
⁴Division of Nephrology, Taipei Veterans General Hospital & National Yang-Ming University, Taiwan
⁵Section of Allergy, Immunology & Rheumatology, Mackay Memorial Hospital, Taiwan

†These authors contributed equally to this work.

*Corresponding Author: Chang-Youh Tsai, Division of Allergy, Immunology & Rheumatology, Taipei Veterans General Hospital & National Yang-Ming University, #201 Sec.2, Shih-Pai Road, Taipei 11217, Taiwan

Chia-Li Yu, Department of Internal Medicine, National Taiwan University Hospital, #7 Chung-Shan South Road, Taipei 10002, Taiwan

Published February 19, 2020
This Book Chapter is a republication of an article published by Chang-Youh Tsai, et al. at International Journal of Molecular Sciences in October 2019. (Tsai, C.-Y.; Hsieh, S.-C.; Lu, C.-S.; Wu, T.-H.; Liao, H.-T.; Wu, C.-H.; Li, K.-J.; Kuo, Y.-M.; Lee, H.-T.; Shen, C.-Y.; Yu, C.-L. Cross-Talk between Mitochondrial Dysfunction-Provoked Oxidative Stress and Aberrant Noncoding RNA Expression in the Pathogenesis and Pathophysiology of SLE. Int. J. Mol. Sci. 2019, 20, 5183.)

**How to cite this book chapter:** Chang-Youh Tsai, Song-Chou Hsieh, Cheng-Shiun Lu, Tsai-Hung Wu, Hsien-Tzung Liao, Cheng-Han Wu, Ko-Jen Li, Yu-Min Kuo, Hui-Ting Lee, Chieh-Yu Shen, Chia-Li Yu. Cross-Talk between Mitochondrial Dysfunction-Provoked Oxidative Stress and Aberrant Noncoding RNA Expression in the Pathogenesis and Pathophysiology of SLE. In: Song Guo Zheng, editor. Prime Archives in Molecular Biology. Hyderabad, India: Vide Leaf. 2020.

© The Author(s) 2020. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License(http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Author Contributions:** C.-L.Y. and C.-Y.T. supervised the writing project of the manuscript; C.-Y.T. and S.-C.H. prepared the manuscript and wrote the draft together; H.-T.L. prepared the figures; C.-S.L., C.-H.W., K.-J.L., Y.-M.K., H.-T.L., T.-H.W. and C.-Y.S. actively participated in the discussion and suggestions for the manuscript.

**Funding:** This research was funded by Ministry of Science & Technology, Executive Yuan, (MOST107-2314-B075-051-MY3, and MOST106-2634-F-075-001) and Taipei Veterans General Hospital (V107D37-002-MY3), Taiwan.

**Acknowledgments:** The authors thanks all of the individuals participating in the investigations.

**Conflicts of Interest:** The authors declare no conflict of interest.
Abstract

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmune disease involving almost every organ. Polygenic predisposition and complicated epigenetic regulations are the upstream factors to elicit its development. Mitochondrial dysfunction-provoked oxidative stress may also play a crucial role in it. Classical epigenetic regulations of gene expression may include DNA methylation/acetylation and histone modification. Recent investigations have revealed that intracellular and extracellular (exosomal) noncoding RNAs (ncRNAs), including microRNAs (miRs), and long noncoding RNAs (lncRNAs), are the key molecules for post-transcriptional regulation of messenger (m)RNA expression. Oxidative and nitrosative stresses originating from mitochondrial dysfunctions could become the pathological biosignatures for increased cell apoptosis/necrosis, nonhyperglycemic metabolic syndrome, multiple neoantigen formation, and immune dysregulation in patients with SLE. Recently, many authors noted that the cross-talk between oxidative stress and ncRNAs can trigger and perpetuate autoimmune reactions in patients with SLE. Intracellular interactions between miR and lncRNAs as well as extracellular exosomal ncRNA communication to and fro between remote cells/tissues via plasma or other body fluids also occur in the body. The urinary exosomal ncRNAs can now represent biosignatures for lupus nephritis. Herein, we’ll briefly review and discuss the cross-talk between excessive oxidative/nitrosative stress induced by mitochondrial dysfunction in tissues/cells and ncRNAs, as well as the prospect of antioxidant therapy in patients with SLE.

Keywords

Noncoding RNA; microRNA; Long Noncoding RNA; Mitochondrial Dysfunction; Oxidative Stress; Nitrosative Stress Exosome; Cross-Talk; Systemic Lupus Erythematosus
Abbreviations

C.V- Cardiovascular; DNA- Deoxyribonucleic Acid; DNMT-DNA Methyltransferase; FcγR- Immunoglobulin G Fragment C-Gamma Receptor; GLUT- Glucose Transporter; GSH-Reduced form Glutathione; GPx- Glutathione Peroxidase; GST-Glutathione S-Transferase; HAT- Histone Acetyltransferase; HDAC- Histone Deacetylase; IFN- Interferon; IL- Interleukin; LN- Lupus Nephritis; LncRNA- Long Noncoding Ribonucleic Acid; MAPK- Mitogen-Activated Protein Kinase; MHC- Major Histocompatibility Complex; MiR- microRNA; MtDNA-Mitochondrial DNA; Mtor- Mammalian Target of Rapamycin; NAC- N-acetylcysteine; ncRNA- Non-coding RNA; NET-Neutrophil Extracellular Trap; Ras- Rat Sarcoma Protein, a Superfamily of Small GTPase; RNS- Reactive Nitrogen Species; ROS- Reactive Oxygen Species; SIRT1- Sirtuin 1; SLE- Systemic Lupus Erythematosus; SLEDAI- SLE Disease Activity Index; SLEDAI-2K- SLEDAI in 2000 year; SOD- Superoxide Dismutase; TET- Ten-Eleven Translocation DNA Dioxygenase; Th- Helper T cell; Treg- Regulatory T Cell

Introduction

Systemic lupus erythematosus (SLE) is a highly heterogeneous disorder with chronic inflammatory and autoimmune reactions all over the body. It is characterized by the production of diverse autoantibodies [1,2] and chronic tissue inflammation [3-6]. There are multiple factors associated with lupus pathogenesis, including genetic predisposition [7-15], epigenetic dysregulation of gene transcription [16-21] and aberrant post-transcriptional events by noncoding (nc)RNAs [19,22-25], sex hormonal imbalance [26-29], environmental stimulation [30,31], mental/psychological stresses [28], dietary/nutritional influence [32-35], mitochondrial dysfunctions [36-39], and other yet-undefined factors [40]. Figure 1 shows the factors contributing to the pathogenesis of SLE, in which environmental factors such as infections, chemicals, heavy metals, medications, exogenous estrogens, and phthalate trigger its development in susceptible
individuals. The genome-wide association study (GWAS) has identified over 100 risk loci for SLE susceptibility across populations [13]. However, functional studies have revealed that many of them fall in the category of noncoding regions of genomes, suggesting that they probably play a regulatory role. Many loci exhibit protean environmental interactions, epigenetic modifications, or association with genetic variants [10]. Nevertheless, the expression of IFN-α in tissues and circulation has been consistently found at a hereditary risk locus in patients with SLE [14]. The genetic predisposition for lupus pathogenesis is summarized in Table 1.

