

Review

Apoptosis of Dendritic Cells and Autoimmune Disease

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Abstract

Dendritic cells (DCs), the most efficient antigen-presenting cells (APCs), bridge the innate and adaptive immune systems. As such, the turn-over of DCs is critical during autoimmune responses, and the dysregulation of DC apoptosis could cause severe immune destruction in the host. For example, reduction of immunogenic DCs by increased apoptosis could lead to immune tolerance to pathogen infection that might allow exposure of nuclear autoantigens, whereas reduced apoptosis could result in long-term lymphocyte activation to break the immune tolerance for the development of autoimmune disease. Thus, keeping a balance between survival and apoptosis of DCs is crucial to maintain immune homeostasis. In this review, we summarize the recent development on the factors inducing DC apoptosis and their underlying mechanisms to provide insights into the immunopathogenesis of some autoimmune diseases, which could lead to effective therapeutic interventions in the clinics.

Keywords: dendritic cells; apoptosis; autoimmune diseases

1. Introduction

Dendritic cells (DCs) are highly efficient antigen-presenting cells (APCs), which are essential for capturing, processing, and transporting antigens if they are periphery DCs to the lymph organs, where they present digested antigenic peptides to T cells [1] to activate the adaptive immune response. DCs exist in two distinct maturation stages with different functions: the immature stage and the mature stage. Immature DCs (iDCs) are better at taking up antigens than mature DCs, and frequently present in the periphery tissues, in which they continuously patrol and sample the local environment to detect any pathogens. The recognition and phagocytosis of pathogens trigger their maturation, migration, and subsequent presentation of antigens to T cells [2].

Antigen processing and presentation by DCs are the cornerstones of adaptive immunity. CD4⁺ T cells use antigen-specific receptors that only recognize antigenic peptide in complex with class II major histocompatibility complex (MHC) molecules expressed by DCs to receive activation signals. Once activated, these CD4⁺ T cells are quickly differentiated into T helper (Th) effector cells to facilitate the activation of other immune cells, such as B cells and CD8⁺ T cells, by secreting various cytokines. Antigen presented to the CD8⁺ T cells, however, need to be assembled with MHC class I molecule on the DCs as peptide-MHC complexes before the cytotoxic T lymphocytes can be effectively mobilized to kill the virus-infected or mutated

host cells [3]. This host-protective adaptive immunity, however, can sometimes be turned against the host itself, causing the autoimmune destruction of self-tissues if autoantigens are mistakenly captured by DCs in the diseased condition. For example, several autoantigens related to autoimmune disease, such as oxidizing low-density lipoprotein (LDL), heat shock protein 60, malondialdehyde-modified-LDL, and β -galactosidase, have been identified in the vascular walls of atherosclerosis [4–8], which are all modified in the diseased condition. These modified antigens from host cells are recognized by DCs as none-self and presented to T cells for the activation in the same manner that foreign antigens are presented. The adaptive immunity launched in this way against these modified antigens will ultimately cause self-damage because they are expressed on the self-tissues albeit modified [9].

Similar to every other cell, DCs have their own life cycles. After accomplishing their mission, die, and give spaces to the newly developed successors. There are several types of cell death, one of which is apoptosis first proposed by Kerr *et al.* in 1972 [10]. Apoptosis is initiated by extrinsic and/or intrinsic pathways in the immune system, which have been extensively reviewed elsewhere [11,12]. The extrinsic pathway is triggered via the binding of death-inducing ligands to their receptors, resulting in the formation of a signaling complex to initiate caspase activation. On the other hand, the intrinsic, or mitochondrial-dependent pathway, is characterized by non-receptor-mediated initiation, which involves the interac-



tion of B-cell lymphoma 2 (Bcl-2) family members within the cell, causing disruption to the mitochondrial membrane and triggering caspase activation. The mitochondrial-dependent intrinsic apoptotic pathway is heavily regulated by Bcl-2 family proteins, which has Bcl-2 homology (BH) domains, and are classified into three subfamilies: pro-apoptotic, anti-apoptotic, and BH3-only proteins [13,14]. DCs possess a mitochondrion-dependent cell death pathway regulated by all members of the Bcl-2 family, resulting in rapid turnover by apoptosis [15].

The life cycle of DCs begins with the differentiation of progenitor cells and ends with apoptosis induction following antigen presentation. A DC population under the steady state conditions can be classified into conventional DCs (cDCs) and plasmacytoid DCs (pDCs) subsets with different survival rates. pDCs live longer than cDCs, which is attributed to the differential expression of Bcl-2 family members [16]. The above findings may promote targeting specific Bcl-2 family members to treat diseases related to a particular DC subset according to its survival mechanism. Furthermore, compared to the DCs in steady state, inflammatory DCs have higher levels of anti-apoptotic genes, leading to prolonged their survival [17].

In the following sections, we summarize the latest studies on DC apoptosis in the immune system and the consequence on immunity including immunodeficiency as well as autoimmune diseases. We believe this review will provide valuable insights into immune-dysregulated diseases from a new perspective and facilitate the advancement of effective therapeutic interventions for such diseases.

2. Regulation of DC Apoptosis

The clearance of redundant, impaired, or hazardous cells is essential for normal host development and tissue homeostasis in multicellular organisms. For the elimination of these unwanted cells, apoptosis, a type of programmed cell death, fulfills the task. This physiological process is manifested at both the morphological and biochemical levels by cell membrane alteration, nuclear condensation, and ultimately chromosomal DNA breakage, after which the unwanted cells are completely phagocytosed by other immune cells [18,19]. The initiation of apoptosis must be tightly regulated, because once the apoptosis of DCs is triggered, it inevitably greatly impacts the host immune system for the development of autoimmune diseases. Both the components involved in the apoptotic pathways and the factors that modulate these pathways are important for the regulation of DC apoptosis, which is summarized in Fig. 1.

2.1 Tumor Necrosis Factor Superfamily

Tumor necrosis factor (TNF)-related activation-induced cytokine (TRANCE), a member of the TNF superfamily, is a DC-specific survival regulator that is predominantly expressed in activated T cells and interacts with receptor activator of nuclear factor kappa B (NF- κ B)

(RANK) on DCs [20]. The TRANCE-RANK interaction prolongs the survival of mature DCs, leading to the activation of transcription factor and c-Jun N-terminal kinase (JNK) pathways, along with the upregulation of Bcl-extra large (Bcl-xl) and anti-apoptotic signaling [21,22]. As with mature DCs, interstitial tissue-residing iDCs exhibit prolonged survival despite a significant decrease in cell viability and Bcl-2 expression [23]. Furthermore, TRANCE confers protection on DCs against apoptosis induced by Fas ligand (FasL), and the relative levels of TRANCE and FasL are associated with the survival of bone marrow-derived DCs (BMDCs) *in vitro* [24]. These findings provide compelling evidence for the crucial roles played by TRANCE in maintaining DC homeostasis. A case-controlled study and meta-analysis showed that the rs2277438 polymorphism of the *Trance* gene increased the risk of rheumatoid arthritis (RA) [25]. Activation of the TRANCE-RANK system is also involved in RA, inflammatory bowel disease (IBD), and cancer [26].

TNF-related apoptosis-inducing ligand (TRAIL), a cytokine belonging to the TNF family, is capable of promoting apoptosis and is expressed by various immune cells including natural killer (NK) cells, natural killer T (NKT) cells, DCs, and macrophages [27,28]. Upon interacting with its receptors, death receptor 4 (DR4) and DR5, TRAIL accelerates the apoptosis of leukemic pDCs, primarily through the extrinsic pathway involving caspases 10, 8, and 3 [29]. These findings have significant clinical implications for the treatment of leukemic pDCs with novel drugs that target TRAIL receptors. Maternal intake of linseed oil, which is rich in omega3 α -linolenic acid, can enhance the expression of TRAIL on pDCs in infant skin and thus prevent allergic dermatitis in infants [30]. The use of monoclonal antibody to TRAIL-R2 partially reverses the microfilariae of *Brugia malayi*-induced cell death in DCs by activating BH3 interacting-domain death (Bid) protein, leading to the release of cytochrome c from mitochondria and subsequently triggering caspase-9 activation [31]. TRAIL is involved in the pathogenesis of systemic lupus erythematosus (SLE). The concentration of serum soluble TRAIL and the mean mRNA expression level of TRAIL in peripheral blood mononuclear cells from SLE patients are significantly higher than those in healthy controls [32,33]. Moreover, TRAIL C1595T and G1525A gene polymorphisms have been suggested as risk factors for SLE development [34,35].

