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REVIEW

Towards a pro-resolving concept in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with prominent chronic inflammatory aspects. SLE most often affects women (9:1) in childbearing age. The multifactorial nature of the etiopathogenesis of SLE involves a deficient clearance of dead and dying cells. This is supported by the occurrence of autoantibodies directed against autoantigens modified in dying and dead cells (dsDNA, high mobility group box 1 protein, apoptosis-associated chromatin modifications, e.g., histones H3-K27-me3; H2A/H4 AcK8,12,16; and H2B-AcK12) that are deposited in various tissues, including skin, kidneys, joints, muscles, and brain. The subsequent hyperinflammatory response often leads to irreparable tissue damage and organ destruction. In healthy individuals, dead and dying cells are rapidly removed by macrophages in an anti-inflammatory manner, referred to as efferocytosis. In SLE, extensive and prolonged cell death (apoptosis, necrosis, neutrophil extracellular trap (NET) formation) leads to autoantigens leaking out of the not cleared cell debris. These neo-epitopes are subsequently presented to B cells by follicular dendritic cells in the germinal centers of secondary lymphoid tissues conditioning the break of self-tolerance. Activation of autoreactive B cells and subsequent production of autoantibodies facilitate the formation of immune complexes (ICs) fueling the inflammatory response and leading to further tissue damage. ICs may also be ingested by phagocytes, which then produce further pro-inflammatory cytokines. These processes establish a vicious circle that leads to sustained inflammation. This review highlights the cell death–related events in SLE, the protagonists involved in SLE pathogenesis, the resolution of inflammation in various tissues affected in SLE, and explores strategies for intervention to restore hemostasis in a hyperinflammatory state.

Keywords Systemic lupus erythematosus (SLE) · Resolution · Inflammation · Apoptosis · Secondary necrosis · Neutrophil extracellular traps (NETs) · Clearance

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Overview of cell death

Cells ceasing to carry out their functions undergo cell death. Naturally old cells die and are replaced by new ones, others die due to disease or injury. The programmed forms of cell death, apoptosis and autophagy, are also referred to as type I and II cell death, respectively. Necrosis, the non-physiological state of cell death, often occurs after infection or injury. During programmed cell death intracellular biochemical cascades operate that often involving proteolytic activation of proteins, e.g., caspases.

Apoptosis is associated with specific morphological changes like membrane blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. During cell development and in homeostasis cells are induced to commit suicide or die by the lack of survival factors, respectively.

During catabolic autophagy large cytoplasmic vacuoles are formed and ingest organelles, bulk cytoplasmic contents, and

abnormally aggregated proteins prior to nuclear disintegration [1]. In addition to nutrient deprivation, cell differentiation and cellular stress are associated with autophagy. Anoikis, cornification, excitotoxicity, ferroptosis, and activation-induced cell death are further examples of programmed cell death. The latter being caused in T-cells by the interaction of death receptors with their ligands and can be considered a negative regulator of activated T-lymphocytes.

Necroptosis, often considered programmed necrosis, is a backup for apoptotic cell death when the canonical apoptosis signaling is inhibited by viruses or mutations. Death receptors, like TNF receptor 1, often drive necroptotic pathways [2]. In *necrosis*, cells swell followed by a rupture of the cytoplasmic membrane. The toxic intracellular contents are expelled and often cause inflammation in nearby cells [2]. Infection with intracellular pathogens is associated with the highly inflammatory pyroptosis that contributes to the antimicrobial response in myeloid cells [3]. The accidental or passive ischemic cell death, or oncosis, is often described a lethal injury. Oncosis is characterized by mitochondrial swelling, cytoplasm vacuolization, and swelling of nucleus and cytoplasm. Therapy-induced cancer cell death may follow after inappropriate entry of cells into mitosis and is often called mitotic catastrophe [4].

Neutrophils constitute the first line of defense against infections. They kill pathogens employing engulfment of microbes, secretion of anti-microbials, and externalization of chromatin referred to as neutrophil extracellular trap (NET) formation. NETs are composed of chromatin fibers able to bind and potentially kill pathogens [5]. The chromatin fibers aggregate into larger threads with a diameter of approximately 50 nm that are decorated with azurophilic granule-derived proteins like neutrophil elastase, cathepsin G, proteinase 3, and myeloperoxidase. In addition, NETs contain lactoferrin and gelatinase from specific and tertiary granules, respectively. NET formation comes in two flavors variants, suicidal and vital. Most of the key components of both types are similar. The processes differ in stimuli and timing. The pathway of suicidal NET formation differs from apoptosis or necrosis and involves calcium release from the endoplasmic reticulum and consecutively activation of NADPH oxidase. The execution of the full pathway can take hours.

After stimulation by bacterial products, toll-like receptor (TLR)-4-activated platelets, or complement fragments in synergy with TLR2 stimulation, viable neutrophils tend to release NETs [6]. During vital NET formation, nucleus-derived DNA-filled vesicles are exocytosed and maintain the integrity of the plasma membrane. The remaining "viable" neutrophil can phagocytose and kill microbes, though it does not contain the complete diploid set of DNA. Vital NET formation can occur in a matter of minutes [7]. Under conditions of high neutrophil density, NETs tend to form dense aggregates (aggNETs) that may contain viable neutrophils, cellular debris, bacteria or other microorganisms, dust, crystals, and further particulate matter [8, 9].

The phagocytes involved in the phagocytosis of dying and dead cells

Efficient clearance of apoptotic cells, especially that of polymorphonuclear leukocytes, is cardinal for the resolution of inflammation, which protects tissues from the toxic contents of dying cells [10–14].

In patients with SLE *monocytes* form an impaired phagocytosis of autologous apoptotic cells like postfight polymorphonuclear leukocytes. This depends on the prey, since SLE-derived monocytes efficiently clear apoptotic polymorphonuclear leukocytes from healthy individuals. In both, SLE and healthy subjects, $CD16^{POS}$ monocytes more efficiently interacted with apoptotic neutrophils than $CD16^{NEG}$ cells. The molecular basis of this defect is still elusive; however, IgG-binding may be a good candidate. The apoptotic cell-dependent LPS-induced induction of IL-10 and TNF-α were blunted and unchanged in monocytes from SLE, respectively [15].

The majority of the clearance of apoptotic cells is performed by *macrophages* before the lysis of the former. Liposomes containing the anionic phospholipid phosphatidylserine inhibit phagocytosis. The first receptor that had been described for the recognition of apoptotic cells was the $\alpha v\beta 3$-integrin known as vitronectin receptor [16]. Currently, a plethora of receptors have been identified to be involved in the so-called phagocytic or efferocytic synapses which form a stabile adhesive interaction between the dying cell and the phagocyte that controls the phagocyte responses. Every macrophage population uses a selection of these receptors [17].