Figure 1: Factors contributing to the development of systemic lupus erythematosus. It is worthy to note that cross-talk between mitochondrial dysfunction and aberrant epigenetic regulation is mediated via excessive oxidative stress.
Table 1: Some of the genetic loci involved in the risk for SLE.

| MHC association [7,8,9]          |
|----------------------------------|
| MHC class II: DR₂, DR₃          |
| MHC class III: C₄ null, TNF-α    |

| Immune complex processing and phagocytosis [7,8,9,10,11,12,13,14,15] |
|---------------------------------------------------------------|
| C₁₉₆₇, C₄A/B, CFB                                             |
| FCGR2A/B, CR2, CR3                                             |
| CRP                                                           |
| ICHMs (intercellular adhesion molecules)                      |
| ITGAM (integrin subunit alpha M)                              |

| TLR and type 1 IFN signaling [7,8,9,10,11,12,13,14,15]:        |
|----------------------------------------------------------------|
| TLR7 (toll-like receptor 7)                                    |
| TREX1 (three prime repair exonuclease 1)                      |
| DNASE₁ (DNA degrading enzyme 1)                               |
| IRAK1/MECP2 (interleukin-receptor-associated kinase 1)        |
| IRF5/7/8 (interferon regulatory factor 5, 7, 8)               |
| STAT1 (signal transducer and activator of transcription 1)    |
| STAT4 (signal transducer and activator of transcription 4)    |
- **B and T cell function and signal genes [7.8.9.10.11.12.13.14.15]**

  - IL10 (interleukin 10)
  - STAT4 (signal transducer and activator of transcription 4)
  - PTPN22 (protein tyrosine phosphatase non-receptor type 22)
  - PDCD1 (programmed cell death 1)
  - TNFSF4 (TNF superfamily member 4)
  - BLK (B lymphoid tyrosine kinase)
  - BANK1 (B cell scaffold protein with ankyrin repeats 1)

- **Others**

  - PXK/ABHD6 (PX domain containing serine/threonine kinase likes)
  - XKR6 (XK related 6)
  - UPF1/SMG7 (RNA helicase and ATPase)
  - NMNAT2 (nicotinamide nucleotide adenyltransferase 2)
  - UHRF1BP1 (ubiquitin like with PHD and ring finger domains 1 binding protein 1)
Recent investigations revealed that increased oxidative and/or nitrosative stress could induce structural and functional changes in different biomolecules, including proteins, lipids, nucleic acids, and glycoproteins [41,42]. The oxidative stress may also modulate proinflammatory cytokine gene expression [43-46] and cell senescence/apoptosis [47,48]. Antioxidants have been tried in the treatment of SLE with effectiveness [49-53]. Accordingly, the presence of oxidative stresses and their associated biomarkers are definitely playing a decisive role in the pathogenesis of SLE [54].

Epigenetics is an investigation of the changes in phenotypic presentation (or gene expression) that are caused by mechanisms other than the polymorphism of genome per se. It is conceivable that more than 97% of cellular RNAs are not transcribed for protein coding in nature. These ncRNAs, including microRNAs (miRs, 20–24 bp in length) and long noncoding (Inc) RNAs, which are >200 bp in length are the major molecules for post-transcriptional modifications of messenger (m)RNAs [55,56]. Interestingly, many reports have demonstrated that oxidative stress can modulate ncRNA expression in different diseases [57,58]. Conversely, ncRNAs have also been found to be regulators of oxidative stresses in different pathological conditions [59]. Furthermore, the cross-talk between miRs and IncRNAs has also been found [60,61]. Based on these facts, we hereby review and discuss briefly the molecular basis of epigenetic regulations, the underlying mechanism of mitochondrial dysfunctions, and the cross-talk between mitochondrial dysfunction-provoked oxidative stress and abnormal expression of ncRNAs during the pathologic development of SLE. At the end, a potential use of antioxidants as the therapy for SLE will also be concisely overviewed.
Epigenetic Regulations of Gene Expression/Silencing in Physiological Conditions

Epigenetic variation is a reversible but heritable change in gene expression without alterations in genetic code. It may include DNA methylation, histone modification, and post-transcriptional mRNA modification by ncRNAs [16]. DNA methylation is a biochemical process that involves a methyl group being added to a cytosine or adenine residue at the position of a repeated CpG dinucleotide (CpG island) in the promoter region to repress gene expression by DNA methyltransferase (DNMT) 1, 3a, and 3b. In contrast, reactivation of DNA by demethylation to restore gene transcription can be achieved by ten-eleven translocation (TET) enzymes TET1, TET2, and TET3.

Abnormal DNA Methylation/Demethylation in SLE

DNA methylation is catalyzed by DNMT1 for gene silencing. A status of DNA hypomethylation to enhance gene expression can be found in CD4+T cells of SLE patients as a result of decreased expression of DNMT1 originating from a deficient ras-MAPK signature [62,63]. In addition, DNA methylation acts as a housekeeping mechanism for physiological inactivation of X-chromosomes in female [26,27,64]. Recent studies have suggested that CD40L demethylation is responsible for CD40L overexpression in T cells of women with SLE [64].

Abnormal Histone Modification in SLE

The degree of chromatin tightness is regulated via complex mechanisms, including structural changes in histones. Usually, double helix-chromatin coils around a protein core composed of histone octamers (H2A, H2B, H3, and H4 with two copies of each). The biochemical processes to change the 3D structure of histones include ubiquitination, phosphorylation, SUMOylation, methylation, and acetylation. The methylation and acetylation of histones are the most extensively studied [17]. These two biochemical changes are controlled by two major enzymes,
histone acetyl transferase (HATs) and histone deacetylase (HDACs), that catalyze the addition/removal of an acetyl group on the lysine residues of histones. Acetylation relaxes the chromatin structures by diminishing the electric charge between histone and DNA as a result of offering an acetyl group. Conversely, deacetylation tightens the chromatin structure to silence gene expression.

The participation of histone modifications in lupus pathogenesis has been well documented. Hu et al. [65] demonstrated a global hyperacetylation of histones H3 and H4 in lupus CD4 T cells. Zhou et al. [66] reported that abnormal histone modifications within TNFSF7 promotor caused CD70 (a ligand for CD27) overexpression in SLE-T cells. Furthermore, Hedrich et al. [67] demonstrated that CREM, a transcription factor, participated in histone deacetylation in active T cells of SLE patients by way of silencing IL-2 expression, which normally recruits HDAC to cis-regulatory element (Cre) sites in IL-2 promoters. Dai et al. [68] showed in GWAS an alteration in histone H3 lysine K4 trimethylation (H3K4me3) by chromatin immunoprecipitation linked to microarray in peripheral blood mononuclear cells of some SLE patients. In addition, Zhang et al. [69] have found global H4 acetylation occurs in monocytes/macrophages in SLE subjects, which is regulated by IFN regulatory factors. The release of SLE-related cytokines such as IL-17, IL-10, and TNF-α was also abnormally increased in H3 acetylation by stat3 [70-72]. In lupus-prone MRL/lpr mice, a histone deacetylation gene, sirtuin-1 (Sirt-1), was found overexpressed [73], indicating a compensatory repression of gene over-reactivation. Hu et al. [73] further noted downregulation of Sirt-1 would transiently enhance H3 and H4 acetylation and subsequently mitigate serum levels of anti-dsDNA, as well as kidney damage in lupus mice. Javierre et al. [74] reported a global decrease in the 5-methylcytosine content in parallel with DNA hypomethylation and high expression levels of ribosomal RNA genes relevant to SLE pathogenesis. In short, abnormal histone modifications are implicated in lupus pathogenesis and immunopathological changes in these patients.
Physiological Functions of ncRNAs

Besides DNA methylation/acetylation and histone modification, the most recently discovered epigenetic mechanisms for gene expression are dependent on the class of ncRNAs that are not translated into proteins. These molecules include both housekeeping ncRNAs and regulatory ncRNA [55]. In total 50% of mRNAs are located in chromosomal regions with liability to undergo structural changes [75]. On the other hand, lncRNA can regulate gene expression by different ways, including epigenetic, transcriptional, post-transcriptional, translational, and peptide localization modifications [56]. Interestingly, the interactions between IncRNAs and miRs, as well as their pathophysiological significance, have recently been reported [60,61]. It is believed that IncRNAs mediate “sponge-like” effects on various miRs and subsequently inhibit miR-mediated functions [60,61]. The regulatory effects of intracellular and extracellular (exosomal) ncRNA on cell functions are illustrated in Figure 2.