Cluster of differentiation 40 (CD40), an essential costimulatory molecule for DC activation, belongs to the TNF receptor superfamily. It interacts with CD40 ligand, which is expressed on activated T cells. Their interaction upregulates the survival of iBMDCs through the activation of phosphatidylinositol 3-kinase (PI3K) and its downstream effector kinase Akt [36]. Consequently, this leads to the increased expression of anti-apoptotic proteins, including Bcl-2 and Bcl-xL [37,38]. Deletion of CD40 in DCs has

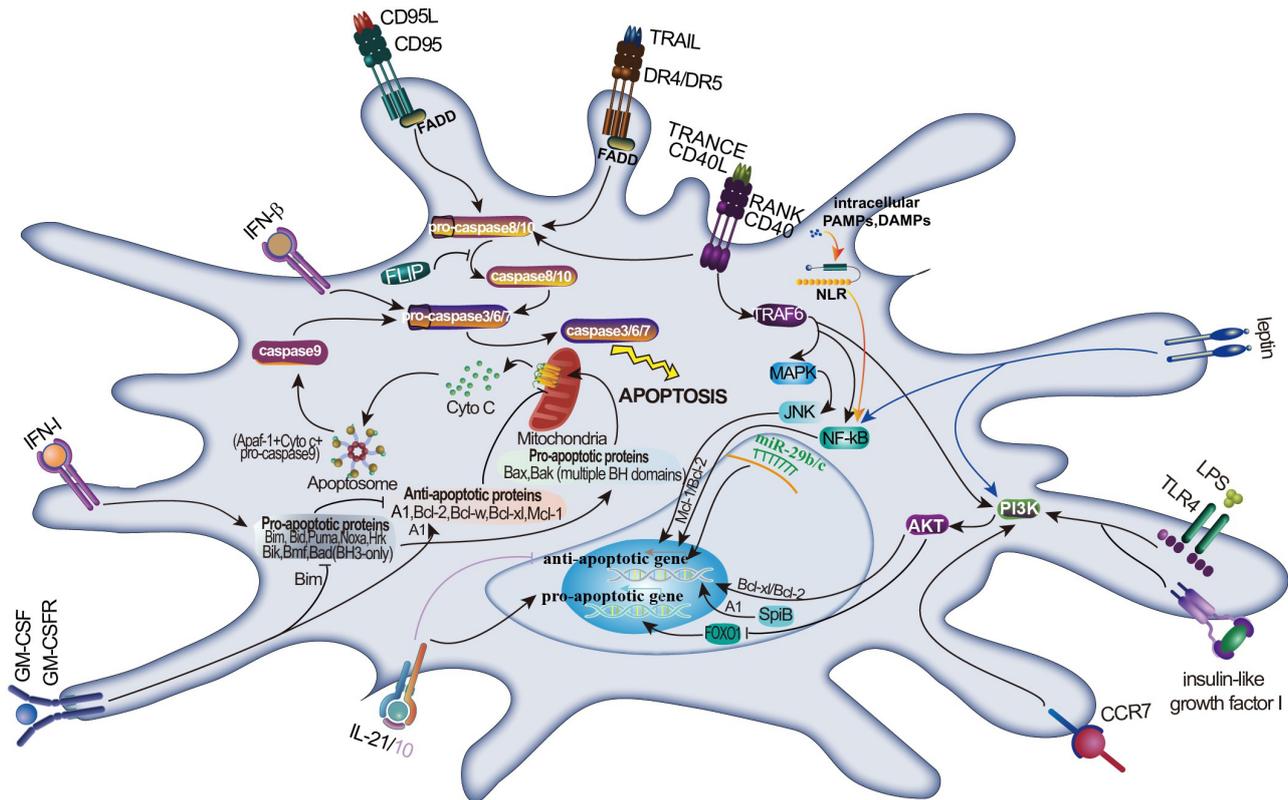


Fig. 1. The regulation of DC apoptosis. DC apoptosis is regulated by (1) TNF superfamily molecules, such as TRANCE/RANK, TRAIL/DR4/5, CD40/CD40L and CD95(Fas)/FasL; (2) Bcl-2 family molecules including pro-apoptotic (Bax, Bak), anti-apoptotic (A1, Bcl-2, Bcl-w, Bcl-xl, Mcl-1) and BH3-only proteins (Bim, Bid, Puma, Noxa, Hrk, Bik, Bmf, Bad); (3) NLR family, for example, NLR4; (4) miRNAs, such as miR-29b/c; (5) cytokines such as GM-CSF, leptin, IL-21/10, IFN-I and IFN- β ; (6) other factors such as insulin-like growth factor I. DC, dendritic cells; TNF, tumor necrosis factor; BH, Bcl-2 homology; FADD, fas-associated protein with death domain; DR, death receptor; FLIP, FADD-like IL-1 β -converting enzyme-inhibitory protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; JNK, Jun Nterminal kinase; LPS, lipopolysaccharide; PI3K, phosphatidylinositol 3-kinase; RANK, receptor activator of NF- κ B; TLR, toll-like receptor; TRAIL, TNF-related apoptosis-inducing ligand; TRANCE, TNF-related activation-induced cytokine.

been shown to markedly reduce the pathogenesis of experimental autoimmune encephalomyelitis (EAE) [39]. Furthermore, the motifs of both TNF receptor associated factor 2/3 (TRAF2/3) and TRAF6 are critically involved in the induction of EAE by priming pathogenic T cells by DCs [40].

CD95 (Fas), a member of the TNF receptor superfamily, enhances apoptotic signaling in iDCs, leading to the upregulation of Fas-associated protein with death domain (FADD)-like interleukin 1 β (IL-1 β)-converting enzyme-inhibitory protein (FLIP) and consequent inhibition of apoptosis [41]. CD95 mutations reportedly cause autoimmune disorders, such as autoimmune lymphoproliferative syndrome [42]. Moreover, the putative role of CD95 mutation defects in CD95-mediated signaling for autoimmune diseases has been extensively described [43]. An improperly regulated Fas/FasL system could pose a serious danger to the organism by selectively destroying target cells within a tissue, which has been well documented in animal models of EAE [44].

2.2 Bcl-2 Family Members

The Bcl-2 family of proteins, which possesses BH domains, can be categorized into three subfamilies: pro-apoptotic, anti-apoptotic and BH3-only proteins [13,14].

Pro-apoptotic Bcl-2 family members, Bcl-2-associated X (Bax) and Bcl-2-antagonist/killer (Bak) with multiple BH domains, mediate intrinsic spontaneous cell death in DCs. DC-specific knockout of these two pro-apoptotic molecules induces spontaneous T cell activation and autoimmunity in mice as they regulate DC killing triggered by regulatory T cells (Tregs) [15]. Mice reconstituted with a Bak/Bax doubly deficient hematopoietic compartment develop a fatal SLE-like autoimmune disease as well as a multiorgan autoimmune disease [45]. The mRNA expression of Bax is significantly upregulated during SLE flare-up [46].

Anti-apoptotic subfamily proteins, namely Bcl-2, Bcl-2-related protein A1 (Bcl2-A1), Bcl-w, Bcl-xL and myeloid

cell leukemia 1 (Mcl-1), which have four BH domains, exhibit a more than two-fold increase in the absolute number of pDCs in the spleen of *vav-Bcl-2* transgenic mice compared to C57BL/6 wild-type (WT) mice [16]. The survival of pDCs largely depends on Bcl-2, as Bcl-2 antagonists has been shown to kill pDCs from lupus-prone mice and suppress interferon alpha (IFN- α) production [47]. Consistent with the mouse data, Bcl-2 expression is also significantly higher in SLE patients [48]. Mcl-1 is crucial for the survival of synovial fibroblasts in RA [49]. Moreover, Bcl2-A1, a specific and direct target of the transcription factor Spi-B, which is critical for the function and development of pDCs, is upregulated in Spi-B-overexpressing pDCs with an enhanced survival rate [50]. Consistently, *in vitro* human pDCs are also impaired when the expression of Bcl2-A1 is inhibited [50]. Taken together, these findings suggest that Spi-B plays a critical role in the regulation of pDC development and survival by targeting Bcl2-A1. Stimulation with Toll-like receptor (TLR) agonists enhances the expression of Bcl-xL and facilitates the survival of pDCs and granulocyte-macrophage colony-stimulating factor (GM-CSF)-treated BM-derived DCs (GMDCs) [51]. pDCs express TLR9, but lack most other TLRs [52]. The specific ligand for TLR9, CpG, induces the upregulation of Bcl-xL in pDCs. In GMDCs, the interaction between the specific TLR4 agonist lipopolysaccharide (LPS) and TLR4 expressed on GMDCs promotes the expression of Bcl-xL through the PI3K signaling pathway [53]. Thus, TLR stimuli may augment a DC survival pathway that relies on the upregulation of Bcl-xL. In addition, the expression of Bcl-xL is decreased in platelets treated with plasma from patients with immune thrombocytopenia [54]. Consistently, in an *in vivo* murine model, adoptive transfer of Tregs expressing both forkhead box P3 (FoxP3) and Bcl-xL has demonstrated more effective suppression of RA than CD4⁺ T cells expressing FoxP3 alone [55].