In the light zone of germinal centers of lymph nodes, most of the developing B cells that have lost their affinity for their cognate antigens die by apoptosis and are immediately taken up by tingible body macrophages. In healthy individuals almost all TUNEL-positive apoptotic nuclei are to be found inside the macrophages; free, not ingested apoptotic cells are extremely rare. A defective clearance of apoptotic cells in germinal centers is associated with SLE [18].

Phagocytosis of apoptotic cells by *dendritic cells* also contributes to the maintenance of peripheral tolerance. Apoptotic cells expose "find me" and "tolerate me" signals that attract and modulate dendritic cells, respectively. Like macrophages the several subpopulations of dendritic cells variably express receptors for phagocytosis of apoptotic cells or apoptotic cell-bound opsonins like complement, protein S, growth arrest-specific gene-6, scavenger receptors, CD36, integrins, and milk fat globule-EGF factor-8 (MFG-E8) that differentially bridge apoptotic cells and phagocytes [19]. Apoptotic cells also contribute to the anti-inflammatory and pro-homeostatic nature of the efferocytotic pathways. They secrete

thrombospondin-1 and adenosine monophosphate and further "calm-down" signals that interact with dendritic cells [19]. The targeting of apoptotic vesicles to dendritic cells was proposed as a treatment option for autoimmune disorders [20].

In a kind of cellular cannibalism viable *granulocytes* ingest apoptotic siblings in the blood stream or after collection of the blood in vitro [21]. The granulocytes that contain the apoptotic prey are referred to as LE-cells. Antibodies binding histone H1 are required for the formation of LE cell [22].

Viable *neighboring cells* (e.g., epithelial and endothelial cells) reportedly also contribute to the clearance of apoptotic cells. The uptake was mediated by megalin and LRP [23]. However, the capacity for the phagocytosis is limited to few apoptotic cells per "amateur phagocyte."

Clearance of dying and dead cells

Anti-inflammatory clearance of apoptotic cells in homeostasis

In human adults, under physiological conditions several billion cells die per day and are substituted by the proliferation of stem cells. Effete cells undergo apoptosis, a highly regulated and controlled form of programmed cell death that occurs in multicellular organisms [24]. A cascade of biochemical events leads to blebbing, cell shrinkage, chromatin condensation, nuclear fragmentation, nuclear DNA cleavage, and mRNA decay. In the intrinsic and extrinsic pathways, the cell kills itself because it senses cell stress or signals from other cells, respectively. Apoptotic cells are usually swiftly cleared by neighboring tissue cells or by professional phagocytes before their contents can spill out [13]. It is well established that impaired clearance of apoptotic cells, especially in germinal centers of lymph nodes [18], is associated with SLE [25, 26].

Clearance of secondary apoptotic cells and NETs at sites of inflammation

Neutrophils, attracted by sentinel cells, arrive at the sites of injury in tissues or on internal or external body surfaces ready to start fighting the pathogens. They have four main options: (I) degranulation to extracellularly kill pathogens by the release of bactericidal mediators together with chemokines and cytokines to further recruit and activate immune cells, (II) phagocytosis and intracellular killing of pathogens, (III) NET formation and immobilization/killing of pathogens, and finally (IV) generation of reactive oxygen species in a process referred to as oxidative burst. The processes of degranulation and phagocytosis are usually initially survived by neutrophils. However, it ends with the execution of the apoptotic program. The apoptotic cells are finally taken up and metabolized by macrophages in an anti-inflammatory macropinocytotic pathway usually referred to as efferocytosis [27–29]. If the clearance capacity is overwhelmed or intrinsically weak, the apoptotic cells may undergo secondary necrosis and release their toxic contents. In these conditions, a plethora of intracellular and intranuclear autoantigens including DNA are exposed and get accessible for the autoantibodies that characterize SLE and murine lupus. In the presence of these autoantibodies, interferogenic pro-inflammatory immune complexes emerge.

Phagocytosis of dying and dead cells in conditions of defective efferocytosis

If the canonical anti-inflammatory clearance is insufficient the uncleared apoptotic cells tend to get (secondarily) necrotic. The phagocytosis of postapoptotic cells shifts to pro-inflammation, especially if anti-nuclear autoantibodies are present [30]. Macromolecular DNA is a stodgy prey for a single phagocyte. Therefore, it is digested into oligonucleotides that are released from the phagocytes [31].

The cholesterol-lowering statins block the prenylation of RhoA, displaying anti-inflammatory properties. RhoA inhibits efferocytosis that is pivotal for the anti-inflammatory clearance of apoptotic cells. Employing primary human macrophages, murine pulmonary macrophages, and human alveolar macrophages from patients with chronic obstructive pulmonary disease, it was shown that lovastatin increased efferocytosis in vitro and in vivo in an HMG-CoA reductase-dependent manner [32].

Efficient efferocytosis is reportedly required to counteract the progression of advanced atherosclerosis. Defective efferocytosis can cause postapoptotic, secondary necrosis, expansion of the necrotic cores of atherosclerotic plaques, and susceptibility to atherothrombosis [33]. Lupus nephritis is a complication of systemic lupus erythematosus for which the current therapy options fail regularly. Renal macrophages and dendritic cells orchestrate lupus nephritis in humans and mice. Macrophages fail to resolve the inflammation and promote tissue remodeling [34].

NETs that have trapped and killed pathogens [5] have to be cleared from the tissues. They can be considered depository of modified autoantigens associated with interferogenic DNA and pro-inflammatory microbial products. Similar to the efferocytosis, the clearance of NETs was defective in a subgroup of patients with SLE. The latter was associated with the development of nephritis [35]. Immune complexes formed from NETs and lupus prototypic (e.g., nuclear) autoantibodies induce the production of interferon (IFN) type I, which is further enhanced by the cathelicidin (LL37)-mediated activation of plasmacytoid DCs [36]. It was reported that NETs are the main inducers of type I IFN in pediatric SLE. LL37, HMGB1, and DNA synergistically activate an interferogenic response that required signaling via the TLR-4 and TLR-9 pathways, respectively [37]. Anti-neutrophil cytoplasmic

antibody (ANCA)-associated vasculitis (AAV) is characterized by autoinflammation, necrosis of blood vessel, and pauci-immune crescentic glomerulonephritis (PiCGN) followed by a rapid decline in renal function [38].

The body has developed several pathways to metabolize remnants from dying and dead cells to prevent the pathological interferon-driven responses described above. Apoptotic cells get cleared by macrophages employing an anti-inflammatory macropinocytotic pathway referred to as efferocytosis [28]. They are recognized by the exposure of anionic phospholipids and altered glucan moieties [11].

