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REVIEW

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The fate of melanocyte: Mechanisms of cell death in vitiligo

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Abstract

Loss of melanocytes (MCs) is the most notable feature of vitiligo. Hence, it is critical to clarify the mechanisms of MC destruction in vitiligo. Apoptosis is most widely studied cell death pathways in vitiligo. In addition, the other two forms of cell death, conventional necrosis and autophagy seem to be involved in the death of vitiligo MCs under certain situations. Moreover, new types of regulated cell death including necroptosis, pyroptosis, and ferroptosis may also participate in the pathogenesis of vitiligo. Anoikis is likely to be connected with the death of detached MCs, which is provoked specifically by loss of anchorage. Primary phagocytosis, later called phagoptosis can execute death of viable cells, probably partly responsible for the loss of MCs in vitiligo. In this review, we aim to summarize the latest insights into various forms of MC death in vitiligo and discuss the corresponding mechanisms.

KEYWORDS

apoptosis, autophagy, ferroptosis, melanocytes, vitiligo

1 | INTRODUCTION

Vitiligo is an acquired pigmentary disorder on skin and/or mucosae, which is characterized by death of melanocytes (MCs), affecting 0.5%-2% of the population worldwide (Krüger & Schallreuter, 2012). Although vitiligo does not affect the survival of patients, it can bring social pressure (Salman, Kurt, Topçuoglu, & Demirçay, 2016) and cause mental diseases (Osinubi et al., 2017), which greatly interferes with the life quality of patients. It has been suggested that several factors may act as the trigger of the onset of disease, including severe sunburn, pregnancy, cutaneous trauma, and significant psychological stress. According to the 2012 international consensus report (Ezzedine et al., 2012), umbrella term "vitiligo" can be applied in all forms of vitiligo, including acrofacial, focal, mucosal, generalized, universal, mixed, and rare variants, except for the segmental variant, which is thought to have distinct prognosis and response to treatment. Over the past decades, numerous studies have attempted to illustrate the pathogenesis behind vitiligo, including neural theory, oxidative stress theory, autoimmune hypothesis, intrinsic theory, melanocytorrhagy hypothesis (Gauthier et al., 2003) and integrated theory. Neural theory was first mentioned in 1950s, and it suggested that accumulation of neurochemicals decreased melanin production (Lerner et al., 1959). Oxidative stress hypothesis showed that reactive oxygen species (ROS) are induced by multiple factors and impaired antioxidant defenses, breaking the MC redox homeostasis. Excessive production of ROS leads to the imbalance of antioxidation system in MCs and leads to cell damage (Dammak et al., 2009). Autoimmune theory indicated that innate immunity and adaptive immunity may take part in destroying MCs through autoimmune response. Numerous studies have mentioned that CD8 + T cells are involved in the destruction of MCs, while regulatory T cells and resident memory T cells also play a role in the reinstatement and reactivation of vitiligo, respectively (Y. Wang, Li, & Li, 2019). Recent studies further demonstrated that innate immunity is likely to work as the bridge between oxidative stress and adaptive immunity (Xie et al., 2015). According to intrinsic theory, the congenital defects make the vitiligo MCs more susceptible to oxidative stress and autoimmune reaction (Boissy et al., 1991; Gong et al., 2015).

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Melanocytorrhagy hypothesis was proposed in 2003 and mainly described chronic MC detachment, caused by trauma, friction, catecholamine, ROS, or autoimmune response (Gauthier et al., 2003). In spite of different theories of pathogenesis, damage of MCs is the coincident outcome in vitiligo.

Over the decades, a number of cell death types have been named and clarified. In this article, we aim to summarize the latest findings on the death of MC in vitiligo and discuss the possible forms of cell death participating in the pathogenesis of vitiligo.

2 | CONVENTIONAL FORMS OF CELL DEATH IN VITILIGO

2.1 | Apoptosis

Apoptosis, as the best-characterized form of programmed cell death, occurs in all multicellular organisms and can be triggered by both physiologic and pathologic stimuli, which initiate multiple signaling pathways regulated by activated caspases and also molecular systems such as bcl-2/bax and Fas/Fas ligand. Among the caspase family members, caspase-3 is a key mediator of apoptosis in mammalian cells (Putt et al., 2006). Elimination of unwanted cells by apoptosis is vital for normal growth, development, and function for human being under physiological or pathological conditions.