The pro-apoptotic BH3-only subfamily, consisting of Bcl-2-like protein 11 (Bim), Bid, p53 upregulated modulator of apoptosis (Puma), horbol-12-myristate-13-acetate-induced protein 1 (Noxa), harakiri, Bcl-2-interacting killer, Bcl-2-modifying factor and Bcl-2-associated agonist of cell death proteins, initiates apoptosis by either inhibiting anti-apoptotic molecules or directly activating pro-apoptotic Bax/Bak [56]. In the absence of Bim protein in DCs, spontaneous cell death via mitochondrion-dependent apoptosis is reduced [57], leading to enhanced T-cell activation both *in vitro* and *in vivo* [58]. The expression of Bim is reduced in RA synovial tissue compared with controls [59]. Furthermore, Bim^{-/-} mice exhibit increased severity and prolongation of arthritis [60]. Apart from RA, Bim suppresses the development of SLE by limiting myeloid inflammatory responses [61]. Moreover, mice deficient in both Bim and Puma spontaneously develop autoimmunity in multiple organs, and their T cells lacking these two proapoptotic proteins can transfer organ-specific autoimmunity [62].

2.3 MicroRNAs

MicroRNAs (miRNAs), small non-coding RNA molecules found in plants, animals, and some viruses, have emerged as a prominent class of gene expression regulators associated with various biologic functions including cell proliferation, differentiation, and tumorigenesis as well as apoptosis.

Silencing miR-221 or overexpressing miR-155 in DCs has been found to upregulate p27 (kip1) protein and subsequent apoptosis. Additionally, DCs from miR-155 knockout mice exhibit reduced apoptotic rates compared to their WT counterparts. This finding emphasizes the crucial involvement of the miR-155/p27kip1 axis in regulating DC apoptosis [63]. miR-146a and miR-146b regulate apoptosis and cytokine production in human DCs by targeting TRAF6 and IL-1 receptor-associated kinase 1 proteins [64]. Meanwhile, miR-29b and miR-29c are involved in the apoptosis of human pDCs through the direct targeting of Mcl-1 and Bcl-2 expression [65]. Additionally, miR-378b has been shown to regulate CpG-stimulated murine BMDCs apoptosis via enhancement of IFN- β expression [66].

Exosomes from DCs overexpressing miR-146a suppress ongoing clinical myasthenia gravis, a neurological autoimmune disease in mice by altering T cell profiles from Th1/Th17 to Th2/Treg both in serum and spleen [67]. In addition, miR-29b is able to decrease the antigen-specific pathogenic activity of CD8⁺ T effector cells and confer protection against diabetes [68]. Moreover, miR-155 has been found to mediate augmented CD40 expression in BM derived pDCs in symptomatic lupus-prone mice [69].

2.4 Cytokines

Functioning as a cytokine, GM-CSF, is a monomeric glycoprotein secreted by various cells, which stimulates the production of white blood cells such as granulocytes and monocytes from multipotent stem cells. Given its nature of supporting the growth of a broad spectrum of hematopoietic cells, it is not surprising that GM-CSF plays a pivotal role in regulating the death of DCs. The withdrawal of GM-CSF from cultured BMDCs results in the upregulation of pro-apoptotic Bim and accelerates cell death in DCs [58]. In Bcl2-A1 deficient-mice, the survival of BMDCs was significantly reduced regardless of GM-CSF stimulation [70]. These findings indicate that GM-CSF could potentially contribute to the maintenance of DC homeostasis by inhibiting Bim or Bcl2-A1-dependent apoptosis. It is noteworthy that GM-CSF exhibits a synergistic effect with Fms-like tyrosine kinase receptor-3 ligand on maintaining the total number of cDCs *in vivo* [71]. GM-CSF and IL-1 β have been proved to act synergistically, ultimately leading to myelin and neuronal damage [72]. Moreover, cytokine-inducible SH2-containing protein is crucial for limiting GM-CSF signaling not only during inflammatory arthritis but also in EAE, a murine model of multiple sclerosis (MS) [73]. Similar to GM-CSF, leptin, a hormone/cytokine derived from adipocytes that modulates immune responses, also protects

DCs from spontaneous, ultraviolet B (UVB)- and hydrogen peroxide -induced apoptosis by activating NF- κ B and Akt pathways, as well as upregulating Bcl-2 and Bcl-xL [74]. Leptin promotes SLE by increasing autoantibody production and inhibiting immune regulation [75]. Recently, the roles of leptin in immune effector cells from SLE have been extensively reviewed [76].

In contrast to the protective effects of GM-CSF and leptin on DCs, IL-21 stimulates the apoptosis of cDC through the signal transducer and activator of transcription 3 pathway and Bim expression [77], whereas IL-10 also promotes cell death in DCs by suppressing the expression of anti-apoptotic proteins Bcl-2 and Bcl-xL [78]. Elevated levels of IL-21 are commonly found in the tissues and/or sera of patients with autoimmune disease [79]. IL-10 allows for the transient activation of DCs to tolerize T cells and protect against autoimmune disease in central nervous system (CNS) [80]. In addition, the IFN family, such as IFN-I, induces splenic CD8 α^+ DC apoptosis via multiple BH3-only proteins including Bid, Noxa, and Puma following poly(I:C) activation [81]. Furthermore, IFN- β triggers mature DC apoptosis through caspase-11/3 activation [82], and long-term exposure to IFN- γ promotes DCs to undergo apoptosis [83]. IFN-I is strongly implicated in the pathogenesis of SLE [84], and the significant roles of IFN- γ in SLE have been comprehensively reviewed [85]. Additionally, tumor-derived transforming growth factor beta 1 (TGF- β 1) was proven to be capable of inducing DC apoptosis in tumor-draining lymph nodes (LNs) [86]. Consistently, the level of TGF- β 1 is reduced in SLE patients with osteoporosis [87].

2.5 Mitochondria

Mitochondria, as an organelle that induces the intrinsic apoptotic pathway, plays a crucial role in regulating DC apoptosis. Currently, targeting mitochondrial energy metabolism is being considered for immune modulation in cancer. Alterations in the mitochondrial energy metabolism pathway are important indicators of lung cancer. A logistic regression model was established using four differentially expressed genes related to the mitochondrial energy metabolism pathway (acyl-CoA dehydrogenase long chain, aldehyde dehydrogenase 18 family, member A1, carnitine palmitoyltransferase 1B, and peroxisome proliferator activated receptor gamma), which effectively diagnose lung cancer [88]. Glycyrrhetic acid, a natural product of licorice with mitochondria targeting properties, exhibits broad anticancer activities. It has been proven to restrict mitochondrial energy metabolism by targeting the mitochondrial enzyme serine hydroxymethyltransferase 2 [89]. For detailed information on the roles of mitochondrial energy metabolism in thyroid cancer, please refer to a comprehensive review elsewhere [90]. Collectively, all of the aforementioned studies demonstrate the critical roles of signaling in mitochondrial energy metabolism in cancer development.

2.6 Other Factors

Apart from the commonly reported factors mentioned above, insulin-like growth factor1 has been found to negatively regulate the apoptosis of immature cord blood monocyte-derived DCs through the MEK and PI3K pathways [91]. Hepatitis B core antigen exhibits a dose-dependent effect on reducing DC apoptosis by regulating the protein kinase C (PKC)/NF- κ B signaling pathway [92]. Upregulation of the chemokine receptor C-C chemokine receptor type 7 (CCR7) promotes DC survival by inhibiting pro-apoptotic glycogen synthase 3 beta and FoxO1 [93]. Genome-wide association studies have shown a strong association between the CCR7/C-C motif chemokine ligand 21 (CCL21) axis and disease severity in patients with several autoimmune disorders such as RA, SLE, polymyositis, ankylosing spondylitis, and asthma [94].