The role of autoantibodies, complement, and annexins

In homeostasis, apoptotic cells are rapidly and silently engulfed by professional phagocytes. This is necessary for the prevention of undesirable inflammatory responses and maintenance of an anti-inflammatory status. This process is referred to as silent apoptosis to convey downregulation of the immune system. In contrast to the uptake of pathogens or Fc receptor (FcR)-mediated phagocytosis, engulfment of apoptotic cells does not induce inflammatory cytokine production. Instead, engulfed apoptotic cells induce the secretion of the anti-inflammatory cytokines interleukin (IL)-10 and transforming growth factor (TGF)-β and simultaneously decrease the secretion of the inflammatory cytokines tumor necrosis factor (TNF)-α, IL-1β, and IL-12 [14, 30]. If this system fails, apoptotic cell remnants leak and modified neoepitopes are rendered accessible for immune cells. Intriguingly, sun exposure leading to apoptosis within the skin (sunburn cells) is a major source of the autoantigens of pathogenic immune complexes that induce flares in patients with SLE. These immune complexes contain autologous cell remnants and are taken up by peripheral blood monocytes, macrophages and dendritic cells in a FcγR-dependent manner. Upon FcγR clustering, vast amounts of inflammatory cytokines are released that lead to chronic inflammation and, ultimately, to multiple organ damage [30, 39, 40].

The role of *complement* in SLE and in murine lupus is established since decades [41–43]. It plays a dual role in the progression of SLE. It augments clearance of apoptotic cells but is also a mediator of renal inflammation. Injection into diseased NZB/W F(1) CR2-fH (an inhibitor of the alternative pathway) reduced albuminuria and glomerulonephritis [44]. In humans, the determination of the levels of complement C3 and/or C4 is useful in the follow-up of SLE and membranoproliferative glomerulonephritis [45]. Though C1q displayed no intrinsic DNase activity, it strongly increased the degradation of necrotic cell-derived chromatin by serum DNase in vitro. High concentrations of DNase I degraded chromatin in the absence of C1q; however, C1q was required for efficient ingestion into monocyte-derived phagocytes [46]. Patients with lupus nephritis display (I) decreased plasma levels of factor H and (II) dysfunctions of factor H. The latter include the impairment of the clearance of apoptotic cells [47].

The classical, the alternative, and the lectin pathway of complement activation orchestrates the clearance of apoptotic cells, precipitates renal inflammation, and plays essential roles in the development of glomerulonephritis, respectively. Masp1/3 knockout MRL/lpr mice showed reduced glomerular C3 deposition and pathology. However, anti-dsDNA antibodies, circulating immune complexes, glomerular IgG and MBL/ficolins deposition, renal interstitial pathology, urea nitrogen, and mortality did not differ between the wild-type and Masp1/3 knockout MRL/lpr mice [48].

Inherited or acquired deficiencies of C1q, C2, and C4 are strongly associated with the loss of tolerance against intracellular self-antigens in SLE. C1q deficiency specifically drove the positive selection of B1b B cells and IgM autoantibodies by an intracellular self-antigen, exposed on dying cells; in a feedback loop, it simultaneously decreased the negative selection of autoreactive conventional B cells by the same antigen. The B1-derived IgM activated C1q and augmented the clearance of dying and dead cells by efferocytosis. The complement inhibitors C4b-binding protein and factor H also interact with dying cells, most likely to decrease complement activation beyond the level of C3 to allow non-inflammatory clearance [49].

These findings suggest that the positive selection of autoreactive B1 cells by self-antigens may contribute to the IgM and C1q-dependent clearance of dying and dead cells in a feedback loop that limits exposure of conventional B cells to immunogenic self-antigens. However, in the presence of T cell help, exposed intracellular Ag activated conventional B cells [50].

Astrocytes and myosatellite cells express the class F scavenger receptor (SR-F3) multiple EGF-like domains 10 (Megf10) required for the phagocytosis of apoptotic cells. Native Megf10 but not Megf10 with EMARDD mutations bind with high affinity to C1q, an eat-me signal for apoptotic cells [51]. In general, functional complement dampens inflammatory responses that may be initiated due to the phagocytic processes. Recognition and uptake of apoptotic cells by murine bone marrow-derived macrophages (BMDM) in vitro was dependent on the presence of natural IgM and active complement. The uptake of apoptotic cells correlated with the amount of C3 deposited to their surfaces in an IgM-dependent matter. Similarly, the in vivo uptake by peritoneal macrophages required complement activation by IgM antibodies and C3 deposition [52]. Complement activation is reportedly required for an efficient uptake of apoptotic cells within the systemic circulation, and early component deficiencies could predispose to systemic autoimmunity by enhanced exposure to and/or aberrant deposition of apoptotic cells [53].

Annexin A1 is a multifunctional protein of the immune system dedicated mainly to the regulation of inflammatory

cells. It is important for the resolution of inflammation since it acts as a failsafe mechanism decorating secondary necrotic cells to be cleared by monocytes upon cleavage by ADAM10 [54, 55]. The majority of the work on annexin A1 is performed in mice; studies on human annexin A1 are scarce [56]. Patients with SLE often harbor high levels of anti-annexin A1 autoantibodies, especially those with renal complications. It is discussed that annexin A1 (I) is involved in SLE-related autoimmunity, (II) undergoes posttranslational modifications when associated with NETs, and that (III) the immunogenic form is citrullinated [56]. The citrullination of annexin A1 which is performed within NETs mimics the condition of rheumatoid arthritis, hallmarked by circulating anti-citrullinated peptides autoantibodies.

The role of annexin A5

Besides α2,6- and α2,3-terminal sialic acids [11], the exposure of anionic phospholipids like phosphatidylserine serves as signal for the internalization of apoptotic cells [57]. Annexin A5 is a natural ligand of apoptotic cells that expose phosphatidylserine [58]. The coating of apoptotic cells with annexin A5 increased their immunogenicity [59]. In vivo annexin A5 coated, irradiated lymphoma cells were targeted to CD8+ dendritic cells and elicited a specific anti-tumor response that was endowed with memory and induced the rejection of growing tumors [60]. The pro-inflammatory annexin A5-driven clearance of apoptotic cells is beneficial in the context of immunological rejection of tumors; on the downside, this reaction is able to foster the pathological inflammation in autoimmune diseases like SLE [61]. The phospholipid-binding annexins A2 and A5 as well as DNA and histones are known ligands for C1q [49]. Genetic or acquired lack of C1q causes impaired clearance of apoptotic material and is the strongest risk factor for the development of SLE.