Figure 2: Different kinds of noncoding RNAs, including groups of small noncoding and long noncoding RNA, distributed in the intracellular and extracellular compartments, such as plasma, urine, and other body fluids, for regulation of messenger RNA translation and remote cell–cell communications in the body.
Aberrant Intracellular and Extracellular Exosomal ncRNA Expression in Association with Pathological Changes in Patients with SLE

It is not surprising that miRs play important roles in the regulation of innate and adaptive immunity, and the aberrantly expressed miRs are associated with autoimmune diseases [22,76-80]. Lu et al. [23,81-83] and Su et al. [84] have found various aberrantly expressed intracellular miRs implicated in the cell signaling abnormalities, deranged cytokine and chemokine release, and Th17/Treg ratio alterations in patients with SLE. Different from miRs, lncRNAs are expressed at lower levels in cells and tissues, more specifically [85-87]. These lncRNA are obviously modulating innate immunity [88] and inflammatory responses [89]. Luo et al. [90], Zhao et al. [91], and Wang et al. [92] reviewed the literature and found that lncRNA expression profiles in SLE were remarkably different from the normal.

The regulatory functions of miRNAs can be validated by transfecting miRNA mimics or antagonists using electroporator. Lu et al. [81] found increased miR-224 could target apoptosis inhibitory protein 5 (API5) and enhance T cell activation, and then activate induced cell apoptosis. Besides, the same group found decreased miR-31 in SLE T cells targeted the Ras homologue gene family member A (RhoA), which led to a decreased nuclear factor of activated T cells (NFAT) and cell apoptosis [23]. In addition, decreased miR-146a may result in upregulation of interferon regulatory factor 5 (IRF-5) and then enhanced production of IFN-α, STAT-1, IL-1 receptor associated kinase-1 (IRAK1), and TRAF6, which then increase innate immune responses, lupus disease activity, and lupus nephritis [23]. Furthermore, increased miR-524-5p that targets Jagged-1 and Hes-1mRNA may enhance IFN-γ production and then increase disease activity of SLE [82]. Su et al. [84] demonstrated that increased expression of miR-199-3p promoted ERK-mediated IL-10 production by targeting poly-(ADP-ribose) polymerase-1 (PARP-1) in SLE.

While their major functions are executed intracellularly, many miRs can be detected extracellularly in plasma/serum and urine.
This extracellular form of ncRNA is protected from degradation by conjugation with carrier proteins or by being enclosed in subcellular vesicles by lipid bilayer exosomes [85]. With characteristics of the tissue- and disease-specific expression, these extracellular ncRNAs can carry out intercellular communication, signal transduction, transport of genetic information, immunomodulation, and can be taken as diagnostic biosignatures or as research tools for understanding the pathophysiology of autoimmune diseases [85-92]. Plasma circulating microRNAs exist in a rather stable form and are incorporated into distant cells to regulate protein translation and synthesis there. Carlsen et al. [87] have found plasma exosomal miR-142-3p, which targets IL-1β, and miR-181a, which targets FoxO1, are increased in active SLE patients. Kim et al. [88] demonstrated that increased plasma circulatory hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p could become novel biosignatures in patients with SLE. The exosomal miRs can be found in other body fluids including breast milk, saliva, and urine, in addition to plasma [89]. Hsieh et al. [93] and Tsai et al. [94] concluded that urinary exosomal miRs could be used as biomarkers/biosignatures in lupus nephritis. Tsai et al. [94] have also noted aberrant miRNA expression in the immune-related cells could become biosignatures in correlation with pathological processes in different autoimmune and inflammatory rheumatic diseases. In addition, Perez-Hernandez et al. [95] and Xu et al. [96] have suggested the potential therapeutic application of exosomal ncRNA in different autoimmune diseases. Not only exosomal miRs, extracellularly expressed lncRNA profiles could also become potential biomarkers for human diseases [97,98].

lncRNAs are another regulatory noncoding RNA, capable of modulating many biological functions more specifically than miRs [99-102]. Aberrant expression of lncRNAs obviously induces different disease entities [99-106]. Table 2 summarizes the aberrant intracellular and circulating plasma exosomal lncRNA expression, their target mRNA, and related pathological processes in patients with SLE. Wang et al. [103] found that increased lncRNA ENST00000604411.1 expression in macrophages/dendritic cells, through targeting the X inactive specific transcript (XIST) that is normally implicated in keeping the active X chromosome in an activated state by protecting it
from ectopic silencing after commencement of the silencing process of the haplotype X chromosome, could induce lupus development. Another IncRNA ENST 00000501122.2 (also known as NEAT1) overexpressed in SLE monocytes may activate CXCL-10 and IL-6 expression. Furthermore, Wu et al. [98] reported that elevated expression of plasma GAS-5, linc 0640, and linc 5150 may activate MAPK signaling pathway. The five IncRNA panels, including GAS-5, linc7074, linc 0597, linc 0640, and linc 5150 in plasma, could be regarded as biosignatures in SLE. The biochemical properties of extracellular ncRNAs and the pathophysiological roles of these aberrant exosomal ncRNAs in SLE are further discussed in the following paragraph.

Table 2: Aberrant expression of long none-coding RNAs, their target mRNAs, and related pathological processes in patients with systemic lupus erythematosus.

| SLE           | Inc RNA Expression | Target mRNA | Pathological Processes |
|---------------|--------------------|-------------|------------------------|
| Intracellular | [103,104,105,106]  |             |                        |
| NEAT1↑*       | IL-6↑, IFN↑, CXCL10↑| DNA hypomethylation |
| MALAT1↑       | IL-21↑, SIRT1↑     | SLEDAI-2K↑  |
| Linc0597↑     | TNF-α↑, IL-6↑      | ESR↑, CRP↑, C3 ↓, |
| Linc DC↑      | STAT3↑             | Th1↑        |
| Linc0597↓     | TNF-α↑, IL-6↑      | Inflammation↑ |
| Linc-HSFY2-3:3↓| -                  | -           |
| Linc-SERP1N139-1:2↓| -             | -           |
| Gas 5↓        | Apoptotic gene↓    | T cell apoptosis↓ |
| Circulating plasma exosomal [98] |                        |            |
| Linc0597↑     | TNF-α↑, IL-6↑      | MAPK signaling↑ |
| Linc0640↑     | Phosphatase 4 (DUSP4)↑ | Lupus pathogenesis |
| Linc5150↑     | Arrestin β2 (ARRB2)↑ |             |
| Ribosomal protein S6 kinase A (RPS6KA5)↑ |             |
| Gas 5↓        | Apoptotic gene↓    | T cell apoptosis↓ |
| Linc 7074↓    |                    |             |

↑: increased expression or production; ↓: decreased expression or production; *: Oxidative stress-induced [107].
Increased Oxidative Stress in Patients with SLE
Causes of Excessive Oxidative Stress in SLE

Li et al. [108] have compared the reduction–oxidation (redox) capacity between normal and SLE immune cells. They found decreased plasma and intracellular glutathione (GSH) levels, and decreased intracellular GSH-peroxidase and gamma-glutamyl-transpeptidase activity in patients with SLE. Besides, the defective expression of facilitative glucose transporter (GLUT) 3 and 6 led to increased intracellular basal lactate levels, as well as decreased ATP production in SLE T cells and polymorphonuclear leukocytes. These results may indicate deranged cellular bioenergetics and defective redox capacity in immune cells that would increase oxidative stress in SLE. Lee et al. [36-39] demonstrated that mitochondrial dysfunctions in SLE patients included decreased mitochondrial DNA (mtDNA) copy number, increased mtDNA D-310 (4977 bp) heteroplasmy, and variants, as well as polymorphism of C1245G in hOGG1 gene in leukocytes. Leishangthem et al. [41] found a significant decrease in enzyme activity of complex I, IV, and V in mitochondria of patients with SLE. Lee et al. [109] have extensively investigated the cause of excessive stress in patients with SLE. They reported a number of antioxidant enzyme deficiencies in SLE leukocytes, including copper/zinc superoxide dismutase (Cu/ZnSOD), catalase, glutathione peroxidase 4 (GPx-4), glutathione reductase (GR), and glutathione synthetase (GS). In addition, the mitochondrial biogenesis-related proteins, such as mtDNA-encoded ND1 peptide (ND1), ND6, nuclear respiratory factor 1(NRF-1), and pyruvate dehydrogenase E1 component alpha subunit (PDHA1), and glycolytic enzymes, including hexokinase II (HK-II), glucose 6-phosphatate isomerase (GPI), phosphofructokinase (PFK), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH), are also reduced in SLE immune cells. These mitochondrial functional abnormalities may further increase oxidative stress and cell apoptosis in patients with SLE, in addition to the defective bioenergetics. Yang et al. [110] and Tsai et al. [111] concluded that enhanced oxidative stress could facilitate mitophagy, inflammatory reactions, cell senescence/apoptosis, neoantigen formation, and NETosis in SLE. The causes of mitochondrial dysfunction to induce
excessive oxidative stresses and their effects on the lupus pathogenesis and pathological processes are illustrated in Figure 3.