Apoptosis signal regulating kinase-1 (ASK-1), which belongs to the mitogen-activated protein kinase kinase (MAP3K) family, acts as an upstream regulator for p38MAPK and c-JNK activation [95–97]. Additionally, the binding of human immunodeficiency virus 1 glycoprotein 120 to DC-specific intercellular adhesion molecule3-grabbing non-integrin (DC-SIGN) promotes ASK-1-dependent apoptosis in activated human DCs [98]. Moreover, migration inhibitory factor binding to CD74 expressed on hepatic DCs mediates hepatic DC apoptosis, which accelerates acetaminophen-induced acute liver injury, and leads to acute liver failure in mice [99]. Histamine, acting through H1/H4 receptors, prevents heat shock-induced apoptosis of DCs by suppressing caspase-3 activity, a mechanism that relies on the activation of PKC [100]. Phosphatase and tensin homology (PTEN)-induced putative kinase 1/E3 ubiquitin ligase/Parkin-mediated mitophagy regulates the apoptosis of DCs in sepsis [101]. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 modulates the development, function, and apoptosis of DCs conditioned by airway epithelial cells [102]. CpG DNA- induced upregulation of TLR9 expression affects apoptosis and immune responses in human pDCs derived from patients with chronic hepatitis B [103]. The protective effects of the deubiquitinating enzyme ovarian tumor (OTU). deubiquitinase 7B on DCs against TNF-induced apoptosis is attributed to its role in enhancing the stability of the E3 ligase TRAF2 [104]. In addition, silencing of the gene encoding nucleotide oligomerization domain (NOD)-like receptor family CARD domain containing protein 4 (NLRC4) results in blockade of the NOD-like receptor pathway, which leads to suppressed inflammation, reduced proliferation, and increased apoptosis of DCs in mice with septic shock [69].

3. External Factors Leading to DC Apoptosis

The apoptosis of DCs is triggered by heterogeneous factors that work with the multifarious regulatory mechanism as described in the above section. These external

apoptotic inducing factors listed below (see Fig. 2 for details) are associated with the development of autoimmune diseases to various degrees.

3.1 Infection by Pathogens

Once entering the body, pathogens can be effectively cleared by host adaptive immune systems, which mostly rely on DC-mediated antigen presentation. Thus, the induction of DC apoptosis can be an evolutionary strategy utilized by pathogens to avoid immune surveillances and subsequent eradication by the host.

Viruses, bacteria, and parasites induce DC apoptosis. For example, human herpesvirus 6, a ubiquitous virus that most individuals have been exposed to at two year of age, can directly induce DC apoptosis accompanied by the inflammatory response involving high mobility group box 1 (HMGB1) release and Th2 skewing [105]. Additional viruses, such as dengue virus [106], foot and mouth disease virus [107], measles virus [108], herpes simplex virus [109], Epstein-Barr virus [110], low-risk human papilloma virus 6E6 [111], and IgG-complexed adenoviruses [112] also observe to induce DC apoptosis. Similar to viruses, bacteria can also contribute to the apoptosis of DCs. The infection of *Mycobacterium bovis* and its attenuated strain *Bacillus Calmette-Guerin* induce DC apoptosis through the unleashing of mitochondrial cytochrome c and up-regulation of caspase-3/8/9 genes [113]. The infection of *Legionella pneumophila* [114] and *Porphyromonas gingivalis* [115] also trigger DC apoptosis. In addition to viral and bacterial infections, parasites are the third type of microorganisms to trigger DC apoptosis. *Fasciola hepatica* fatty acid binding protein (Fh12), a *hepatica*-derived antioxidant molecule, directly promotes the late apoptosis of BMDCs [116]. Eosinophils with a broken nucleus and caspase-3 are abundant in the liver of *hepatica*-infected sheep [117]. As Fh12 is part of the excretory-secretory products of *Fasciola hepatica*, it is possible that similar apoptotic mechanisms are induced by Fh12 in DCs. Interestingly, these pathogenic infection-induced DC apoptosis is the leading cause of morbidity and mortality in autoimmune disease SLE, accounting for up to 55% of deaths [118–120]. Recently, Prof. Akiko Iwasaki demonstrated that expression of the endogenous retrovirus (ERVs) locus ERV-K102, which encodes an envelope protein, is significantly elevated in SLE patient blood. This elevation was correlated with autoantibody levels and higher type I IFN signature metrics [121]. Interestingly, it was observed that IFN drives the apoptosis of DCs [81,82], indicating the impact of ERVs on SLE. Additionally, Prof. Akiko Iwasaki also discovered that the phagocytosis of ERV-K102 immune complexes leads to the formation of neutrophil extracellular traps (NETs) consisting of DNA, neutrophil elastase, and citrullinated histone H3 [121]. Previous studies have reported that NETs downregulate LPS-induced maturation and cytokine production in monocyte-derived DCs

(moDCs) [122,123]. Therefore, these data suggest that infection-induced DC apoptosis plays an important role in autoimmune disease.

In addition to viruses, bacterial infections have been shown to contribute to the exposure of nuclear autoantigens to the immune system in SLE [124]. Bacterial infections could cause host cell-induced release of nuclear autoantigen for autoimmune recognition. In addition, molecular mimics between bacterial and host DNA components might also form the mechanism in the bacterial infection-induced autoimmunity.

3.2 Malignant Disorders

Tumor is an abnormal growth of cells, often due to dysregulated cell death, which eventually causes the enlargement of tissue and forms a mass burden. Some studies have suggested that certain tumors may evade immune destruction by modulating the death of DCs, whereas others have indicated that a tumorigenic environment promotes DC apoptosis.

For instance, DCs co-cultured with melanoma cells exhibits an increased rate of apoptosis, the decreased secretion of IL-12 and IL-10, as well as a reduction in allostimulatory activity [125]. Since IL-12 exhibits protective effects against apoptosis in DCs [126], the reduced levels of IL-12 and IL-10 could partially account for the rapid apoptosis observed in melanoma-co-cultured DCs. Therefore, the inhibition of DC apoptosis to enhance cellular immunity may serve as a promising therapeutic strategy for tumor treatment. In line with the inverse correlation between tumor and DC apoptosis, tumor-containing sentinel LNs (SLNs) exhibit a lower density of DCs compared to tumor-free SLNs [127]. Mechanistically, it has been reported that melanoma-secreted factors such as gangliosides [128] or lysosomes [129] can reduce viable cell yield and induce the significant apoptosis of DCs.

The involvement of DC apoptosis in the development of malignancies can, in some cases, lead to autoimmunity. For instance, a male-biased gene-zinc finger (CCCH type), RNA-binding motif and serine/arginine rich 2 (ZRSR2) mutation in myeloid malignancies associated with the treatment of nonmalignant conditions, notably autoimmune diseases such as IBD and RA [130], was found to impede the activation and apoptosis of DCs following inflammatory stimuli through intron retention and downregulation of transcription factor interferon regulatory factor 7 [131], indicating the crucial role of DC apoptosis in malignancy-associated autoimmune disease.

3.3 Pharmaceutical Compounds

Although drug administration induces physiological changes in the body that promote well-being, certain medication efficiently modulates immune responses by regulating DC apoptosis. Thymol, a component from several plants, can induce suicidal DC death with the typical fea-