However, excessive apoptosis can result in diseases such as autoimmune disorders, neurodegenerative conditions as well as vitiligo. In 2000, one study claimed that they found no evidence to support that vitiligo might be related to dysregulation of apoptosis regulatory molecules (van den Wijngaard et al., 2000), whereas their conclusion has been challenged later (Huang et al., 2002). Among Bcl-2 family, Bcl-2 can protect cells from numbers of apoptotic stimuli, while Bax is an apoptosis agonist which acts via hetero-dimerization with Bcl-2. Since apoptosis is triggered when pro-death signals outweigh pro-survival signals, the ratio of Bcl-2/Bax is important in determining cell susceptibility to apoptosis induction. It was reported that lower ratio of Bcl-2/Bax was detected in perilesional MCs as compared to the control MCs (Kumar et al., 2012). Thus, altered expression of Bcl-2 and Bax might render MCs from vitiligo patients susceptible to the induction of apoptosis (Kumar et al., 2012).

The extrinsic apoptosis signaling pathways that initiate apoptosis involves transmembrane receptor-mediated interactions. To date, the best-characterized ligands and corresponding death receptors comprise Fas/FasL and TNF-α/TNFR1. T lymphocyte-mediated mechanism has been strongly suggested to play a great role in the loss of MCs. Cytotoxic T lymphocytes (CTLs) can directly induce cytotoxicity in MCs through release of cytotoxic mediators such as tumor necrosis factor (TNF)-α, interferon as well as Fas-FasL interaction (Jimbo et al., 2019). As a death receptor interacting with FasL, Fas recruits the adaptor protein Fas-associated protein with death domain (FADD) and procaspase-8 to form a death-inducing signaling complex (DISC) in which procaspase-8 is cleaved and activated. Activated caspase-8 then results in the proteolytic stimulation of downstream effector caspases, such as caspases-3 and caspases-7, finally inducing apoptosis. One study (M. Li et al., 2008) demonstrated that polymorphisms of the FAS gene may influence the risk and clinical progression of vitiligo in Han Chinese populations and elevated level of Fas was indeed observed in vitiligo MCs (Jimbo et al., 2019). Moreover, alteration of cytokine expression has been demonstrated in vitiligo patients. TNF-α, the ligand that binds to tumor necrosis factor receptor superfamily (TNFRSF), has been shown to accumulate both in the skin and serum of vitiligo patients (Birol et al., 2010). Several members of TNFRSF have been found significantly upregulated in MCs to various extent after treatment with H2O2 (Sastry et al., 2019), indicating the involvement of TNF-α/TNFR pathway in MC apoptosis of vitiligo. Besides, the level of interferon (IFN)-γ was also reported to be elevated in lesional skin of patients with vitiligo (Jimbo et al., 2019). In addition to CTLs, T helper 1 (Th1) cells, natural killer (NK) cells, and innate lymphoid cells (ILC)1 are able to secret IFN-γ, as well (Tulic et al., 2019). Yang, L. et al. (L. Yang et al., 2015) demonstrated that IFN-γ treatment could result in concentration-dependent increase in chromatin condensation and nuclear fragmentation, indicating IFN-γ may directly induce MC apoptosis. Recent research further revealed that MCs from vitiligo patients exhibited strong basal expression of chemokine-receptor-3 (CXCR3) isoform B which was directly regulated by IFN-γ. Conversely, IFN-γ could induce a more significant increase of chemokine (C-X-C motif) ligand (CXCL) 10 in vitiligo MCs (Tulic et al., 2019). Collectively, CXCR3B activation by CXCL10 at the surface of cultured human MCs induce apoptosis, which may provide another explanation for the effect of IFN-γ on MC damage. Furthermore, immune checkpoint inhibitor (ICI) has brought great therapeutic advances in melanoma care, while ICI, such as programmed cell death-1 (PD-1) inhibitors, was reported to induce vitiligo-like lesions as unique side effects. Elevation of serum CXCL10 and skin infiltration of CD8 + CXCR3+ T cells with production of IFN-γ and TNF-α were also detected in patients with anti-PD-1 therapies (Larsabal et al., 2017), supporting the role of apoptosis in MC destruction.

