Neutrophil extracellular traps in systemic lupus erythematosus
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Introduction
Systemic lupus erythematosus (SLE) can be broadly defined as a chronic inflammatory autoimmune disease characterized by the hallmark of producing autoantibodies. These autoantibodies have the capability of binding to tissue-forming complexes that are subsequently deposited within the affected tissues in association with complement fixation and widespread systemic inflammation \cite{1–3}.

SLE is a multisystem affection morbidity of a generalized nature. It causes pronounced disturbance of all domains of quality of life in the affected patients. This includes diminished physical abilities, altered psychological status, and impaired social well-being. Despite the proven link between SLE and increased mortality, significant improvements in patients’ survival was documented throughout the recent years thanks to the tremendous achievements in the fields of diagnosis.

Objectives
To study the role of neutrophil extracellular traps (NETs) in the pathogenesis, clinical manifestations, and treatment of systemic lupus erythematosus (SLE).

Materials and methods
All medical databases including PubMed, Google Scholar, ScienceDirect, and Springer were searched for relevant data and the studies were published according to specific criteria and all materials available on the internet from 2011 to 2018.

Search methodology
All medical databases including PubMed, Google Scholar, ScienceDirect, and Springer were searched for relevant data.

Data sources
All medical databases including PubMed, Google Scholar, ScienceDirect, and Springer were searched for relevant data and all materials available on the internet from 2011 to 2018.

Language covered
English.

Study selection
(a) Published in English language. (b) Focused on NETs and lupus. (c) We used the latest publication giving the most relevant data. (d) All materials available on the internet from 2011 to 2018.

Data extraction
If the studies not fulfill the above criteria, then they were excluded.

Data synthesis
Short reviews were made on NETs and its role in SLE.

Recent findings
NETs are involved in the pathogenesis of SLE. They are associated with increased disease activity and considered as a potential therapeutic target. The ineffective clearance of NETs in patients with SLE exposes self-molecules to the immune system and contributes to the development of autoantibodies and proinflammatory cytokines, driving the pathogenesis of SLE.

Conclusion
Being in its early phase, studies related to the role of NETs in autoimmune diseases including SLE should be directed toward a better understanding of SLE pathogenesis and focusing on the association between the formation of NETs and various clinical aspects in SLE. Moreover, the relation between NET formation and other pathological and genetic determinants of SLE development is a rich area of future research.

Keywords:
disease activity, immunopathogenesis, neutrophil extracellular traps, systemic lupus, therapeutic target
and treatment. Of these, the introduction of biological therapy constituted the major milestone [4–6].

In spite of the fact the pathogenesis of SLE remains to be uncovered completely, cumulative evidence derived from both experimental and human studies suggests that disease causation and progression entails paramount dysregulation of the cytokine milieu including altered expression and impaired signaling [7,8].

This dysregulation is just an initial step in a cascade of pathophysiological sequelae in addition to the activation of autoreactive B cells. It involves dysregulation in many other types of immune cells, including CD4 + T cells, dendritic cells, macrophages, and neutrophils [9].

Profoundly, neutrophils are engaged in this process in multiple dimensions where neutrophil dysfunction has a substantial role in SLE. In general, neutrophils exert their protective functions through various integrated mechanisms. These mechanisms include: first, attacking the microbial agents through isolation of antimicrobial peptides (gAMP); second, neutrophils are strongly involved in the process of microbial phagocytosis. The phagocytosed microbial materials are subsequently subjected to biochemical degradation under the influence of reactive oxygen species within the phagolysosomal membranes; third, neutrophils can perform efficient bactericidal action through the formation of the so-called neutrophil extracellular traps (NETs) by collaborating the chromatin network with glycine-rich antibacterial peptide (gAMP) [10].

This histobiological structure – NETs – is a less-recognized form of cell death which is distinguishable from the programmed cell death (apoptosis) or necrosis. For physiological quiescence, a delicate balance between the formation and degradation of NETs should be maintained. The imbalance between the degradation and formation of NETs has been widely considered to be closely associated with the activity of autoimmune diseases such as SLE [11].

From the mere pathological perspective, NETs are web-like structures composed of chromatin backbones and granular molecules. They are released by activated neutrophils through a process called ‘NETosis’ [12].

**Materials and methods**

**Data sources**

All medical databases including PubMed, Google Scholar, ScienceDirect, Springer were searched for relevant data.

**Article selection**

Inclusion criteria of the published studies:

1. Published in English language
2. Focused on NETs and lupus
3. We used the latest publication giving the most relevant data.

**Exclusion criteria**

If the studies did not fulfill the above criteria, then they were excluded (Fig. 1).