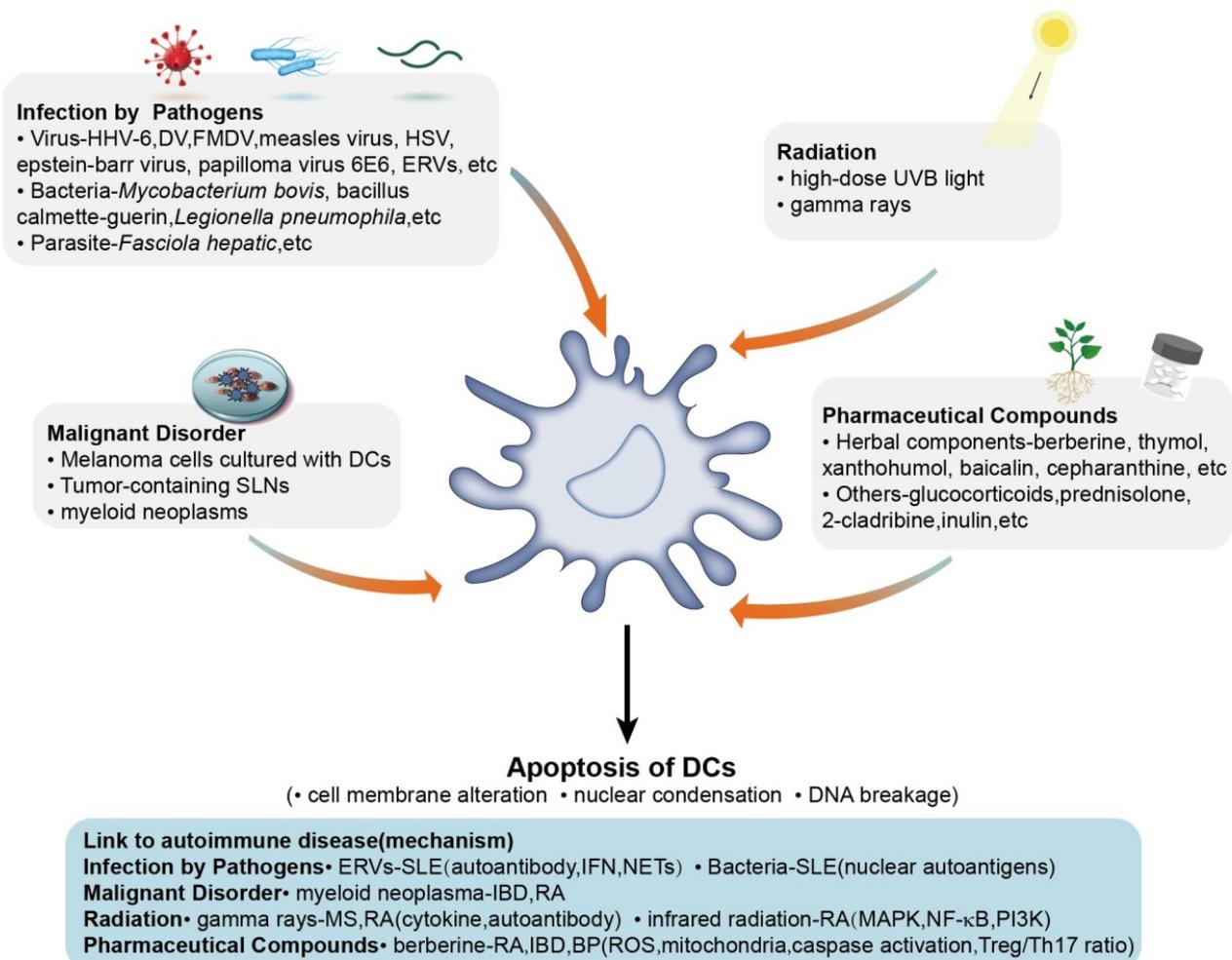


Fig. 2. Extracellular factors leading to DC apoptosis and autoimmune disease. DC apoptosis can be induced by a variety of factors. These factors include (1) pathogen infection caused by viruses, bacteria and parasites; (2) tumors that may evade immune destruction by modulating the number of DCs; (3) drugs with main components from herb herbaceous plants or other medicine; (4) exposure to high-dose of UVB radiation and gamma rays. DC conditioned by those factors undergo significant changes in morphology and biochemistry such as cell membrane alteration, nuclear condensation, DNA breakage, which are ultimately linked to the development of autoimmune diseases under certain circumstances. HHV-6, human herpesvirus 6; DV, dengue virus; FMDV, foot and mouth disease virus; HSV, herpes simplex virus; ERVs, endogenous retroviruses; SLE, systemic lupus erythematosus; IFN, type I interferon; NETs, neutrophil extracellular traps; DCs, dendritic cells; SLNs, sentinel lymph nodes; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; UVB, ultraviolet B; MS, multiple sclerosis; ROS, reactive oxygen species; BP, bullous pemphigoid.

tures of cell shrinkage and phosphatidylserine exposure through activation of acid sphingomyelinase (Asm) at concentrations exceeding 20 $\mu\text{g}/\text{mL}$. This leads to the formation of ceramide, which results in the reduction of anti-apoptotic Bcl-2 and Bcl-xL proteins, activation of caspase-3/8, fragmentation of DNA, and scrambling of cell membrane [132,133]. However, these effects are virtually absent in DCs from *Asm*-mutant mice or in WT cells with their *Asm* activity inhibited, indicating that *Asm* is the target of thymol-mediated apoptosis in DCs. In addition to thymol, *Asm* can also be stimulated by xanthohumol, a flavonoid that is found in beer. This stimulation leads to caspase activation and apoptosis of BMDCs [132]. Moreover, cepha-

ranthine isolated from the plant *Stephania cepharantha Hayata* induces the apoptosis of murine DCs via the mitochondria/caspase pathway [134].

Berberine, an isoquinoline alkaloid found in various plants belonging to the *Berberis* and *Coptis* genera, selectively induces apoptosis in mouse splenic and LN DCs with collagen-induced arthritis. This process is accompanied by the production of reactive oxygen species (ROS), a decline in mitochondrial membrane potential, and the initiation of caspase-3 in DCs [135]. These results suggest that the induction of apoptosis in DCs by berberine involves the participation of ROS and disruption of the mitochondrial membrane potential. In the context of autoimmunity, berberine

exerts a superior anti-arthritis effect in RA, and the mechanism may involve the balance between Treg and Th17 cells accompanied by an increase in levels of IL-10 and TGF- β , as well as a decrease in the levels of IL-6 and IL-17 [136]. Moreover, inflammation of RA is effectively suppressed by ROS-responsive berberine polymeric micelles, which targets mitochondria [137]. In IBD, berberine acts as an antagonist at both dopamine D1- and D2-like receptors and ameliorates experimentally induced colitis by suppressing immune responses [138]. In addition, a case report demonstrated that a patient with bullous pemphigoid was effectively treated with hormone therapy combined with topical berberine, resulting in complete healing of 95% of the patient's lesions after 1 month [139]. These studies highlight the significant role of berberine in anti-inflammation and immunomodulation in autoimmune diseases.

In addition to the aforementioned herbal components, glucocorticoids are commonly used for managing acute symptoms related to inflammatory and autoimmune disorders, wherein cell apoptosis including DCs is induced [65,140]. Several studies have demonstrated that glucocorticoids can induce apoptosis through various mechanisms including mitochondria [141], metabolic processes [142], and signaling transduction [143,144]. Prednisolone has also been demonstrated to induce the apoptosis of pDCs [145]. 2-cladribine causes apoptosis in human moDCs [146]. Inulin, a fructooligosaccharide, is a constituent of oral biofilm fructan that serves as an energy source for oral bacteria. Inulin-treated BMDCs undergo apoptosis through the activation of apoptotic pathways [147]. Therefore, experiments inhibiting ROS, caspases, or other apoptosis mediators need to be conducted for a complete elucidation of the apoptosis pathways in DCs.

3.4 Radiation

One of the largest promoters of apoptosis is the exposure to UV light. Although UV light is essential to human life, it can also lead to detrimental effects such as cancer, immunosuppression, photoaging, inflammation, and apoptosis.

UVB radiation poses a significant stressor on the majority of bodily surfaces. High-dose UVB radiation can efficiently induce the apoptosis of human DCs, which is accompanied by early mitochondrial alterations and is mediated through the activation of multiple caspases, leading to fragmentation in both cytosolic and nuclear compartments [148,149].

DC maturation involves enhanced resistance to UVB irradiation and an increase in key anti-apoptotic factors, such as FLIP and Bcl-2. FLIP competes with caspase-8 for FADD binding, thereby impeding the clustering and auto-activation of caspase-8 [150]. Due to the fact that the expression levels of caspase-8 and FADD remain unchanged during DC maturation, it is likely that the observed delay (compared to iDCs) in caspase-8 activation follow-

ing UVB irradiation in mature DCs can be attributed to the approximately 10-fold increase in FLIP [148]. Therefore, the upregulation of FLIP and Bcl-2 during DC maturation may confer a survival advantage by providing protection against UVB-induced effects. Similar to UVB irradiation, the exposure of DCs to gamma ray results in an elevated rate of apoptosis and reduces cell viability [151]. Collectively, these findings offer valuable mechanistic insights into radiation-induced immunosuppression.

A case report demonstrated that a patient who had been suffering from autoimmune RA for 10 years experienced near-complete recovery after undergoing 15 months of therapy with low doses of ionizing radiation [152]. Furthermore, therapeutic effects have also been reported in SLE patients through low-dose UVA and X-ray irradiation. For example, exogenous exposure to low-dose UV-A1 radiation directly attenuates disease in lupus by reducing B cell activity, preventing the suppression of cell-mediated immunity, slowing down epigenetic progression towards SLE, and improving discoid and subacute cutaneous lupus [153]. Interestingly, whole-body irradiation, excluding the head, attenuates SLE-like morbidity *in vivo* and reduces the proportion of radiosensitive CD180-negative cells that contribute to the development of SLE-like morbidity in NZBWF1 mice [154]. Low-dose gamma irradiation attenuates EAE by suppressing pro-inflammatory cytokines, reducing cytotoxic T cells and inducing Tregs [155]. In addition to SLE, low-dose gamma-ray irradiation can also attenuate by suppressing pro-inflammatory cytokines and autoantibody production, as well as inducing Tregs [156]. Far-infrared radiation has been observed to suppress experimental arthritis in rats through the suppression of MAPK, PI3K/Akt, and NF- κ B signaling pathways. This suggests that far-infrared radiation may offer an alternative non-pharmacological and non-surgical therapeutic approach for treating RA [157].