The intrinsic apoptosis signaling pathways, also called mitochondrial pathways, initiate apoptosis under a diverse array of non-receptor-mediated stimuli that produce intracellular signals which can act directly on targets within the cell. Mitochondrial dysfunction leads to the loss of the mitochondrial transmembrane potential, the open of calcium channel, and the release of cytochrome (Cyt) C into the cytosol, which then initiates the formation of a complex, called apoptotic protease activating factor-1(Apaf-1) thereby activating caspase-9, in turn activates caspase-3 and eventually triggers cell apoptosis, making it a mitochondrial-initiated event (Ding et al., 2002). Clinical and biochemical studies have suggested that overexpressed transient receptor potential cation channel subfamily M member 2 (TRPM2) and calcitonin gene-related peptide (CGRP) in perilesional MCs are related to calcium channel sensitive to oxidative stress in vitiligo (Kang et al., 2018; Zhou et al., 2015). H_2O_2 induced demethylation of the promoter region in TRPM2 gene and increased the expression of TRPM2 in MCs, mediating the calcium influx into the cytoplasm (Kang et al., 2018), while the Bax/Bcl-2 ratio and the cytosol Cyt C level significantly increased under CGRP

treatment, accompanied by higher expression of caspase-3 and caspase-9 (Zhou et al., 2015), indicating the involvement of mitochondrial apoptosis in vitiligo under oxidative stress. What's more, baicalein, which is an antioxidant proved beneficial to patients with vitiligo, was found to protect MCs by reducing the release of Cyt C, the Bax/Bcl-2 ratio and caspase-3 level in a concentration-dependent manner in vitro (B. Liu et al., 2012).

Taken together, apoptosis has been confirmed to take a vital position in the death of vitiligo MCs. However, a number of researches have reported MC death distinct from apoptosis, suggesting other forms of cell death may participate in the pathogenesis of vitiligo as well.

2.2 | Necrosis

Necrosis is defined as a type of uncontrolled cell death that can occur in response to various stimuli, such as infection, toxins, chemicals, or injury. Different from apoptosis, necrotic cells present the features including cytoplasmic swelling, rupture of the cell membrane, and swelling of cytoplasmic organelles morphologically. What makes a sharp pathophysiological distinction between necrosis and apoptosis is inflammation. The uncontrolled release of antigens in necrosis leads to activation of immune response and inflammation whereas in apoptosis cell-bound bodies are formed which are phagocytosed by neighboring cells in the absence of inflammation (Edinger & Thompson, 2004).

A small number of necrotic cells have been observed among apoptotic cells in non-lesional vitiliginous skin (van den Wijngaard et al., 2000). Other studies also suggested that MCs could undergo both apoptosis and necrosis under stimulation in vitro. The percentage of necrotic cell increased with higher concentrations of H_2O_2, while vitiligo MCs suffered from more necrosis than normal MCs with the treatment of H_2O_2 at same concentrations (Y. Zhang et al., 2014). Mono-benzyl ether of hydroquinone (MBEH) has been known to cause chemically induced vitiligo. It was reported that MBEH can induce cell death in a non-apoptotic pathway without activating the caspase cascade or DNA fragmentation but following necrotic MC death and distant CTLs response instead (Hariharan et al., 2010).

Therefore, necrosis may play a role in some special types of vitiligo concerning the specific stimulus. However, it may not be the major type of MC death because strong stimuli could unnecessarily be found in most of vitiligo patients and vitiligo lesional skin does not manifest substantial macroscopic signs of inflammation.

2.3 | Autophagy and autophagic cell death

Autophagy is a highly conserved catabolic process induced under cellular stress by degrading damaged organelles and proteins through a lysosome-dependent degradation process, featuring an extensive vacuolization of the cytoplasm (Dikic & Elazar, 2018). Signals that activate autophagy originate from various stress conditions, such as starvation, hypoxia, oxidative stress, protein aggregation, and endoplasmic reticulum (ER) stress. Under stress, phagophore assembly by the unc-51-like autophagy activating kinase 1 (ULK1) complex and nucleation by the class III phosphatidylinositol 3-kinase (PI3KC3)-Beclin1 (yeast Atg8) complex together initiate the formation of autophagosome. Then, the Atg12-Atg5-Atg16 complex promotes the conversion of the microtubule-associated protein 1 light chain 3 (LC3) into LC3-II complex with phosphatidylethanolamine (PE), elongating the membranes of the forming autophagosome. Working as the characteristic signature of autophagic membranes, the LC3-II complex maintains bounding to the mature autophagosome until it fuses with the lysosome to form an autolysosome.