The role of FcR on NET formation

Antibodies cross-linking FcγRIIIb robustly induced NET formation dependent on NADPH-oxidase, PKC and ERK activation; cross-linking with antibodies of FcγRIIa and of integrins did not promote NET formation [62]. Immobilized or planted IC (iIC) is a hallmark of several autoimmune diseases. They reportedly induce the formation of NETs by primary human neutrophils. The iIC-induced NET formation required active NADPH oxidase, myeloperoxidase, and crosslinking of FcγRIIIb. Blocking Mac-1 abolished iIC-induced NET formation [63]. This points to FcγRIIIb as a major player in the IgG-induced NET-formation. However, using cell lines expressing various human neutrophil FcγRs, it has been shown that FcγRIIA and FcγRIIIB, the latter even in the absence of its signaling partners FcγRIIA and Mac-1, take up soluble IC employing a pathway used by GPI-anchored receptors and fluid-phase endocytosis. The formation of NETs requires FcγRIIA but not FcγRIIIB-mediated neutrophil interaction with extravascular soluble IC [64]. Neutrophils in vivo activated via TLR7/8-engagement show a furin-dependent cleavage of the N-terminal part of FcgRIIA. The neutrophils displayed a similar phenotype like those isolated from patients with active SLE. They reduced the engulfment by neutrophils of IC and favors NET formation. The neutrophils also promoted the cleavage of FcgRIIA on plasmacytoid dendritic cells and monocytes in trans and caused an impaired overall clearance of IC. One may assume that blocking TLR7/8 activation will increase the phagocytic clearance of circulating IC, while alleviating their inflammatory potential [65]. The severe immune response to heparins, accompanied by excessive thrombocytopenia and thrombus formation, is referred to as heparin-induced thrombocytopenia/thrombosis (HIT). IgG autoantibodies that recognize heparin/platelet factor 4 complexes are responsible for this disease which is associated with high morbidity and mortality. These immune complexes interact with FcγRIIa on neutrophil/platelet complexes and induce NET formation in vitro and in vivo. Non-functional PADI4 abrogates thrombus formation but not thrombocytopenia, suggesting the use of independent pathways [66]. Furthermore, the 3-phenylcoumarin derivative 6,7-dihydroxy-3-[3′,4′-methylenedioxyphenyl]-coumarin downmodulates oxidative metabolism, release of elastase, and formation of neutrophil extracellular traps in a FcγR- and CR-dependent manner [67].

The lack of the inhibitory FcγRIIB combined with the autoimmune accelerator mutation coded on the Y-chromosome precipitates severe lupus glomerulonephritis in FcγRIIB−/−yaa mice. In later stage of lupus nephritis, loss of renal DNase I precedes the development of end stage kidney disease [68]. Recently, among other mutations, rare null-alleles for the deoxyribonuclease 1 like 3 and the FcgR IIB (FCGR2B) have been described in patients with SLE and genetic mouse models. Double-deficient Dnase1l3−/− and FcgR2b−/− mice in the C57BL/6 background exhibit a massive IgG anti-dsDNA production already at 10 weeks of age. This was accompanied by a spontaneous hyperactivation of germinal centers, expansions of T follicular helper cells, and elevated occurrence of splenic plasmablasts. The authors concluded that Dnase1l3 and FcgR2b synergize in the generation of somatically mutated, potentially pathogenic IgG anti-dsDNA antibodies [69].

Not only IgG but also the other classes of immunoglobulin display profound effects on health and disease. IgA autoantibodies reportedly worsen rheumatoid arthritis via triggering the IgA Fc receptor (FcαRI; CD89) on neutrophils and induction of NETs. Under these conditions, no phagocytosis of IgM and marginal endocytosis of IgG IC were to be observed. If blocking of FcαRI represents a new therapeutic option requires extensive future studies [70].

Circulating nucleases for dismantling and clearance of NETs

The timely removal of NETs is crucial for tissue homeostasis and to avoid presentation of self-antigens. The fate of NETs in the circulation was determined by serum endonuclease DNase1 that was essential for the disassembly of the DNA backbone of the NETs. The sera from subset of patients with SLE patients degraded NETs poorly. There were two mechanisms that impaired NET degradation: (I) antibodies to DNase1 inhibited its enzymatic activity and (II) anti-NET antibodies blocked the access of DNase1 to the NETs. The failure to dismantle NETs correlated with kidney involvement [35].

Both murine endonucleases DNase1 and DNase1-like-3 are able to digest circulating extracellular DNA. To maintain vascular homeostasis especially in conditions of leukocytosis the activity of at least one of these enzymes is required to prevent vascular thrombotic events. Indeed, DNase1−/−/DNase1-like-3 −/− mice suffer from vascular occlusion by aggNETs when they were challenged by leukocytosis or low-grade bacteremia. The obstructed blood vessels are frequently fatal [71]. In a translational approach, non-canonical hematoxylin-positive, NET-based thrombi were also detected in pulmonary vessels of individuals that suffered from severe inflammation in acute respiratory distress syndrome and/or sepsis [71].

Loss of renal nuclease activity precedes the development of murine lupus

Deposition of nephritogenic immune complexes in subendothelial and/or subepithelial regions of the kidney and thickening of glomerular basement membranes are hallmarks of lupus nephritis. Mesangial chromatin, propagating as electron-dense structures in electron microscopy, serves as target for nephritogenic autoantibodies in vivo [72]. In lupus-prone (NZBxNZW) F1 mice an impaired fragmentation of chromatin from apoptotic cells was associated with murine nephritis [73]. The nephritogenic impact of anti-dsDNA autoantibodies in (NZBxNZW)F1 mice was not determined by their affinity but by the presence of their cognitive autoantigens, chromatin, or nucleosomes associated with the glomerular basement membranes [74]. In (NZBxNZW) F1 mice, nephritogenic autoantibodies can develop in the presence of DNaseI on the basis of a clinical silent nephritis; however, end-stage lupus nephritis is preceded by a drop in DNaseI protein and activity [75, 76]. In contrast to nephritis mice that have developed dermatitis maintained stable dermal DNase1 mRNA levels and total nuclease activity. In this case, the intradermal gelatinolytic activity of MMPs disrupts basement membranes and allows access, binding and deposition of chromatin-containing immune complexes [77].

TNFα and IL-1β increased DNase1 expression and activity in renal tubular cells and nuclear translocation of endonuclease-inactive DNase1, respectively. DNase1 and the anti-apoptotic tumor necrosis factor receptor-associated protein 1 (Trap 1) are mutually expressed due to transcriptional interference. Central data indicate that stimulating the tubular cells with TNFα promoted increased DNase1 and reduced Trap 1 expression, while TNFα and IL-1β stimulation induced nuclear translocation of the DNase1 [78].

Male BXSB mice carrying the Y chromosomal yaa gene developed murine lupus [79] which was strongly aggravated by the knockout of the IgG-Fc-receptor FcγRIIB$^{-/-}$yaa. In this lupus model, the occurrence of IgG-bound glomerular electron-dense deposits preceded the development of anti-dsDNA autoantibodies in the sera. Initially, the electron dense deposits were confined to the mesangium; later, they spread to the basement membranes of glomerular capillaries. The loss of renal and urinary DNase1, both transcriptional and on the protein level precipitated the renal disease in this model [68, 80].