4. Impact of DC Apoptosis on Immunological Consequences in the Host

4.1 DC Apoptosis and Immune Tolerance

Considering the critical roles played by DCs in immune initiation and regulation, it is not surprising that DC apoptosis holds great importance for the maintenance of immune tolerance. Naturally, viable iDCs have the capacity to uptake apoptotic cells, which is normally regarded as an immunological insignificant occurrence. The nature of apoptotic cells that are up-taken, however, can determine the outcomes of immunological responses. If apoptotic DCs are taken up by iDCs, they convert iDCs into tolerogenic DCs accompanied by the suppression of subsequent iDCs maturation upon LPS stimulation. These tolerogenic DCs produce elevated amounts of TGF- β 1, which mediates the induction of naive T cells into Foxp3⁺ Tregs and subsequently inhibits the proliferation of T cells. However, if apoptotic splenocytes are taken up by viable iDCs, it does

not lead to the secretion of TGF- β 1 or the induction of Tregs [158]. These results indicate that challenging the immune system with apoptotic DCs can induce tolerance to a subsequent immunogen. Additionally, human invariant NKT cells promote tolerance by preferential apoptotic induction of cDCs [159].

In addition to immune tolerance induction by apoptotic DCs, the reduced number of DCs (the most powerful APCs) due to apoptosis will also compromise the host immunity and lead to immune quiescence. For example, fingolimod (FTY720), an agonist of the sphingosine1-phosphate receptor, reduces the number of DCs that are chemoattracted to the maternal-fetal interface by downregulating the expression of CCR7, ultimately inducing maternal-fetal immune tolerance [160]. Mechanistically, it has been discovered that DC expression of the signaling molecule TRAF6 is required for immune tolerance in the lung [161]. On the other hand, defective DC apoptosis in the DC-p35 mice results in DC accumulation, which eventually leads to chronic lymphocyte activation and systemic autoimmune manifestations [162].

Furthermore, some DC apoptosis-inducing agents, such as vitamin D [163,164], dexamethasone [165,166], and ethyl pyruvate [167] can also induce immune tolerance simultaneously. Moreover, programmed cell death protein 1 (PD-1), which is involved in peripheral immune tolerance, is expressed in innate immune cells including DCs. The expression of PD-1 in DCs decreases the survival of DCs [168].

4.2 Targeting DC Apoptosis for the Treatment of Autoimmune Diseases

Since the apoptosis of immunogenic DCs results in immune tolerance, while the apoptosis of tolerogenic DCs promotes autoimmunity, disturbed DC apoptosis is associated with the development of autoimmune diseases in various ways [58,162,169]. Indeed, the pathogenesis of many autoimmune diseases, whether tissue-specific or systemic, is partially attributed to dysregulated DC activation of autoreactive lymphocytes, ultimately resulting in tissue and organ damage. For example, DC-mediated auto-immunity constitutes principal pathological disorders for RA, SLE, MS, type 1 diabetes (T1D), and IBD. Therefore, the induction of DC apoptosis can be an attractive therapeutic strategy for these autoimmune diseases.

RA: RA is a common autoimmune polyarthritis characterized by chronic and inflammatory synovitis. A variety of synthetic compounds (e.g., baricitinib, tofacitinib, etanercept, infliximab, leflunomide, azathioprine etc.) and natural compounds (e.g., apigenin, atractylodin, berberine, crotonoside, naringenin etc) have been used for RA therapy through the regulation of DCs have been well reviewed elsewhere [170].

Distinct populations of DCs, such as myeloid DCs, pDCs, and moDCs, exist in high concentrations in syn-

ovial joint tissues [171]. Myeloid DCs from the synovial fluid of RA patients display an activated phenotype with elevated levels of human leukocyte antigen-DR (HLA-DR) and co-stimulatory molecules. Myeloid DCs are enriched in the LN tissue of early RA patients but not in individuals at risk [172]. Consistent with patients, studies in a murine model of early RA further showed the importance of myeloid DCs, whose number increased in nearby LNs before histological changes were observed [173]. In contrast to myeloid DCs, pDCs exhibit a suppressive effect on the development of RA. For example, depletion of pDCs exacerbate arthritis severity and an inflammatory response in mice [174]. The pleiotropic functions of pDCs in the pathogenesis of the RA have been well documented [172]. In addition, moDCs from RA patients secrete more pro-inflammatory chemokines (CXCL8 and CCL3) and cytokines (IL-6 and IL-23). Furthermore, these moDCs tend to promote Th17 differentiation while suppressing Treg development. Additionally, they demonstrate an enhanced ability to attract increased numbers of macrophages, neutrophils, and monocytes compared to healthy controls [170], which suggests that moDC activities could lead to increased leukocyte infiltration of the synovium and exacerbate inflammation. moDCs from RA patients have the capacity to develop tolerogenic features at both the transcriptional and translational levels in order to overcome disease-related effects when modulated with dexamethasone and monophosphoryl lipid A [175]. In turn, DC maturation is influenced by the synovial microenvironment in RA, with the upregulated expression of CD83 and CCR7 while downregulating CCR5 expression and reducing phagocytic capacity [176]. The targeting of CD1c⁺ classical DCs prevents T-cell chemotaxis mediated by thymus and activation-regulated chemokine in RA [177]. Indeed, the non-responders among RA patients treated with antibodies against citrullinated peptide antigens IgG show a significant increase in CD1c⁺ classical DCs [178]. In addition, encapsulating triptolide with DC-derived exosomes is a new method to induce immunosuppression in RA mice by inhibiting DC activation and inducing DC apoptosis, which further leads to T-cell immunosuppression [179]. Furthermore, piperlongumine suppresses DC maturation by reducing the production of ROS and has therapeutic potential for RA [180].

SLE: SLE, a complex and multifactorial autoimmune disease affecting predominantly young females (9:1 ratio compared to men), is characterized by the overproduction of IFN- α , proinflammatory cytokines, autoantibodies, substantial accumulations of immune complexes, and hyperactivity of both innate and adaptive immunity. These abnormalities result from a breakdown in immune tolerance involving DCs [181].

The 200–1000 times greater production of IFN- α by pDCs than any other cell type make this DC subset a major contributor to SLE in both humans and mice [182]. IFN- α

secreted by pDCs induces co-stimulatory molecules such as CD80 and CD86, resulting in the survival, expansion, and differentiation of autoreactive CD4⁺ T cells [183]. It has been proposed that CCL19 might induce circulating pDC accumulation in the T cell zone of LNs, thereby enhancing the priming of autoreactive T cells and contributing to the pathogenesis of SLE [184]. Moreover, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an efficient pDCs stimulator, causes the strong induction of IFN- α [185,186]. Collectively, these results suggest that pDCs and its major product, IFN- α , have a possible link to explain SLE development or flare-up during SARS-CoV-2 infection [187]. Moreover, a correlation has been observed in SLE patients between the increased production of IFN- α by pDCs through upregulation of TLR7, disease activity, and the responses of TLR7/TLR9 [188]. Therefore, apoptosis of pDCs can decrease the production of IFN- α , which might provide an attractive therapeutic target for SLE. In addition to pDCs, the number of peripheral tolerogenic CD1c⁺ DCs and the serum levels of FLT3L are significantly decreased in SLE patients, especially those with lupus nephritis, compared to healthy controls [189]. At the molecular levels, HMGB1 activates myeloid DCs by upregulating the mammalian target of rapamycin pathway in SLE [190].