Many studies have shown that autophagy might play a role in vitiligo. One study found that the ratio of LC3II/LC3I and Atg5 expression were higher in vitiligo MCs than that in normal controls MCs, while P62, mTOR protein expression, and tyrosinase activity in vitiligo MCs were significantly lower than those of normal MCs (Yu et al., 2019). Another study demonstrated that autophagy of MCs may be present in vitiligo and autophagy could affect the expression of functional molecules and is related to clinical type of vitiligo (Nie et al., 2016). Mitophagy is one kind of autophagy which could degrade impaired mitochondria and maintain the homeostasis of cells under stress. A decline in mitophagy was found in MCs derived from vitiligo patients which might lead to aberrant accumulation of impaired mitochondria (X. Li et al., 2013). Genetic basis for defective autophagy may be involved in the pathogenesis of vitiligo, as well. The ultraviolet radiation resistance-associated gene (UVRAG), an autophagy-related gene, can activate the PI3KC3 complex, promoting autophagy. A study from Korea showed that UVRAG polymorphism may contribute to increased susceptibility to non-segmental vitiligo (NSV) in the Korean population, indicating possible association between autophagy and susceptibility to NSV (Jeong et al., 2010). Tuberous sclerosis complex (TSC) gene mutations result in a broad range of symptoms, including hypopigmented macules as the earliest sign. MCs from patients with TSC displayed autophagic dysregulation and depigmentation in TSC2-KD MCs can be accelerated by inhibiting autophagy and completely reversed by induction of autophagy (F. Yang et al., 2018).

The ability of autophagy to recycle nutrients, maintain cellular energy homeostasis, and degrade toxic cytoplasmic constituents makes it responsible for defending MCs against oxidative stress. Antioxidation drugs, such as calcipotriol (Gong et al., 2015) and madecassoside (Ling et al., 2017) have been reported to function through the activation of autophagy with increased Beclin1 and LC3-II/LC3-I in MCs. It has been observed that both the level of LC3-II and the ratio of LC3-II/-I are relatively lower with apparently less cytoplasmic vesicles in vitiligo MCs compared to that in normal MCs under H_2O_2 treatment (He et al., 2017). Aberrant nuclear factor E2-related factor 2 (Nrf2)-p62 signaling pathway was reported be partly responsible for impaired autophagy in vitiligo MCs under oxidative stress (He et al., 2017).

Our previous work revealed that autophagy deficiency led to premature growth arrest, ROS accumulation and over-activation

of Nrf2 signaling pathway in murine MCs (C. F. Zhang et al., 2015). Subsequently, we reported that autophagy played an important role in the redox homeostasis and the biological functions of primary human MCs. Autophagy deficiency could inhibit the proliferation of primary human MCs and lead to premature growth arrest and accumulated ROS damage. ATG7-dependent autophagy was responsible for the regulation of the Nrf2-ARE signaling pathway under oxidative stress in MCs and was involved in the balance between oxidative stress and antioxidant defense system. Nrf2 target genes including γ-glutamyl cysteine ligase (GCLC), SQSTM1/p62, glutamyl cysteine ligase modulatory subunit (GCLM), NAD(P)H dehydrogenase, quinone 1 (NQO1), heme oxygenase-1 (HO-1), and glutathione S-transferase Mu 1 (GSTM-1) were expressed higher and the activity of antioxidant defense components including catalase (CAT), the glutathione peroxidase (GPX) and superoxide dismutase (SOD) were significantly increased in autophagy-deficient primary human MCs. Moreover, autophagy deficiency could facilitate oxidative stress-induced apoptosis in primary human MCs, suggesting an interplay between autophagy and apoptosis (Qiao et al., 2020).

Besides the growing evidence that autophagy can exert cytoprotective effects, there has been evidence for a contribution of autophagy to a mode of cell death that has been defined as autophagic cell death (Kroemer & Levine, 2008), whose subroutine can be limited or delayed by the pharmacologic or genetic inhibition of the autophagic machinery (Denton et al., 2012). It has been reported that autophagic process is required for IL-17 induced MC death (Zhou et al., 2018). The glutamate/cysteine antiporter (System Xc-) deficiency has also been claimed to cause cell death through activating ER stress and autophagic process in MCs (Zheng et al., 2016). Moreover, one study reported that keratinocytes and the scarce remaining MCs in vitiligo lesions had significantly more autophagic vacuoles, in comparison with control and non-lesional skin (Raam et al., 2018). However, although autophagic process is frequently induced in a vast number of pathophysiologic settings, autophagic cell death rather than cell death with autophagy is another condition (Kroemer & Levine, 2008). Therefore, autophagic process may be involved in the death of MCs in vitiligo, while the presence of autophagic cell death is still under debate.