Postphagocytic processes

After the ingestion of dying or dead cells, the phagocyte contains a big load of macromolecules that have to be metabolized. Most proteins can be cleaved and recycled as amino acids. Catabolism of DNA and membranes increased the phagocytes' content of several metabolites like uric acid and cholesterol that may harm the cells. Macrophages are prepared to contact monosodium urate crystals (MSUc). Indeed, monocytes but not mature macrophages secrete TNF-α after ingestion of MSUc. Furthermore, coincubation with MSUc abolished the zymosan-induced inflammatory response of macrophages characterized by the secretion of TNF-α [81]. It is established that oxidized low-density lipoproteins are cytotoxic for macrophages and can cause cell death. Oxidized cholesterol, as found in apoptotic cells, destabilized lysosomes and causes their leakage. Cytoplasmic oxidized cholesterol enhanced protective autophagocytotic pathways. However, it also damaged mitochondria and often induced apoptosis and postapoptotic necrosis after exposure [82]. Co-culture with apoptotic cells of macrophage resulted in three major protective phagocyte responses: (I) endoplasmic reticulum-borne acyl-CoA:cholesterol acyltransferase (ACAT) efficiently esterifies the cholesterol, (II) massive efflux of apoptotic prey-derived cholesterol, and (III) activation of survival pathways involving PI-3 kinase/Akt and NFκB [83]. Defective responses have implications for the clearance of apoptotic cells especially in atherosclerotic plaques. The anti-inflammatory response usually triggered by the clearance of apoptotic cells (TGF-β and IL-10) is rendered pro-inflammatory (TNF-α and IL-1β) when the phagocytes get in contact to free cholesterol loaded apoptotic cells. Abrogation of Mer signaling even accelerated the inflammatory response [84].

ATP-binding-cassette transporter 1 (ABC1) promotes (I) Ca^{2+}-related exposure of the anionic phospholipid

phosphatidylserine, (II) efferocytosis of apoptotic dead cells, and (III) release of cholesterol to apo-AI, the protein core of the cholesterol-shuttling high-density lipoprotein (HDL) particle [85]. Apolipoprotein E (apoE) is a glycoprotein involved in lipoprotein transport through interaction with the low-density lipoprotein receptor. Compared to wild-type cells ApoE-deficient macrophages ingest fewer apoptotic cells (but not latex beads) and produce more pro-inflammatory TNF-α and fibrinogen [86].

If DNA of engulfed dead cells is not digested, macrophages produce inflammatory cytokines including TNF-α and type I interferon to promote autoimmune diseases [87]. An overload of the macrophage with toxic prey or an insufficient response to urate and (oxidized) cholesterol precipitate inflammation after apoptotic cell uptake. This is of major importance for the phagocytosis in atherosclerotic plaques and has implications for coronary artery disease frequently observed in patients with SLE [88].

Resolution of cell death-related inflammation in the renal system

Resident renal macrophages are long-lived and self-renewing. They are initially derived from embryonic sources and are complemented from bone marrow with age. The tissue specificity of the macrophages is implemented by the microenvironment and maintained by epigenetic modifications. In acute renal injury, initially inflammatory macrophages are recruited and then replaced by wound healing/pro-resolving cells. In lupus nephritis, dendritic cells enter the kidneys, start antigen presentation, and initiate the formation of pro-inflammatory, tertiary lymphoid structures. Due to failed resolution infiltrating and resident macrophages display mixed inflammatory and alternatively activated phenotypes and tend to cause tissue fibrosis and irreversible damage [89]. In macrophages, indoleamine 2,3-dioxygenase 1 and signals of its downstream effector, the metabolic-stress sensing GCN2 have been identified as regulators of the tolerogenic response to apoptotic cells [90]. Healing of mesangioproliferative glomerulonephritis requires degradation of surplus extracellular matrix, normalization of hypercellularity by apoptosis, and α8-integrin-dependent clearance of the apoptotic cells by mesangial cells [91].

Autophagy protects kidney from acute, chronic, metabolic, and aging-related kidney inflammatory insults and its therapeutic targeting may be employed for the treatment of kidney disease [92]. Kidney injury molecule-1 (KIM-1, also known as TIM-1) is upregulated in proximal tubule cells after injury. It is a phosphatidylserine receptor able to transform epithelial cells into phagocytes. KIM-1-mediated phagocytosis requires autophagy, is not associated with oxidative bursts, and is followed by pro-tolerogenic antigen presentation [93]. In addition its anti-inflammatory activity involves downregulation of NF-κB [94] and the interaction with the dynein light chain protein, Tctex-1. The latter associates with KIM-1 at baseline, but dissociates from KIM-1 after initiation of efferocytosis [95]. Treatment with MFG-E8 reduced the levels of proinflammatory mediators and, consequently, sepsis-induced acute kidney injury [96].

In vessels

It is widely accepted that vascular NETs are formed during infectious and sterile forms of inflammation. These NETs expose pro-coagulant activities that are involved in G-CSF-driven thrombosis [97]. NETs reportedly bound and activated platelets, initiated their aggregation and induced the formation of canonical thrombi; thrombogenesis was inhibited by DNase or heparin [98]. Purified histones alone were sufficient to initiate platelet aggregates that generated red venous thrombi together with NET-bound red blood cells and fibrin [98]. Recently, we reported that aggNETs are prone to directly occlude blood vessels and thus form non-canonical thrombocyte-poor thrombi. The deoxyribonucleases (DNases), DNase1 and DNase1-like 3 controlled the occlusive effects of circulating NETs. Their absence caused obstruction of vessels and precipitated mortality during sterile leukocytosis and in bacterial sepsis [71]. Missing or non-functional serum DNases are a well-established for SLE [99] and murine lupus [73]. Indeed, development of severe murine lupus nephritis was immediately preceded by a drop in DNase protein and activity [76]. Interestingly, a rare autosomal recessive familial form of SLE was associated for a loss-of-function variant in DNASE1L3 [100]. All these data suggest that failed clearance of circulating NET remnants is associated with a deficient resolution of thrombi and are followed by a clinically overt state of chronic inflammation.

In ducts

In addition to vessels, aggNETs have been shown to clog the pancreatic duct in phases of leukocytosis and thus cause acute pancreatitis [101]. Pancreatic fluid contains high concentrations of bicarbonate that are involved in the process of NET formation [102]. Whether occlusions of any duct (e.g., pancreatic, biliary, salivary, lacrimal, or others) by aggNETs are increased in patients with SLE and/or contribute to its etiopathogenesis is still unknown. However, it can be speculated that occluded ducts containing dying and dead cells, viable and dead microorganisms, cell-toxic molecules, aggNETs, and occasional pus serve as reservoirs for modified autoantigens. These are able to form immune complexes with anti-dsDNA autoantibodies and, furthermore, are able to stimulate a prototypical interferogenic response in SLE.