**Figure 3:** The origins of excessive oxidative stresses and their roles in abnormal epigenetic regulation and pathological processes in patients with SLE.

**Effects of Excessive Oxidative Stress on the Pathogenesis and Pathophysiology in SLE Patients**

The modifications of intra- and extracellular biomolecules by oxidative stress result in glycation and nitrosation of proteins [112], lipid peroxidation [42], as well as mitochondrial [113] and nuclear DNA strand breaks [114]. These biochemical and structural modifications of intracellular biomolecules would induce histone modification, nuclear and mitochondrial DNA damage, and aberrant ncRNA expression. As a consequence, the resulting sensitivity to environmental stress and sex hormone dysregulation [26-31] may further trigger the occurrence of lupus flare-ups. In addition, cardiovascular morbidities are enhanced due to increased glycation end products in patients with SLE [111,112,115]. The molecular basis and adverse effects of excessive oxidative stress in lupus pathogenesis and pathology are summarized in Figure 4.
Figure 4: The molecular basis of excessive oxidative stress in the pathogenesis and pathological changes in patients with SLE.

Cross-Talk between Oxidative Stress and ncRNAs in Physiological Condition

Recently, ever-increasing studies have emphasized the significance of the interactions between redox signaling and expression of ncRNAs in normal physiological conditions, as well as in disease status [44-46,57-59]. Sustained high levels of oxidative stress can cause cell senescence and even cell death, while optimal oxygen radicals are important for cell signaling. Dandekar et al. [44] and Lin et al. [116] have found mutual cross-talk among endoplasmic reticulum stress, oxidative stress, inflammatory response, and autophagy.

Excessive Oxidative Stress May Influence ncRNA Expression in Various Diseases

Many authors have demonstrated that redox-dependent signaling is essential for host’s cellular decisions on differentiation, senescence, or death to maintain homeostasis of the body [117-119]. Figure 5 summarizes the aberrant miR expression resulting
from excessive oxidative stress in different diseases, which include Alzheimer’s disease [120], Parkinson’s disease [121], hearing disorders [122], aging [123], osteoarthritis [124], cardiomyopathy in diabetes [125], and cancers [126]. However, despite the association of aberrant ncRNA expression with various pathological changes in SLE, as listed in Table 2 and Table 3, there has been no literature demonstrating direct evidence for specific oxidative-induced ncRNA in patients with SLE. The combination of Table 3 and Figure 5 leads us to speculate that miR-21, miR-29b, miR-146a, and miR-126b may be induced by excessive oxidative stress in SLE as asterisked in Table 3 and its footnote.

Figure 5: The effect of excessive oxidative stress on aberrant microRNA expression in various degenerative, malignant, cardiovascular, and autoimmune diseases. (?): increased miR-21, miR-29, miR-126b, and miR-146a expression induced by excessive oxidative stress is suspected in SLE patients, but no direct evidence has been published in the literature.
Table 3: Aberrant expression of microRNAs, their target mRNAs, and pathological effects in patients with SLE.

| SLE                      | miRNA       | Target mRNA                        | Pathological Process                                                                 |
|--------------------------|-------------|------------------------------------|---------------------------------------------------------------------------------------|
| **Intracellular**        |             |                                    |                                                                                       |
| [82,83,84,85,86]         |             |                                    |                                                                                       |
| • Increase in:           |             |                                    |                                                                                       |
|                          | miR-21*     | Arylamide small nucleotide inhibitors | DNA hypomethylation†                                                                     |
|                          | miR-524-5p  | Jagged-1, Hex-1                     | IFN-γ↑, SLEDAI↑                                                                        |
|                          | miR-126     | KRAS                               |                                                                                        |
|                          | miR-148a    | PTEN                               |                                                                                        |
| • Decrease in:           |             |                                    |                                                                                       |
|                          | miR-142-3p  | HMGB-1                             | T and B activation†                                                                     |
|                          | miR-142-5p  | PD-L1                              |                                                                                        |
|                          | miR-146a*   | IRF-5, STAF-1                       | Innate immune response↑, lupus nephritis†                                               |
|                          | miR-224†    | API5                               | Type 1, IFN↑                                                                           |
|                          | miR199-3p†  | PARP-1                             | IL-10†                                                                                |
| • Decrease in:           |             |                                    |                                                                                       |
|                          | miR-31      | RhoA                               | Cell apoptosis↑                                                                        |
|                          | miR-142-3p  | HMGB-1                             |                                                                                        |
|                          | miR410      | STAT3                              |                                                                                        |
|                          | miR-123a    | STAT3, hexokinase 2, NEDDNG         | IL-10†                                                                                |
|                          | miR-125b*   | Claudin 2, cingulin, SYVN1           |                                                                                        |
|                          | mi-1273c    |                                    | Th17/Treg ratio↑                                                                       |
|                          | miR-3201    |                                    |                                                                                        |
| **Circulating plasma**   |             |                                    |                                                                                       |
| [87,88,89,90,91,92,93,94]|             |                                    |                                                                                       |
| • Increase in:           |             |                                    |                                                                                       |
|                          | miR-142-3p  | IL-1β                              |                                                                                        |
|                          | miR-181a    | FoxO1                              |                                                                                        |
|                          | has-miR-30e-5p |                                    | Oral ulcer and lupus anticoagulant                                                      |
|                          | has-miR-92a-3p |                                    |                                                                                        |
|                          | hsa-miR-223-3p |                                    |                                                                                        |
|                          | miR-16-5p   | p38MAPK, NF-κB                       |                                                                                        |
|                          | miR-223-3p  | Voltage-gated K⁺ channel Kv4.3       |                                                                                        |
|                          | miR-451     | LKB1/AMPK                           |                                                                                        |
| • Decrease in:           |             |                                    |                                                                                       |
|                          | miR-106a    | THBS₂                              |                                                                                        |
|                          | miR-17      | JAB1/CSN5                           |                                                                                        |
|                          | miR-20a     | IκBβ                               |                                                                                        |
|                          | miR-203     | ZEB1                               |                                                                                        |
|                          | miR-92a     | p63                                |                                                                                        |
|                          | miR-146a    | JAK2/STAT3                          |                                                                                        |
|                          | miR-1202    | cyclin dependent kinase 14          |                                                                                        |
| Urinary exosomal (lupus Nephritis) [95,96] | Increase in: | Decrease in: |
|------------------------------------------|--------------|--------------|
| miR-125a | STAT3, hexokinase 2, NEDDG | Glomerulonephritis |
| miR-146* | NF-xB | |
| miR-150 | Akt3 | |
| miR-155 | PTEN, Wnt/β-catenin | |
| **Decrease in:** | | |
| miR-141 | Tram1, GL/2, TGF-β | Glomerulonephritis |
| miR-192 | nin one binding protein | |
| miR-200a | HMGB1/RAGE | |
| miR-200c | ZEB1, Notch 1 | |
| miR-221 | BIM-Bax/Bak, TIMP3 | |
| miR-222 | PPP2R2A/Akt/mTOR, PCSK9 | |
| miR-429 | TRAF6, DLC-1, HIF-1α | |
| **Decrease in:** | | |
| miR-3201 | | Endocapillary glomerular inflammation |
| miR-1273e | | |

†: increased expression or function; *: oxidative stress-induced microRNAs.
Aberrant ncRNA Expression Induces Oxidant/Antioxidant Imbalance in Different Pathological Processes