**Discussion**

**Neutrophil extracellular traps and pathogenesis of systemic lupus erythematosus**

As previously discussed, immune dysregulation is the main suggested pathological process in the development of SLE. Mature neutrophils in SLE patients are in-vivo primed by type I interferon (IFN-I) and subsequently encounter catastrophic death upon contact with SLE-derived anti-ribonucleoprotein antibodies, thus releasing NETs. The produced SLE NETs contain DNA in addition to ample quantities of LL37 (antimicrobial peptide), high mobility group box 1 (HMGB1), and neutrophil proteins that enable the uptake and recognition of mammalian DNA by plasmacytoid dendritic cells [13].

Evidently, circulating neutrophils in lupus patients produce more abundant NETs as compared with those from healthy control counterparts; a response that was additionally aggravated by the autoantibodies derived from antimicrobial elements, signifying a proposed source for the chronic manner of

![Figure 1](http://www.mmj.eg.net)
immunogenic complexes' production in patients with SLE [14].

The malfunctioning removal of apoptotic products, besides NETs, is a source of plentiful chromatin or self-dsDNA to elicit the release of anti-dsDNA antibodies, despite the pathophysiological processes involved in these interactions remain to be identified [15].

The majority of studies addressing this issue agreed that apoptosis is a source in many clinical states, but NET formation may significantly cause the cfDNA production in SLE patients in particular [16].

Hazards resulting in endothelial damage in lupus include oxidized low-density lipoprotein, autoantibodies against endothelial cells and phospholipids, type I IFN and NETs directly or through the activation of type I IFN pathway [17].

Of note, the difference between NETs produced in SLE patients does not differ from those produced in healthy controls from the quantitative perspective but from qualitative aspects also. In comparison to NETs from healthy volunteers, the NETs histones formed by neutrophils derived from SLE patients contain extra amounts of methylated and acetylated structures, which were previously noted to be linked with apoptosis and SLE [18].

NETs are also related to drug-induced lupus which is a spectrum of drug-induced reactions often characterized by a clinical phenotype similar to that of idiopathic SLE, but usually lacking major SLE complications [19].

**Neutrophil extracellular traps and clinical manifestations and disease activity in systemic lupus erythematosus**

In SLE patients, diminished NETs ruining was linked to glomerulonephritis manifestations and low complement levels and increased levels of antibodies against histones and DNA. Additionally, the odds for the patient to have alopecia and fever after decreased NETs ruining was augmented [20]. However, no significant association was found between NETosis and disease activity in SLE [21].

**Neutrophil extracellular traps as therapeutic targets in systemic lupus erythematosus**

In spite of the steady progress in the treatment of SLE, achieving definitive treatment is still far beyond our reach. The suggested roles of NETs in the pathogenesis of SLE can provide a new therapeutic approach. Recently, Kraaij et al. [22] showed interfering with immune complexes' formation using a combination of rituximab and belimumab where rituximab is a chimeric mouse/human monoclonal antibody therapy with binding specificity to CD20 [23] and belimumab is a fully humanized monoclonal antibody against B lymphocyte stimulator that is approved for the treatment of patients with active refractory SLE [24,25]. The combination led to specific reductions in antinuclear antibodies (ANA) and regression of excessive NET formation. This study sheds light on the probable value of utilizing NETs reduction as an antagonizing agent for ANA production. This promising result awaits confirmation when the phase-2 study comes to final conclusions in the near future.

Vitamin D could reduce endothelial damage by decreasing NETosis activity. This result may reveal the possibility of vitamin D as supplementary therapy for SLE patients with hypovitaminosis D to prevent endothelial damage [26].

**Conclusion**

Being in its early phase, research related to the role of NETs in autoimmune diseases including SLE should be directed toward a better understanding of SLE pathogenesis. Focusing on the association between NET formation and various clinical aspects in different settings should be addressed. Moreover, the relation between NET formation and other pathological and genetic determinants of SLE development is a rich area of future research.

**Results**

NETs are involved in the pathogenesis of SLE. The imbalance between their formation and degradation was linked to the development of SLE by providing an increased amount of free DNA that is responsible for the production of anti-dsDNA antibodies.

Increased levels of NET in SLE are associated with lupus nephritis. However, no significant association was found between NETosis and disease activity in SLE [21]. Neutrophils in SLE patients release more NETs than those from healthy donors causing chronic release of immunogenic complexes in SLE [14]. NETs provide abundant chromatin or self-dsDNA to trigger the production of anti-dsDNA antibodies. Therapies targeting NETs results in significant improvement of clinical manifestations.
Neutrophils activate plasmacytoid dendritic cells by releasing vitamin D prevents endothelial damage induced by increased neutrophil.

References

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