In wounds and skinfolds

Skin covers the body's outer surface and builds a well-controlled barrier protecting the vital parts of a body from influences of the hostile environment. Healthy skin is a reliable shield against external influences. Due to its frontal position, the skin is endangered by biological, chemical, or physical impacts. Wounded skin serve as perfect entrance for pathogens and, therefore, neutrophils are immediately recruited to wounds where they form NETs and aggNETs. The latter mechanically create a temporary wound closure that repels microbial invaders and initiates the resolution of inflammation and the process of healing. In the case of internal wounds in patients with acute pancreatitis, matted aggNETs have been shown to separate necrotic from viable areas [103].

In certain places, the skin forms warm and moist wrinkles, especially in the elderly. When these wrinkles are infected, a rash known as intertrigo develops, which itches, seeps, and sores. Preferred sites are located between the thighs below the breasts and abdomen, behind the ears, on the genitals and armpits, and between the toes and fingers. Intertrigo-borne inflammation is often caused by bacteria like Streptococci and Corynebacterium minutissimum [104], viruses, and fungi (e.g., *Candida albicans*) [104] and has the tendency not to resolve and thus to become chronic.

Wounds and intertrigos and their secretions contain viable and dead bacteria, cytokines, chemokines, other inflammatory mediators, and autoantigens of dying and dead immune cells and NETs. The autoantigens are often modified during the cell death processes and, in the case of apoptosis, expose oxidized [105] and proteolytically cleaved neo-autoantigens [106]. The autoantigens contained in NETs are similarly modified during NET formation. The most dominant modifications are citrullination and oxidation introduced by protein-arginine deiminase type-4 (PADI4), and NADPH oxidase 2 (NOX2), respectively. Consequently, chronic wounds and intertrigos are prototypical repositories of pro-inflammatory mediators, bacterial pyrogens, modified autoantigens and nucleic acids that have escaped resolution. They are prone to continuously challenge immune tolerance, to stimulate immunity and to serve as autoantigens for interferogenic immune complexes that characterize SLE [107].

In eye tissues and on ocular surfaces

Retinopathy is an established feature of patients with SLE. It is dominated by a microangiopathy and vascular occlusions often causing severe retinal ischemia. The plugging of ocular microvessels by circulating NETs or NET remnants [108] is a candidate mechanism for the complications observed in the SLE-related eye disease [71]. Due to a better therapy and follow-up of the patients, occlusive events apparently declined in the last decades. However, there is a relatively high incidence of papilloedema that are often asymptomatic [109]. The most vision-threatening complications occurring in SLE are vasculitis of retinal vessels and neuritis of the optical nerves. Both are manifestations of the failure to resolve the systemic inflammation, a hallmark of the disease [110]. The warm and continuously wet ocular surface is a highly specialized tissue covered by a three layered tear film. Open eyes are exposed to a plethora of pathogenic microorganisms and viruses as well as dust. To avoid irreversible scarring of the translucent cornea by T cells, the protection of the outer eye tissues is executed by antibodies, complement and the cells of the innate immune system like polymorphonuclear [8] or mononuclear phagocytes. Whereas the former initiate

Table 1 Potential drugs for the therapy of SLE. Targets and examples for drugs

Target	Example
T cells	Abatacept
B cells	Rituximab, ocrelizumab, ofatumomab, epratuzumab (anti-CD22)
Calcineurin	Voclosporin
Granulocytes	Anti-CD15
IL-1	Anakinra, canakinumab
IL-17/23	Ixekizumab, ustekinumab (IL-12/23), secukinumab (IL-17Ai), guselkumab (IL-23i), brodalumab (IL-17A), bimekizumab (IL-17A,Fi), tildrakizumab
IL-5	Mepolizumab, reslizumab, benralizumab
IL-6	Tocilizumab (IL-6r), sarilumab (IL-6r)
IL-10	B-N10
TGFβ	Anti-TGFβ
TNFα	Infliximab, etanercept, certolizumab-pegol, golimumab, adalimumab
IL-18/IL-18 BP	(IL-18-binding protein) = tadekinig alpha
IL-15	Eculizumab
IFN	Anifrolumab; sifalimumab, rontalizumab, AMG811
APRIL/BAFF	Briobacept, atacicept, belimumab
JAK-STAT	Tofacitinib, baricitinib, upadacitinib, ruxolitinib, filgotinib
Proteasome	Boretzumib
TYK2	BMS-986165
p38 MAP kinase	SB2203580
NETs	Anti-NET
SNECs	Anti-SNEC
Phosphatidylserine	Annexin A5, bavituximab
IVIG	IVIG
Antioxidants	N-acetylcysteine, cysteamine
ROS	ROS donors, ROS accelerators
BM transplant	
Immunoadsorption	

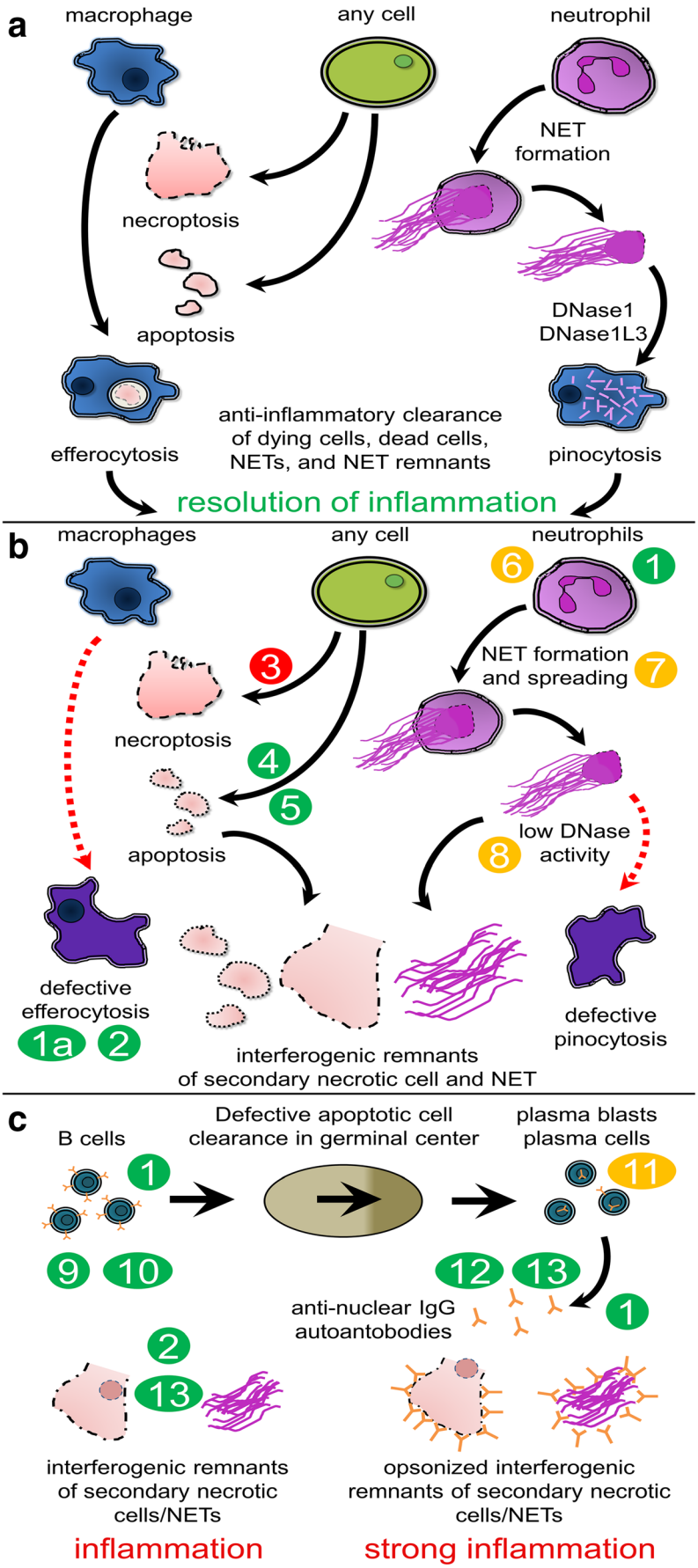
the inflammation and fight the pathogens, both types of cells clear the site and thus synergize in the resolution of inflammation [9]. *Pseudomonas aeruginosa* can form ocular biofilms. A timely recruitment of neutrophils to the outer eye surface and the formation of a barrier-forming "dead zone" prevented the dissemination of the bacteria into the murine brain. The clearance of established ocular biofilms and the resolution of the inflammation required the synchronous blockade of Psl and T3SS as well as appropriate antibiotic therapy [111].