It has been demonstrated that excessive oxidative stress can affect ncRNA expression in Section 4.1. However, it is quite interesting that aberrant expression of ncRNAs conversely regulates redox balance in some pathological conditions. Esposti et al. [127] found miR-500a-5p could modulate oxidative stress-responsive genes in breast cancer and predict breast cancer progression as well as survival. Sangokoya et al. [128] have demonstrated that miR-144 modulates oxidative stress tolerance and, thus, is associated with changes in anemia severity in sickle cell disease. Kim et al. [129] found the roles of IncRNA and RNA-binding proteins in oxidative stress, cellular senescence, and age-related diseases. Tehrani et al. [130] further demonstrated multiple functions of IncRNAs in regulating oxidative stress, DNA damage response, and cancer progression. Mechanistically, ncRNAs can regulate enzymatic activity of different glutathione S-transferases (GSTs) to affect redox homeostasis [58]. These GSTs include microsomal GST, GST zeta 1, GST mu1, GST theca 1, and sirtuin 1, superoxide dismutase 2 and thioredoxin reductase 2. In addition, the cellular oxidant/antioxidant balance can also be regulated by IncRNAs [59]. The abnormal ncRNA expression to affect the oxidant/antioxidant system is summarized in Figure 6.
Antioxidant Therapy and Manipulation of Epigenetic Expression to Treat Patients with SLE

In addition to increased oxygen free radicals in the plasma of SLE patients, there are other novel findings regarding the pro-oxidant/antioxidant balance in SLE. Mohan et al. [131] firstly confirmed that plasma concentrations of lipid peroxidase and nitric oxide were increased, whereas antioxidant molecules such as catalase, superoxide dismutase (SOD), GSH peroxidase, and vitamin E were decreased. Obviously, the pro-oxidant/antioxidant balance in SLE is disturbed [53]. Antioxidant therapy has been advocated for ameliorating tissue damage caused by excessive pro-oxidant radicals. Supplemented with GSH precursor, N-acetyl-cysteine (NAC) can improve disease activity in lupus-prone mice [50]. Delivering the oxidation resistance-1 (OXR1) gene to mouse kidneys by genetic manipulation can protect the kidney from damage induced by serum nephrotoxic agents, and prevent the animal from developing lupus nephritis [52]. Many authors, by administering
NAC, have found remedies to ameliorate lupus activities in human SLE. Kudaravalli et al. [132] reported the improvement of endothelial dysfunction in patients with SLE by NAC and atorvastatin. Lai et al. [133] reported that NAC reduced disease activity by blocking mammalian targets of rapamycin (mTOR) in T cells of SLE patients. Tzang et al. [134] found cystamine attenuated lupus-associated apoptosis in ventricular tissue by suppressing both intrinsic and extrinsic apoptotic pathways. Nevertheless, much more clinical data are necessary to validate the efficacy of antioxidant therapy in managing patients with SLE.

Since there are so many intricate interactions among oxidative/nitrosative stress, epigenetic regulations, and gene expression in SLE, as discussed in the above sections, interference with epigenetic mechanisms such as modifying the activity of histone acetylase and/or DNA methylation, or inducing up- or downregulation of ncRNA expression may be helpful and can also be advocated to detour lupus pathogenesis and to diminish SLE disease activity in the future [135,136].

**Conclusions**

Mitochondrial dysfunction-provoked excessive oxidative stress is a crucial downstream contributory factor for lupus pathogenesis in addition to the dysregulation of upstream genetic/epigenetic functions. Recent studies have revealed that mutual interactions between oxidative stress and epigenetic regulation can perpetuate pathogenesis and pathological processes in SLE and other autoimmune diseases, as well as ageing-related diseases. In the ncRNA regulatory system, cross-talk between lncRNAs and miRs can occur for fine tuning of gene expression. Excessive oxidative stress-derived ROS and RNS may trigger autoimmune reaction and increase cell senescence/cell death in lupus-susceptible individuals. Antioxidant therapy and epigenetic modulators might become novel therapeutic strategies to treat SLE in the future.
References

1. Wang L, Mohan C, Li QZ. Arraying autoantibodies in SLE—lessons learned. Curr. Mol. Med. 2015; 15: 456–461.
2. Yaniv G, Twig G, Shor DB, Furer A, Sherer Y, et al. A volcano explosion of autoantibodies in systemic lupus erythematosus: A diversity of 180 different antibodies found in SLE patients. Autoimmun. Rev. 2015; 14: 75–79.
3. Kahlenberg JM, Kaplan MJ. The inflammasome and lupus—Another innate immune mechanism contributing to disease pathogenesis? Curr. Opin. Rheumatol. 2014; 26: 475–481.
4. Weidenbusch M, Kulkarni OP, Anders HJ. The innate immune system in human systemic lupus erythematosus. Clin. Sci. 2017; 131: 625–634.
5. Tsai CY, Li KJ, Hsieh SC, Liao HT, Yu CL. What’s wrong with neutrophils in lupus? Clin. Exp. Rheumatol. 2019; 37: 684–693.
6. Zharkova O, Celhar T, Crarens PD, Satherthwaite AB, Fairhurst AW, et al. Pathways leading to an immunological diseases: Systemic lupus erythematosus. Rheumatology. 2017; 56: i55–i66.
7. Harley ITW, Kaufman KM, Langefeld CD, Haraey JB, Kelly JA. Genetic susceptibility to SLE: New insights from fine mapping and genome-wide association studies. Nat. Rev. Genet. 2009; 10: 285–290.
8. Liu Z, Davidson A. Taming lupus—A new understanding of pathogenesis is leading to clinical advances. Nat. Med. 2012; 18: 870–882.
9. Ghodke-Puranick Y, Niewold TT. Immunogenetics of systemic lupus erythematosus: A comprehensive review. J. Autoimmun. 2015; 64: 125–136.
10. Teruel M, Alacon-Riguelme ME. The genetic basis of systemic lupus erythematosus: What are the risk factors and what have we learned. J. Autoimmun. 2016; 74: 161–175.
11. Iwamoto T, Niewold TB. Genetics of human lupus nephritis. Clin. Immunol. 2017; 185: 32–39.
12. Hiraki LT, Silverman ED. Genomics of systemic lupus erythematosus: Insights gained by studying monogenic young-onset systemic lupus erythematosus. Rheum. Dis. N. Am. 2017; 43: 415–434.
13. Saeed M. Lupus pathology based on genomics. Immunogenetics. 2017; 69: 1–12.
14. Goulielmos GN, Zervou MI, Vazgiourakis VM, Ghodke-Puranik Y, Garyballos A, et al. The genetics and molecular pathogenesis of systemic lupus erythematosus (SLE) in populations of different ancestry. Gene. 2018; 668: 59–72.
15. Javinani A, Ashraf-Ganjouei A, Asloni S, Janshidi A, Mahmoudi M. Exploring the etiopathogenesis of systemic lupus erythematosus: A genetic perspective. Immunogenetics. 2019; 71: 283–297.
16. Wu H, Zhao M, Chang C, Lu Q. The real culprit in systemic lupus erythematosus: Abnormal epigenetic regulation. Int. J. Mol. Sci. 2015; 16: 11013–11033.
17. Miceli-Richard C. Epigenetics and lupus. Jt. Bone Spine. 2015; 82: 90–93.
18. Hedrick CM, Mabert K, Rouen T, Tsokos GC. DNA methylation in systemic lupus erythematosus. Epigenomics. 2017; 9: 505–525.
19. Zhan Y, Guo Y, Lu Q. Aberrant epigenetic regulation in the pathogenesis of systemic lupus erythematosus and its implications in precision medicine. Cytogenet. Genome Res. 2016; 149: 141–155.
20. Wang Z, Chang C, Peng M, Lu Q. Translating epigenetics into clinic: Focus on lupus. Clin. Epigenet. 2017; 9: 78.
21. Ren J, Panther E, Liao X, Grammer AC, Lipsky PE, et al. The impact of protein acetylation/deacetylation on systemic lupus erythematosus. Int. J. Mol. Sci. 2018; 19: 4007.
22. Long H, Yin H, Wang L, Gershwin ME, Lu Q. The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. J. Autoimmun. 2016; 74: 118–138.
23. Lai NS, Koo M, Yu CL, Lu MC. Immunopathogenesis of systemic lupus erythematosus and rheumatoid arthritis: The role of aberrant expression of non-coding RNAs in T cells. Clin. Exp. Immunol. 2017; 187: 327–336.
24. Zununi Vahed S, Nakhjarvani M, Etemadi J, Jamashidi N, Pourlak T, et al. Altered levels of immune-regulatory microRNAs in plasma samples of patients with lupus nephritis. Bioimpacts 2018; 8: 177–183.
25. Honarpisheh M, Kohler P, von Rauchhaupt E, Lech M. The involvement of microRNAs in modulation of innate and
adaptive immunity in systemic lupus erythematosus and lupus nephritis. J. Immunol. Res. 2018; 4126106.
26. McMurray RW. Sex-hormones in the pathogenesis in systemic lupus erythematosus. Front Biosci. 2001; 6: E193–E206.
27. Khan D, Dai R, Ahmed SA. Sex differences and estrogen regulation of miRNA in lupus, a prototypical autoimmune disease. Cell Immunol. 2015; 294: 70–79.
28. Assad S, Khan HH, Ghazanfar H, Khan ZH, Mansor S, et al. Role of sex-hormone levels and psychological stress in the pathogenesis of autoimmune diseases. Cureus. 2017; 9: E1315.
29. Christou EAA, Banos A, Kosmara D, Bertsias GK, Boupas DT. Sexual dimorphism in SLE, above and beyond sex hormones. Lupus. 2019; 28: 3–10.
30. Sari-Puttini P, Atzeni F, Laccarino L, Doria A. Environment and systemic lupus erythematosus: An overview. Autoimmunity. 2005; 38: 465–472.
31. Parks CG, de Souza Espinodola Santos A, Barbhaiya M, Costenbader KH. Understanding the role of environmental factors in the development of systemic lupus erythematosus. Best Pract. Res. Clin. Rheumatol. 2017; 31: 306–320.
32. Brown AC. Lupus erythematosus and nutrition: A review of the literature. J. Ren. Nutr. 2000; 10: 170–183.
33. Minami Y, Sasaki T, Arai Y, Kurisu Y, Hisamichi S. Diet and systemic lupus erythematosus: A 4 year prospective study of Japanese patients. J. Rheumatol. 2003; 30: 747–754.
34. Hsieh CC, Lin BF. Dietary factors regulate cytokines in murine models of systemic lupus erythematosus. Autoimmun. Rev. 2011; 11: 22–27.
35. Klack K, Bonfa E, Borba Neto EF. Diet and nutritional aspects in systemic lupus erythematosus. Rev. Bras. Rheumatol. 2012; 52: 384–408.
36. Lee HT, Lin CS, Chen WS, Liao HT, Tsai CY, et al. Leukocyte mitochondrial DNA alteration in systemic lupus erythematosus and its relevance to the susceptibility to lupus nephritis. Int. J. Mol. Sci. 2012; 13: 8853–8868.
37. Lee HT, Wu TH, Lin CS, Lee CS, Wei YH, et al. The pathogenesis of systemic lupus erythematosus—From the
viewpoint of oxidative stress and mitochondrial dysfunction. Mitochondrion. 2016; 30: 1–7.