Interestingly, glucocorticoids (GCs), commonly used to manage various acute disease manifestations associated with inflammatory and autoimmune disorders, induce the apoptosis of pDCs, which can be utilized as an attractive therapeutic target. Mechanistically, the pathway of GC-induced apoptotic pDCs was achieved by enhancing the expression of miR-29b and miR-29c that directly targets Mcl-1 and Bcl-2, which subsequently improves GC efficacy for the treatment of SLE [65]. Moreover, miR-31-5p is involved in SLE pathogenesis by increasing the levels of IFN- α production from pDCs by negatively regulating solute carrier family 15 member 4, which is critical for endolysosomal TLR activation in pDCs [191]. In addition, IgE has been found to suppress the production of IFN- α by pDCs in SLE patients through its inhibitory effects on TLR7 and TLR9 signaling pathways [192]. Therefore, targeting pDCs, for depletion or inhibition of their cytokine production represents a more targeted approach to disrupt the positive feed-back loop associated with IFN- α production and signaling in SLE.

MS: MS is a devastating autoimmune disease characterized by progressive neurological dysfunction resulting from demyelination of the CNS [193]. The heritability of MS risk is estimated to be about 25%. It is believed that environmental factors, epigenetic modifications, and interactions between genes or the gene environment play a role in the remaining susceptibility [194]. The EAE model, commonly used in murine studies of MS, is initiated and driven by myelin-specific CD4⁺ T cells that produce granzymes along with IFN- γ and GM-CSF (by Th1 cells) in the spinal cord and IL-17 (by CCR6⁺CXCR6⁺ Th17 cells)

in the peripheral nerve with heavy involvement of pDCs and myeloid DCs in its pathogenesis [193].

Myeloid DCs exhibit defects in activation and function in MS patients [195]. pDCs accumulated in the CNS and cerebrospinal fluid [196]. Furthermore, the ratio of myeloid DCs over pDCs is decreased in remitting MS patients, which returns to normal values in relapse phases [197]. Consistent with human MS, in EAE mice, pDC depletion results in the rapid exacerbation of severity during both the primary acute and relapse phases, but relapse severity resumes to control levels once pDCs return to normal levels [198], which indicates that the apoptosis of pDCs may promote the pathogenesis of EAE. Indeed, pDCs constitute the primary DC population infiltrating the CNS in EAE, despite their limited involvement in T cell activation and epitope dissemination [199,200]. Mechanistically, pDCs suppressed myeloid DC-mediated induction of CNS Th17 and Th1 cells in an indoleamine 2,3-dioxygenase - independent pathway, rather than via the killing of T cells, suggesting that the recruitment of pDCs to the CNS plays a crucial role in mitigating the pathology through regulating T cell activation and cytokine production [198]. Moreover, the upregulation of programmed death-ligand 1 via DNA hypomethylation in DCs has been demonstrated, resulting in the downregulation of autoimmune effector T cell functions and subsequently halting the progression of EAE [201]. Thus, the apoptosis of pDCs could have a profound effect on EAE.

Moreover, the exacerbation of EAE has been observed when pDCs specifically lose their expression of MHC-II, potentially due to a decrease in the generation of myelin antigen-specific Tregs following immunization [202]. In addition, the GM-CSF-activated production of IL-23 by APCs including DCs is regarded as a pro-inflammatory cytokine capable of promoting EAE [203]. Therefore, GM-CSF withdrawal-induced DC apoptosis could have therapeutic potential to suppress EAE. Interestingly, the activation of CpG enhances the selective migration of pDC precursors to the inflamed spinal cord, inducing their prompt generation of TGF- β and IL-27 following migration. Receiving TGF- β and IL-27 from CpG-pre-pDCs provide early and late phases defense, respectively, against the disease [204]. Furthermore, IFN- β has the capacity to regulate DC migration in EAE [205]. Pharmacological Sirtuin 6 inhibition impairs CCL19/CCL21-induced DC migration, ultimately downregulating pathogenic T cell inflammatory responses and delaying EAE onset [206].

Deficiency of the G protein G α_q ameliorates EAE with impaired DC-derived IL-6 production and Th17 differentiation [207]. The flavonoid compound Silybin, derived from the fruit and seeds of *Silybum marianum*, effectively alleviates EAE via inhibition of DC activation with reduced costimulatory molecules (e.g., CD80 and CD86), MHC-II expression, and suppression of pathogenic Th17 inflammatory cell responses [208]. Similar to silybin, betaine treat-

ment also ameliorates MS pathogenesis by inhibiting DC-derived IL-6 production and Th17 differentiation [209]. 6-Gingerol, a major dietary compound found in ginger rhizome, ameliorates the severity of EAE by suppressing the activation of DCs induced by LPS and promoting the development of tolerogenic DCs [210].

T1D: T1D is an immune-related disease resulting from insufficient insulin production by the pancreas, distinguished by the infiltration of immune cells into the pancreatic islets. This leads to subsequent destruction of β -cells responsible for insulin synthesis through T-cell mediation [205]. Both genetic and environmental factors can impair tolerance induction in T1D by affecting lymphocyte activities [211] and APCs.

Disrupted functioning of DCs or impaired tolerogenic activities of DC contributed to the loss of self-tolerance in T1D [212]. Pancreatic islets and LNs of T1D patients have been found to contain activated cDCs, which promote the activation of auto-reactive T cells and release pro-inflammatory cytokines, as well as dysfunctional tolerogenic DCs [213,214]. Moreover, DC-10, a population of human tolerogenic DCs expressing HLA-G, plays a crucial role in IL-10-mediated immune tolerance [215]. Indeed, impairment in the number and phenotype of DC-10 cells, particularly reduced CD83 expression, is associated with an increased risk of developing T1D, which suggests the potential utility of CD83⁺ DC-10 cells for stratifying individuals at risk of T1D alongside conventional prognostic factors [216].

Several publications have proposed unique and significant functions of pDCs in the onset and progression of human T1D [217,218] as well as diabetes observed in the NOD mouse model [219]. Depletion of pDCs in NOD mice results in the diminished capacity of pancreatic CD8⁺ T cells to produce IFN- γ [220]. This suggests that the Th1-polarization of T-cell responses, which is sensitive to pDCs, leads to the destruction of insulin-producing β -cells. Consistently, a reduction in the number of pDCs has been observed in T1D patients with an increase in TLR-9-mediated IFN- α production noted [221]. Furthermore, conditionally knocking out E2-2, a transcription factor specifically required for pDC maturation, results in the reduced recruitment of pDCs to pancreatic islets and decreased production of IFN- α during insulinitis. As a result, insulinitis exhibits a milder expression profile of the Th1 cytokine IFN- γ and demonstrates a significantly lower occurrence of diabetes [222], which indicates a disease-promoting role of E2-2 dependent pDCs in pancreatic T1D. Similar to pDCs, the activation of moDCs can also be induced by neutrophils releasing neutrophil extracellular traps that infiltrates the pancreas prior to T1D onset, which results in Th1 polarization accompanied by a decrease in the expression of TGF- β and an increase in the expression of IFN- α and IFN- γ [223]. Therefore, it is beneficial to incorporate DC strategy in T1D treatment.

IBD: IBD, which includes two main clinical forms, ulcerative colitis and Crohn's disease, is a chronic and recurring inflammatory disorder caused by the breakdown of intestinal immune homeostasis [224]. The incidence of IBD is elevated in western countries, affecting 3 million individuals in the United States and 2.5 million individuals across Europe [225,226]. Furthermore, the prevalence of IBD is increasing in numerous newly industrialized countries due to their adoption of Western lifestyles. For instance, the incidence of IBD patients in Japan has witnessed a remarkable 20-fold increase over the past three decades [227].

The malfunctioning of DC function and activation plays a critical role in promoting pathological inflammatory responses in patients with IBD. Aberrant or sustained activation of intestinal DCs by pathogen recognition receptors, in reaction to infectious agents, triggers the initiation of NF- κ B signaling and subsequent generation of pro-inflammatory cytokines IL-23, IL-6, IL-12, and TNF- α . Additionally, it triggers inflammasome signaling, leading to the secretion of IL-1 β and IL-18 [228]. These effector cytokines facilitate the activation of both innate and adaptive immune cells, thereby contributing to the pathogenesis of IBD through chronic intestinal inflammation. TNF- α inhibitors, such as infliximab and adalimumab, promote mucosal healing in patients with IBD by suppressing TNF- α -driven DC activation [229,230]. However, up to 40% of patients fail to respond to this therapy [231]. Compared to those who do not respond, the responders exhibit a significantly higher proportion of cDCs with elevated expression of HLA-DR in the inflamed mucosa prior to treatment [232]. In addition to cDCs, the responses of another DC phenotype, regulatory DCs, in IBD patients is inhibited by outer membrane vesicles derived from *Bacteroides thetaiotaomicron*, a prominent constituent of the human intestinal microbiota. This process involves a balance between protective IL-6 and regulatory IL-10 production, which is contributed to by both local and systemic DCs [233]. A recent study demonstrated that cellular stress can enhance TLR5 responses in intestinal epithelial cells, resulting in the increased activation of DCs [234]. This finding suggests a previously unknown mechanistic connection between DC activation and epithelial endoplasmic reticulum stress in the context of IBD. By contrast, miR-10a, a small non-coding RNA, impedes the activation of DCs and suppresses Th1/Th17 cell-mediated immune responses in IBD. The expression of miR-10a is reduced in the mucosa affected by inflammation in IBD patients. It exerts an anti-inflammatory effect by inhibiting IL-12/IL-23p40 and NOD2 expression, as well as blocking Th1/Th17 cell immune responses [235]. NOD2-dependent signaling in intestinal APCs has been demonstrated to modulate TLR-dependent activation of NF- κ B [236,237]. Additionally, it promotes autophagy processes that play a crucial role in maintaining intestinal homeostasis and regulating inflammation [238,239].