In the oral cavity

Neutrophils, NETs, and aggNETs can regularly be detected in the oral cavity even of healthy individuals. The cells may gain direct access via mucosal exit or the manifold oral glands. In addition, there is a continuous delivery of pulmonary NETs via the bronchial system. The NETs and aggNETs are associated with a plethora of viable and dead microorganisms as well as dust particles to which humans are exposed, whenever they breathe or eat. Therefore, the oral cavity can be

Table 2 Potential drugs for the therapy of SLE. Rationale and role in the treatment of SLE

Target	Role in SLE	Rationale
Immune cells		
T cells	Autoreactive T and B cells are activated in a T-cell-dependent manner that relies on T-follicular helper cells.	Targeted suppression of inflammation
B cells	Central and peripheral B cell tolerances to self-antigens are defective in SLE.	Targeted suppression of inflammation
Calcineurin	Immunosuppression	Suppression of inflammation
Granulocytes	Culprits in Flares, produce interferogenic NETs and SNECs	Targeted suppression of inflammation
Cytokines		
IL-1	Pro-inflammatory	Reduction of inflammation
IL-17/23	Tissue inflammation, T-cell activation, B-cell proliferation	Reduction of inflammation
IL-5	Pro-inflammatory	Reduction of inflammation
IL-6	Accelerated autoantibody production, elevated in SLE Sera, pro-inflammatory	Specific reduction of activation in DCs containing apoptotic cell remnants, reduction of inflammation
IL-10	Anti-inflammatory	Reduction of inflammation
TGFβ	B cell activation, T cell suppression	Reduction of inflammation
TNFα	Pro-inflammatory	Reduction of inflammation
IL-18/IL-18 BP	Pro-inflammatory	Reduction of inflammation
IL-15	Stimulating lymphocytic expression of Bcl-2 and CD25 (in both B and T cells)	Reduction of inflammation
Signaling		
IFN	Disease activity, inflammation, AAb production, possible induction of lupus-like syndromes	Reduction of inflammation
APRIL/BAFF	Protect self-reactive B cells from apoptosis	Reduction of inflammation
JAK-STAT	Survival and activation signaling	Reduction of inflammation
Proteasome	Highly required for plasma cell survival	Targeting of plasma cells, induces misfolded protein overload and cell death
TYK2	Inhibit IL-12/IL-18 induced interferon gamma production	Reduction of inflammation
p38 MAP kinase	Regulates production of pro-inflammatory cytokines TNF-α, IL-1	Reduction of inflammation
Cell remnants		
NETs	Source of autoantigens, vicious cycle	Reduction of autoantigen source, induction of efferocytosis, pro-resolving
SNECs	Source of autoantigens, vicious cycle	Reduction of autoantigen source, induction of efferocytosis, pro-resolving
Phosphatidylserine	Immunosuppressive in onset of disease, flare and efferocytosis	Induction of silent phagocytosis, anti-inflammatory engulfment of SNECs, pro-resolving
Other		
IVIG	Immunomodulatory properties	IVIG suppresses the activation of B cells through enhancing expression of FcγR on B cells and DCs.
Antioxidants	Immunomodulatory properties	High ROS: oxidative stress, cell/tissue damage, pathway modifications
ROS	Immunomodulatory properties	Low ROS: delayed cytokine degradation, persisting infections, defective NET formation, influence on cell subset distribution
BM transplant	Severe cases	Ultima ratio
Immunoadsorption	Severe cases	Ultima ratio


a
macrophage
any cell
neutrophil
NET formation
necroptosis
apoptosis
DNase1 DNase1L3
efferocytosis
anti-inflammatory clearance of dying cells, dead cells, NETs, and NET remnants
pinocytosis
resolution of inflammation
b
macrophages
any cell
neutrophils
NET formation and spreading
necroptosis
apoptosis
low DNase activity
defective efferocytosis
1a 2
interferogenic remnants of secondary necrotic cell and NET
defective pinocytosis
c
B cells
Defective apoptotic cell clearance in germinal center
plasma blasts plasma cells
anti-nuclear IgG autoantobodies
interferogenic remnants of secondary necrotic cells/NETs
inflammation
opsonized interferogenic remnants of secondary necrotic cells/NETs
strong inflammation

◀ **Fig. 1** Pathophysiology of SLE with therapeutic interventions. **a** Phagocytosis, pinocytosis, and enzymatic degradation cooperate for the silent clearance of dying cells, dead cells, and NETs in healthy individuals. **b** Reduced phagocytosis, pinocytosis, and/or enzymatic degradation cause the accumulation of cellular debris and immune complex aggregates in patients with chronic inflammatory rheumatic diseases, which start systemic inflammatory responses. **c** Deficient phagocytosis of apoptotic cells and the consecutive erroneous selection of autoreactive B cells initiate autoantibody production mostly targeting nuclear proteins. The autoantibody nucleoprotein complexes induce the SLE prototypic cytokine interferon and precipitate the inflammatory responses. The therapeutic interventions are indicated in the figure and are listed below. Green: drug available; orange drug not approved; red: experimental. For details, see main text