38. Lee HT, Wu TH, Lin CS, Lee CS, Pan SC, et al. Oxidative DNA and mitochondrial DNA change in patients with SLE. Front Biosci. Landmark. 2017; 22: 493–503.

39. Lee HT, Lin CS, Pan SC, Wu TH, Lee CS, et al. Alterations of oxygen consumption and extracellular acidification rates by glutamine in PBMCs of SLE patients. Mitochondrion. 2019; 44: 65–74.

40. Marion TN, Postlethwaite AE. Chance, genetics, and the heterogeneity of disease and pathogenesis in systemic lupus erythematosus. Sem. Immunopathol. 2014; 36: 495–517.

41. Leishangthem BD, Sharma A, Bhatnagar A. Role of altered mitochondria functions in the pathogenesis of systemic lupus erythematosus. Lupus. 2016; 25: 272–281.

42. Kuren BT, Scofield RH. Lipid peroxidation in systemic lupus erythematosus. Indian J. Exp. Biol. 2006; 44: 349–356.

43. Das UN. Oxidative, anti-oxidants, essential fatty acids, eicosanoids, cytokines, gene/oncogene expression and apoptosis in systemic lupus erythematosus. J. Assoc. Physicians India. 1998; 46: 630–634.

44. Dandekar A, Mendez R, Zhang K. Cross talk between ER stress, oxidative stress, and inflammation in health and disease. Methods Mol. Biol. 2015; 1292: 205–214.

45. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, et al. Oxidative stress and inflammation: What polyphenols can do for us? Oxidative Med. Cell Longev. 2016; 2016: 7432797.

46. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. Hypertension. 2017; 70: 660–667.

47. Plotnikov E, Losenkov I, Epimakhova E, Bohan N. Protective effects of pyruvic acid salt against lithium toxicity and oxidative damage in human blood mononuclear cells. Adv. Pharm. Bull. 2019; 9: 302–306.

48. Lee D, Lee SH, Noh I, Oh E, Ryu H, et al. A helical polypeptide-based potassium ionophore induces endoplasmic reticulum stress-mediated apoptosis by perturbing ion homeostasis. Adv. Sci. (Weinheim). 2019; 6: 1801995.
49. Das UN. Current and emerging strategies for the treatment and management of systemic lupus erythematosus based on molecular signatures of acute and chronic inflammation. J. Inflamm. Res. 2010; 3: 143–170.
50. Perl A. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. Nat. Rev. Rheumatol. 2013; 9: 674–686.
51. Su YJ, Cheng TT, Chen CJ, Chiu WC, Chang WN, et al. The association among antioxidant enzymes, autoantibodies, and disease severity score in systemic lupus erythematosus: Comparison of neuropsychiatric and nonneuropsychiatric groups. BioMed Res. Int. 2014; 2014: 137231.
52. Li Y, Li W, Liu C, Yan M, Raman I, et al. Delivering oxidation resistance-1 (OXR1) to mouse kidney by genetic modified mesenchymal stem cells exhibited enhanced protection against nephrotoxic serum induced renal injury and lupus nephritis. J. Stem Cell Res. Ther. 2014; 4: 231.
53. Jafari SM, Salimi S, Nakhae A, Kalani H, Tavallaie S, et al. Prooxidant-antioxidant balance in patients with systemic lupus erythematosus and its relationship with clinical and laboratory findings. Autoimmune Dis. 2016; 2016: 4343514.
54. Shah D, Mahajan N, Sah S, Nath SK, Paudyal B. Oxidative stress and its biomarkers in systemic lupus erythematosus. J. Biomed. Sci. 2014; 21: 23.
55. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics. Oncol. Rep. 2017; 37: 3–9.
56. Li J, Liu C. Coding or noncoding, the converging concepts of RNAs. Front. Genet. 2019; 10: 496.
57. Banerjee J, Khanna S, Bhattacharya A. MicroRNA regulation of oxidative stress. Oxid. Med. Cell Longev. 2017; 2872156.
58. Bu H, Wedel S, Cavinato M, Jansen-Dürr P. MicroRNA regulation of oxidative stress-induced cellular senescence. Oxid. Med. Cell Longev. 2017; 2017: 2398696.
59. Wang X, Shen C, Zhu J, Shen G, Li Z, et al. Long non-coding RNAs in the regulation of oxidative stress. Oxid. Med. Cell Longev. 2019; 1318795.
60. Bayoumi AS, Sayed A, Broskova Z, Teoh JP, Wilson J, et al. Crosstalk between long noncoding RNAs and microRNAs in health and disease. Int. J. Mol. Sci. 2016; 17: 356.
61. Yamamura S, Imai-Sumida M, Tanaka Y, Dahiya R. Interaction and cross-talk between non-coding RNAs. Cell Mol. Life Sci. 2018; 75: 467–484.

62. Deng C, Yang J, Scott J, Hanash S, Richardson BC. Role of the ras-MAPK signaling pathway in the DNA methyltransferase response to DNA hypomethylation. Biol. Chem. 1998; 379: 1113–1120.