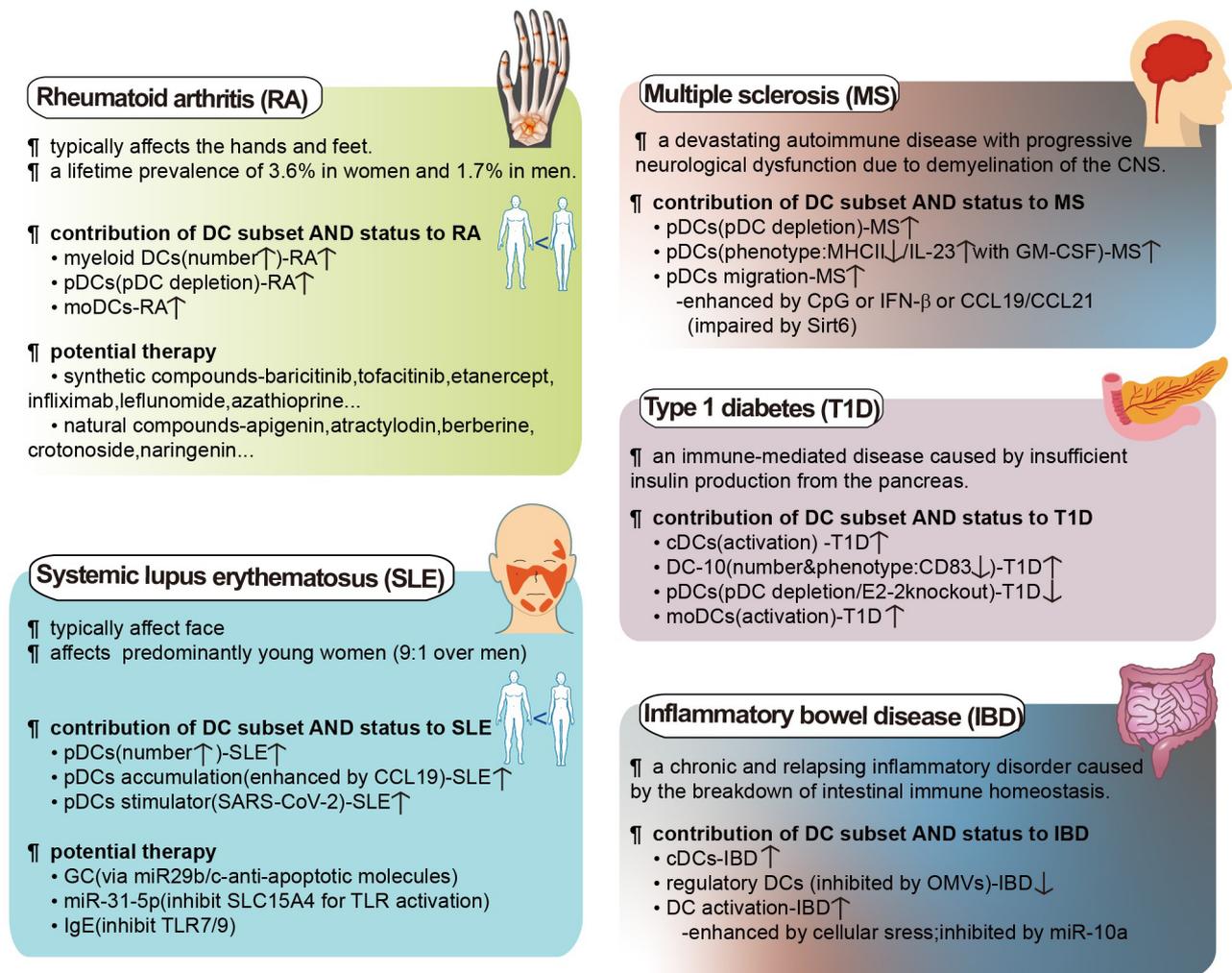


Fig. 3. Contribution of DC activity to the pathogenesis of autoimmune diseases. The association of DC activity to the pathogenesis of RA, SLE, MS, T1D and IBD is itemized in the figure. DCs, dendritic cells; pDCs, plasmacytoid DCs; moDCs, monocyte-derived DCs; GC, glucocorticoids; TLR, toll-like receptor; CNS, central nerve system; cDCs, conventional DCs; OMV, outer membrane vesicles.

Fig. 3 summarizes the contribution of DCs to the pathogenesis of RA, SLE, MS, T1D, and IBD.

5. Conclusion

Apoptosis of immune cells is a tightly regulated process that naturally occurs during cellular activation, maturation, and senescence, which plays a crucial role in the timely removal of redundant components after they have fulfilled their tasks in a highly efficient immune system. DCs exhibit a high turnover rate, and their apoptosis is affected by numerous factors and regulated by various apoptotic molecules and pathways. The frequent incidence and complex regulation of DC apoptosis indicate that the activity of this cell type is critical to maintain immunological balance, whose tipping could lead to serious consequences. Indeed, DC apoptosis is essential for the establishment of immune tolerance and autoimmunity, as DC apoptosis serves as a pivotal event in the maintenance of tolerance, and the breakdown of which leads to autoimmunity. Recent stud-

ies have indicated that viable DCs have the ability to uptake apoptotic DCs, leading to the induction of tolerance. However, this area is still in its stage of infancy and additional research is necessary to determine whether DC apoptosis plays an active role in the immune system to maintain tolerance towards self-antigens by generating or sustaining the Treg population. Current studies on DC apoptosis and diseases mainly focus on BMDCs and splenic DCs, although certain progress on human moDCs has been made. Further studies are needed combined with human settings to have more clinical implications. Ultimately, extensive research on the life and death of DCs in actual diseased settings will likely lead to the identification of more target molecules that link DC apoptosis to host autoimmunity for potential translational application in the clinic.

Abbreviations

APCs, antigen-presenting cells; Asm, acid sphingomyelinase; ASK-1, apoptosis signal-regulating kinase

1; BH, Bcl-2 homology; BMDCs, bone marrow-derived DCs; cDCs, conventional DCs; CNS, central nervous system; DCs, dendritic cells; DR, death receptor; EAE, experimental autoimmune encephalomyelitis; ERVs, endogenous retrovirus; FADD, fas-associated protein with death domain; Fh12, *Fasciola hepatica* fatty acid binding protein; FLIP, FADD-like interleukin 1 beta-converting enzyme-inhibitory protein; GCs, glucocorticoids; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMDCs, GM-CSF-treated BM-derived DCs; HMGB1, high mobility group box 1; IBD, inflammatory bowel disease; iDCs, immature DCs; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; LNs, lymph nodes; LPS, lipopolysaccharide; MHC, major histocompatibility complex; miRNAs, microRNAs; moDCs, monocyte-derived DCs; MS, multiple sclerosis; NETs, neutrophil extracellular traps; NLRC4, nucleotide oligomerization domain-like receptor family CARD domain containing protein 4; pDCs, plasmacytoid DCs; PI3K, phosphatidylinositol 3-kinase; RA, rheumatoid arthritis; RANK, receptor activator of NF- κ B; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SLNs, sentinel LNs; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; TRANCE, TNF-related activation-induced cytokine; Tregs, regulatory T cells; T1D, type 1 diabetes; UVB, ultraviolet B; WT, wild-type.

Author Contributions

LS wrote the initial draft of the manuscript. LS and FD made the figures. LZ, JW, ML, PZ, JL, CD and HW searched the literatures and participated in the initial draft preparation. YX made substantial contributions to the conception of the work and revised the manuscript. All authors contributed to editorial changes in the manuscript and have made a substantial, direct, and intellectual contribution to the work, and agreed to be accountable for all aspects of the work, and approved it for publication.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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