No.	Drug or treatment	Mechanism
1	Glucocorticoids	Depress action of eicosanoid and display broad anti-inflammatory and immunosuppressant effects (dose-dependent).
1	NSAIDS	Depress action of eicosanoid and display less broad anti-inflammatory and immunosuppressant effects.
1A	Glucocorticoids	Promote macrophage phagocytosis of leukocytes undergoing apoptosis
2	Fresh-frozen plasma	Provides complement components and increases anti-inflammatory clearance of immune complexes and cell remnants
3	Necrostatin	Blocks necroptosis
4	UV protection	Reduces excessive dermal cell death
5	Stress avoidance	Reduces excessive cell death
6	β-Blocker	Stuns neutrophils
7	PAD inhibitors	Inhibits spread of NETs
8	DNase-1	Degrades NETs and aggNETs
9	Anti-CD20	Kills B cells
10	Anti-BAFF	Reduces activation of plasma cells
11	Proteasome inhibitor	Kills plasma cells
12	IVIG	Reduces antibody production by activated plasma cells via a feedback loop
13	Plasmapheresis	Removes autoantibodies; reduces pathogenic inflammatory phagocytosis of immune complexes and cell remnants

considered chronically but usually asymptomatically infected. Indeed, it is one of the most heavily colonized parts of the human body; surprisingly the function of the oral innate immune system is scarce. The humoral defense involves several antimicrobial components like secretory IgA (sIgA), IgG, lysozyme, and mucins. The IgA is synthesized by local plasma cells of the salivary glands, whereas IgG is derived from serum via the gingival crevices. Oral neutrophils undergo NET formation at least partially induced by the binding of sialyl Lewis(X) of salivary mucins to neutrophil-borne surface L-selectin. This pathway does not depend on elastase and less on the production of reactive oxygen species by NADP-oxidase activity during the execution of the oxidative burst. Oral NETs displayed high bactericidal activities [112] and are involved in the resolution of infection-related inflammation. Interestingly, saliva from patients with aphthous ulcers or Behçet disease prone to oral ulcers showed impaired NET formation [112]. Neutropenia or functional neutrophil deficiencies cause inflammatory conditions in the oral cavity like periodontitis, gingivitis, and ulcerations. The effect of neutrophil dysfunction is most dramatically observed in pediatric patients suffering from Papillon–Lefèvre syndrome which display a devastating destructive periodontitis. They are not able to clear oral infections, to preserve homeostasis and to keep the oral inflammation on a subclinical level [113–115]. Other individuals with periodontitis, gingivitis, and ulcerations often display a disturbed oral microflora. In Behçet disease, the saliva-dependent NET formation was reportedly deficient, causing inflammatory condition and recurrent oral ulcerations [116]. In patients with SLE or discoid lupus erythematosus (DLE) the inflammation of the oral discoid lesions often escape the pro-resolving processes of homeostasis and get chronic. They were lupus-associated pathological sequelae that were independent of the skin lesions [117]. The oral cavity thus represents a further repository of modified autoantigens in a pro-inflammatory context [107]; whether the latter induce or drive SLE needs further investigation. Alternatively, the oral disease can be the consequence of the misbalanced immune system in patients with SLE.

Therapy of SLE

The pivotal role of sun exposure and *UV protection* for patients with SLE [11] places cell death and faulty efferocytosis in the center of disease progress. UV-induced skin damage leads to the accumulation of apoptotic cells that are not cleared by efferocytosis, but instead induce a flare in patients with SLE via immunogenic FcγR-mediated phagocytosis. To prevent the inflammatory response elicited by the uptake of immune complexes via FcγR-mediated phagocytosis, many new therapeutics either targenting FcγRs or the neonatal FcR (FcRn) are currently under development with promising results in first clinical trials [118]. Another approach currently under investigation is the modification of the IgG Fc glycan to diminish the pro-inflammatory properties of IgG ICs [119].

Antimalarials like hydroxychloroquine remain the first-line therapy in mild cases together with non-steroidal anti-inflammatory drugs. Antimalarials were shown to inhibit phagosome function and consequently TLR activation. This downregulates IFN-α and decreases the antigen processing necessary for autoantigen presentation. Hydroxycholorquine also downregulates the expression of NADPH oxidase [120], increases NO production, and thus improves endothelial function [121]. The subsequent reduction of ROS ameliorates oxidative cell stress and tissue damage, momentarily. However,

chronically low ROS levels impair cytokine degradation, affect the distribution of immune cell populations, and impair the antimicrobial defense [122].

As with most autoimmune diseases, glucocorticoids are the gold standard for patients with SLE, especially at the onset of a flare. Patients with chronic inflammation receiving high-dose prednisone therapy displayed substantially increased MFG-E8 mRNA levels in circulating monocytes, and this substantially contributed to improve efferocytosis [123]. Corticosteroids have strong anti-inflammatory effects at low doses on both acquired and innate immune pathways. By inhibiting NF-κB activity they reduce B and T cell responses and effector functions of monocytes and neutrophils, ultimately relieving the inflammatory state [124].

Immunosuppressive therapies target the initiation of inflammation and not its resolution. Additionally, these agents have severe side effects and often worsen quality of life. In the last decades, the immunosuppressive drugs methotrexate, azathioprine, cyclophosphamide, ciclosporin, and mycophenolatmofetil have been shown to be effective for the treatment of active SLE. *Methotrexate* is a folic acid analogue and competitive inhibitor of dihydrofolate reductase. In high doses, it inhibits both DNA and RNA synthesis of proliferating cells. In the treatment of SLE low-dose methotrexate has a role in the management of resistant arthritis and skin disease. Furthermore, it is known as steroid-sparing agent. In the low doses employed for the treatment of autoimmune diseases, rather than suppressing hematopoesis or inducing cytoreduction methotrexate stimulates adenosine release from connective tissue cells and inhibits neutrophil functions [125].

In over 50 years, only belimumab (anti-BLyS) was approved in USA and Europe for the treatment of SLE including pediatric patients. Belimumab targets the soluble form of B lymphocyte stimulator (BLyS) (also known as B cell lymphocyte activating factor or BAFF) [126]. It prevents BLyS from binding to its receptors TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor), BCMA (B cell maturation antigen), and BAFF-R (B cell lymphocyte activating factor receptor). BAFF levels are elevated in many patients with SLE and in some studies correlate with disease activity. Treatment with belimumab led to the decrease of the total number of B cells, naïve B cells, and plasmablasts and induced the drop of the anti-dsDNA autoantibodies with IgG, IgA, IgM, and IgG isotypes [127]; [128]. Some future therapeutic approaches are listed in Tables 1 and 2. An schematic overview of the pathophysiology of SLE and the most important therapeutic interventions is shown in Fig. 1.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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