63. Sawalha AH, Jeffries M, Webb R, Lu Q, Gorelik G, et al. Defective T cell ERK signaling induces interferon-regulated gene expression and overexpression of methylation sensitive genes similar to lupus patients. Genes Immun. 2008, 9, 368–378.

64. Lu Q, Wu A, Tesmer L, Ray D, Yousif N, et al. Demethylation of CD40LG on the inactive X in T cells from women with lupus. J. Immunol. 2007; 179: 6352–6358.

65. Hu N, Qiu X, Luo Y, Yuan J, Li Y, et al. Abnormal histone modification patterns in lupus CD4+T cells. J. Rheumatol. 2008; 35: 804–810.

66. Zhou Y, Qiu X, Luo Y, Yuan J, Li Y, et al. Histone modifications and methyl-CpG binding domain protein levels at the TNFSF7 (CD70) promoter in SLE CD4+ T cells. Lupus. 2011; 20: 1365–1371.

67. Hedrich CM, Tsokos GC. Epigenetic mechanisms in systemic lupus erythematosus and other autoimmune diseases. Trends Mol. Med. 2011; 17: 714–724.

68. Dai Y, Zhang L, Hu C, Zhang Y. Genome-wide analysis of histone H3 lysine 4 trimethylation by ChIP-chip in peripheral blood mononuclear cells of systemic lupus erythematosus patients. Clin. Exp. Rheumatol. 2010; 28: 158–168.

69. Zhang Z, Song L, Maurer K, Petri MA, Sullivan KE. Global H4 acetylation analysis by ChIP-chip in SLE monocytes. Genes Immun. 2010; 11: 124–133.

70. Apostolidis SA, Rauen T, Hedrich CM, Tsokos GC, Crispin JC. Protein phosphatase 2A enables expression of interleukin 17 (IL-17) through chromatin remodeling. J. Biol. Chem. 2013; 288: 26775–26784.

71. Hedrich CM, Raurex J, Apostolidis SA, Grammatikos AP, Rodriguez Rodrigues N, et al. Stat3 promotes IL-10 expression in lupus T cells through trans-activation and
chromatin remodeling. Proc. Natl. Acad. Sci. USA. 2014; 111: 13457–13462.

72. Sullivan KE, Suriano A, Dietzmann K, Lin J, Goldman D, et al. The TNF-alpha locus is altered in monocytes from patients with systemic lupus erythematosus. Clin. Immunol. 2007; 123: 74–81.

73. Hu N, Long H, Zhao M, Yin H, Lu Q. Aberrant expression pattern of histone acetylation modifier and mitigation of lupus by SIRT1-siRNA in MRL/lpr mice. Scand. J. Rheumatol. 2009; 38: 464–471.

74. Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Sabero JJ, et al. Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. Genome Res. 2010; 20: 170–179.

75. Ruvkun G. Molecular biology. Glimpses of a tiny RNA world. Science. 2001; 294: 797–799.

76. Dai R, Ahmed SA. MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. Transl. Res. 2011; 157: 163–179.

77. Qu B, Shen N. miRNAs in the pathogenesis of systemic lupus erythematosus. Int. J. Mol. Sci. 2015; 16: 9557–9572.

78. Chen JQ, Papp G, Szodoray P, Zeher M. The role of microRNAs in the pathogenesis of autoimmune diseases. Autoimmun. Rev. 2016; 15: 1171–1180.

79. Le X, Yu X, Shen N. Novel insights of microRNAs in the development of systemic lupus erythematosus. Curr. Opin. Rheumatol. 2017; 29: 450–457.

80. Long H, Wang X, Chen Y, Wang L, Zhao M, et al. Dysregulation of microRNAs in autoimmune diseases: Pathogenesis, biomarkers and potential therapeutic targets. Cancer Lett. 2018; 428: 90–103.

81. Lu MC, Lai NS, Chen HC, Yu HC, Huang KY, et al. Decreased microRNA (miR)-145 and increased miR-224 expression in T cells from patients with systemic lupus erythematosus involved in lupus immunopathogenesis. Clin. Exp. Immunol. 2013; 171: 91–99.

82. Lu MC, Yu CL, Chen HC, Yu HC, Huang HB, et al. Aberrant T cell expression of Ca2+ influx-regulated miRNA in patients with systemic lupus erythematosus promotes
lupus pathogenesis. Rheumatology (Oxford). 2015; 54: 343–348.
83. Tsai CY, Hsieh SC, Lu MC, Yu CL. Aberrant non-coding RNA expression profiles as biomarker/biosignature in autoimmune and inflammatory rheumatic diseases. J. Lab. Preci. Med. 2018; 3: 51.
84. Su X, Ye L, Chen X, Zhang H, Zhou Y, et al. MiR-199-3p promotes ERK-mediated IL-10 production by targeting poly(ADP-ribose)polymerase-1 in patients with systemic lupus erythematosus. Chemo-Biol. Interact. 2019; 306: 110–116.
85. Heegaard NHH, Carlsen AL, Skovgaard K, Heegaard PMH. Circulating extracellular microRNA in systemic autoimmunity. Exp. Suppl. 2015; 106: 171–195.
86. Turpin D, Truchetet ME, Faustin B, Augusto JF, Contin-Bordes C, et al. Role of extracellular vesicles in autoimmune diseases. Autoimmun. Rev. 2016; 15: 174–183.
87. Carlsen AL, Schetter AJ, Nielsen CT, Lood C, Knudsen S, et al. Circulating microRNA expression profiles associated with systemic lupus erythematosus. Arthritis Rheum. 2013; 65: 1324–1334.
88. Kim BS, Jung JY, Jeon JY, Kim HA, Suh CH. Circulating hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p may be novel biomarkers in systemic lupus erythematosus. HLA. 2016; 88: 187–193.
89. Ishibe Y, Kusaoi M, Murayama G, Nemoto T, Kon T, et al. Changes in the expression of Circulating microRNAs in systemic lupus erythematosus patient blood plasma after passing through a plasma absorption membrane. Ther. Apher. Dial. 2018; 22: 278–289.
90. Natasha G, Gundogan B, Tan A, Farhatnia Y, Wu W, et al. Exosomes as immunotheranostic nanoparticles. Clin. Ther. 2014; 36: 820–829.
91. Tan L, Wu H, Liu Y, Zhao M, Li D, et al. Recent advances of exosomes in immune modulation and autoimmune diseases. Autoimmunity. 2016; 49: 357–365.
92. Rekker K, Saare M, Roost AM, Kubo AL, Zarovni N, et al. Comparison of serum exosome isolation methods for microRNA profiling. Clin. Biochem. 2014; 47: 135–138.
93. Hsieh SC, Tsai CY, Yu CL. Potential serum and urine biomarkers in patients with lupus nephritis and the unsolved problems. Open Access Rheumatol. 2016; 8: 81–91.
94. Tsai CY, Lu MC, Yu CL. Can urinary exosomal micro-RNA detection become a diagnostic and prognostic gold standard for patients with lupus nephritis and diabetic nephropathy? J. Lab. Precis. Med. 2017; 2: 91.
95. Perez-Hernandez J, Redon J, Cortes R. Extracellular vesicles as therapeutic agents in systemic lupus erythemaotusus. Int. J. Mol. Sci. 2017; 18: E717.
96. Xu H, Jia S, Xu H. Potential therapeutic applications of exosomes in different autoimmune diseases. Clin. Immunol. 2019; 205: 116–124.
97. Kelemen E, Danis J, Göblös A, Bata-Csörgö Z, Szell M. Exosomal long non-coding RNAs as biomarkers in human diseases. J. Int. Fed. Clin. Chem. Lab. Med. 2019; 30: 224–236.
98. Wu GC, Hu Y, Guan SY, Ye DQ, Pan HF. Differential plasma expression profiles of long non-coding RNAs, reveal potential biomarkers for systemic lupus erythematosus. Biomolecules. 2019; 9: E206.
99. Gloss BS, Dinger ME. The specificity of long noncoding RNA expression. Biochim. Biophys. Acta. 2016; 1859: 16–22.
100. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, et al. The GENCODE v7 catalog of human lung noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res. 2012; 22: 1775–1789.
101. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev. 2011; 25: 1915–1927.
102. Hadjicharalambous MR, Lindsay MA. Long non-coding RNAs and the innate immune response. Noncoding RNA. 2019; 5: E34.
103. Wang Y, Chen S, Chen S, Du J, Lin J, et al. Long noncoding RNA expression profile and association with SLEDAI score in monocyte-derived dendritic cells from patients with systemic lupus erythematosus. Arthritis Res. Ther. 2018; 20–138.
104. Mathy NW, Chen XM. Long non-coding RNAs (lncRNAs) and their transcriptional control of inflammatory responses. J. Biol. Chem. 2017; 292: 12375–12382.

105. Luo Q, Li X, Xu C, Zeng L, Ye J, et al. Integrative analysis of long non-coding RNAs and messenger RNA expression profiles in systemic lupus erythematosus. Mol. Med. Rep. 2018; 17: 3489–3496.

106. Zhao CN, Mao YM, Liu LN, Li XM, Wang DG, et al. Emerging role of lncRNAs in systemic lupus erythematosus. Biomed. Pharm. 2018; 106: 584–592.

107. Simchovitz A, Hanan M, Niederhoffer N, Madrer N, Yayon N, et al. NEAT1 is overexpressed in Parkinson’s disease substantia nigra and confers drug-inducible neuroprotection from oxidative stress. FASEB J. 2019; 33: 11223–11234.

108. Li KJ, Wu CH, Hsieh SC, Lu MC, Tsai CY, et al. Deranged bioenergetics and defective redox capacity in T-lymphocytes and neutrophils are related to cellular dysfunction and increased oxidative stress in patients with active systemic lupus erythematosus. Clin. Dev. Immunol. 2012; 2012: 548516.

109. Lee HT, Lin CS, Lee CS, Tsai CY, Wei YH. Increase 8-hydroxy-2′-deoxyguanosine in plasma and decreased mRNA expression of human 8-oxoguanine DNA glycosylase 1, antioxidant enzymes, mitochondrial biogenesis-related proteins and glycolytic enzymes in leukocytes in patients with systemic lupus erythematosus. Clin. Exp. Immunol. 2014; 176: 66–77.

110. Yang SK, Zhang HR, Shi SP, Zhu YQ, Song N, et al. The role of mitochondria in systemic lupus erythematosus: A glimpse of various pathogenetic mechanisms. Curr. Med. Chem. 2018.

111. Tsai CY, Shen CY, Liao HT, Li KJ, Lee HT, et al. Molecular and cellular bases of immunosenescence, inflammation, and cardiovascular complications mimicking “inflammaging” in patients with systemic lupus erythematosus. Int. J. Mol. Sci. 2019; 20: 3878.

112. Vlassopoulos A, Lean MEJ, Combet E. Oxidative stress, protein glycation and nutrition-interactions relevant to health
and disease throughout the lifecycle. Proc. Nutr. Soc. 2014; 73: 430–438.

113. McGuire PJ. Mitochondrial dysfunction and the aging immune system. Biology (Basel). 2019; 8: E26.

114. Ye B, Hou N, Xiao L, Xu Y, Xu H, et al. Dynamic monitoring of oxidative DNA double strand break and repair in cardiomyocytes. Cardiovasc. Pathol. 2016; 25: 93–100.

115. de Leeuw K, Graaff R, de Vries R, Dullaart RP, Smit AJ, et al. Accumulation of advanced glycation endproducts in patients with systemic lupus erythematosus. Rheumatology. 2007; 46: 1551–1556.

116. Lin Y, Jiang M, Chen W, Zhao T, Wei Y. Cancer and ER stress: Mutual crosstalk between autophagy, oxidative stress and inflammatory response. Biomed. Pharmacother. 2019; 118: 109249.

117. Zhang Y, Du Y, Le W, Wang K, Kieffer N, et al. Redox control of the survival of healthy and diseased cells. Antioxid. Redox Signal. 2011; 15: 2867–2908.

118. Cao SS, Kaufman RJ. Endoplasmic reticulum stress and oxidative stress in cell fate decision and human disease. Antioxid. Redox Signal. 2014; 21: 396–413.

119. Pervaiz S. Redox dichotomy in cell fate decision: Evasive mechanism or Achilles heel? Antioxid. Redox Signal. 2018; 29: 1191–1195.

120. Prasad KN. Oxidative stress and pro-inflammatory cytokines may act as one of the signals for regulating microRNAs expression in Alzheimer’s disease. Mech. Ageing Dev. 2017; 162: 63–71.

121. Prasad KN. Oxidative stress, pro-inflammatory cytokines, and antioxidants regulate expression levels of microRNAs in Parkinson’s disease. Curr. Aging Sci. 2017; 10: 177–184.

122. Prasad KN, Bondy SC. MicroRNAs in hearing disorders: Their regulation by oxidative stress, inflammation and antioxidants. Front Cell Neurosci. 2017; 11: 276.

123. Guillaumet-Adkins A, Yañez Y, Peris-Díaz MD, Calabria I, Palanca-Ballester C, et al. Epigenetics and oxidative stress in aging. Oxid. Med. Cell Longev. 2017; 2017: 9175806.
124. Cheleschi S, De Palma A, Pascarelli NA, Giordano N, Galeazzi M, et al. Could oxidative stress regulate the expression of microRNA-146a and microRNA-34a in human osteoarthritic chondrocyte cultures? Int. J. Mol. Sci. 2017; 18: E2660.

125. Zhang W, Xu W, Feng Y, Zhou X. Non-coding RNA involvement in the pathogenesis of diabetic cardiomyopathy. J. Cell. Mol. Med. 2019; 23: 5859–5867.

126. Lan J, Huang Z, Han J, Shao J, Huang C. Redox regulation of microRNAs in cancer. Cancer Lett. 2018; 418: 250–259.

127. Esposti DD, Aushev VN, Lee E, Cros MP, Zhu J, et al. miR-500a-5p regulates oxidative stress response genes in breast cancer and predicts cancer survival. Sci. Rep. 2017; 7: 15966.

128. Sangokoya C, Telen MJ, Chi JT. microRNA miR-144 modulates oxidative stress tolerance and associates with anemia severity in sickle cell disease. Blood. 2010; 116: 4338–4348.

129. Kim C, Kang D, Lee EK, Lee JS. Long noncoding RNAs and RNA binding proteins in oxidative stress, cellular senescence, and age-related diseases. Oxid. Med. Cell Longev. 2017; 2017: 2062384.

130. Tehrani SS, Karimian AS, Parsian H, Majidinia M, Yousefi G. Multiple functions of long non-coding RNAs in oxidative stress, DNA damage response and cancer progression. J. Cell. Biochem. 2018; 119: 223–236.

131. Mohan IK, Das UN. Oxidant stress, anti-oxidants and essential fatty acids in systemic lupus erythematosus. Prostaglandins Leukot. Essent Fatty Acids. 1997; 56: 193–198.

132. Kudaravalli J. Improvement in endothelial dysfunction in patients with systemic lupus erythematosus with N-acetylcysteine and atorvastatin. Ind. J. Pharmacol. 2011; 43: 311–315.

133. Lai ZW, Hanczko R, Bonilla E, Caza TN, Clair B, et al. N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: A randomized double blind,
placebo-controlled trial. Arthritis Rheum. 2012; 64: 2937–2946.

134. Tzang BS, Hsu TC, Kuo CY, Chen TY, Chiang SY, et al. Cytamine attenuates lupus-associated apoptosis of ventricular tissue by suppressing both intrinsic and extrinsic pathways. J. Cell. Mol. Med. 2012; 16: 2104–2111.

135. Portal-Núñez S, Esbrit P, Alcaraz MJ, Largo R. Oxidative stress, autophagy, epigenetic changes and regulation by miRNAs as potential therapeutic targets in osteoarthritis. Biochem. Pharmacol. 2016; 108: 1–10.

136. Dong D, Zhang Y, Reece EA, Wang L, Harman CR, et al. microRNA expression profiling and functional annotation analysis of their targets modulated by oxidative stress during embryonic heart development in diabetic mice. Reprod. Toxicol. 2016; 65: 365–374.