Taken together, autophagy not only plays an important role in MC protection, but is also involved in the pathogenesis of vitiligo. Whether protective autophagy or autophagic cell death predominates in vitiligo MCs needs to be further investigated.

3 | NEW FORMS OF REGULATED CELL DEATH IN VITILIGO

3.1 | Necroptosis

Originally necrotic cell death (NCD) solely referring to necrosis was defined as uncontrolled cell injury caused by nonspecific trauma. It is now clear, however, NCD can also be driven by defined molecular pathways as a regulated cell death (RCD) in some contexts. Unlike apoptosis, NCD can induce innate and adaptive immune responses through release of damage-associated molecular pattern (DAMP) (Linkermann & Green, 2014). The best-characterized form of regulated NCD is necroptosis (Gudipaty et al., 2018). Necroptosis can be triggered by members of the TNF family, Toll-like receptors, DNA and/or RNA sensors through a different mechanism dependent on inhibition of caspase-8, when compared with apoptosis (Kaczmarek et al., 2013). Necroptotic stimuli promote the interaction of receptor-interacting protein (RIPK)1 and RIPK3, forming the central components of a multiprotein complex called the necrosome. Downstream of necrosome formation, mixed lineage kinase domain-like protein (MLKL) phosphorylation and translocation is induced, finally resulting in pore formation and influx of calcium ions without caspase-8 activation.

Reactivation of necroptosis pathway may have therapeutic significance in metastatic melanoma due to the lack of expression of RIPK3 in melanoma tumor cells (Broussard et al., 2018). In a zebrafish vitiligo model, Nicastrin deficiency results in depigmentation with MCs featured by ruptured melanosomes, swollen mitochondria, necrotic-like nuclei, indicating neither the classical apoptosis nor necrosis (Hsu et al., 2019). It has been demonstrated that primary MCs express high level of RIPK3 and can be induced necroptosis through CD95L-induced MLKL phosphorylation (Geserick et al., 2015); however, according to the research of Sun. et al., RIPK1 seems to play a protective role in ER stress induced by tunicamycin in human MCs (Sun, Wang, Huang, Ruan, & Xu, 2020). As RIPK1 may exert pro-survival and pro-death functions as reported (Dondelinger et al., 2019), the role of RIPK1 in MCs needs to be further elucidated.

High-mobility group box 1 (HMGB1) is normally found in the nucleus, whereas external stress or cytokines may prompt its cytoplasmic translocation and then breaches extracellular space via NCD, acting as a DAMP molecule. After intermittent ultraviolet B (UVB) exposure or H2O2 treatment, expression of HMGB1 may apparently increase in MCs and extracellular HMGB1 is usually detected, while JAK1/2 inhibitor can diminish the increase (K. Zhang et al., 2018). The translocation of HMGB1 into cytoplasm was observed in the MCs of vitiligo perilesional skin but not in that of non-lesional area or healthy controls (Cui et al., 2019) and plasma levels of HMGB1 in patients with vitiligo were increased (Kim et al., 2016), both indicating the release of HMGB1 by epidermal MCs in vitiligo. Another DAMP, S100B is also expressed in MCs. S100B serum levels were found significantly increased in patients with active NSV and strongly correlated with the affected body surface area (Speeckaert et al., 2017).

Collectively, the release of DAMPs makes it clear that NCD is present in vitiligo MCs. Further research is needed to explore whether necroptosis is indeed involved in the MC loss of vitiligo.

3.2 | Pyroptosis

Pyroptosis is a highly inflammatory form of NCD regulated mainly by caspase-1, which is initiated following large supramolecular complex termed inflammasome activation. The inflammasome-activated caspases then cleave the pyroptosis-inducing protein gasdermin D

(GSDMD), which forms a pore in the plasma membrane and causes cell lysis as well as the secretion of IL-1β typically (X. Liu et al., 2016).

Pyrin domain-containing protein 1 (NLRP1) is a key component of the NLRP1 inflammasome which activates IL-1β. Genome-wide analysis showed that NLRP1 variants are related to NSV in the context of associated autoimmune diseases (Jin et al., 2007). Another research demonstrated that in perilesional skin from active vitiligo patients, NLRP1 staining was strongly positive including in MCs and Langerhans cells, which was the same case for IL-1β (Marie et al., 2014), indicating the possible involvement of inflammasome and IL-1β in MC loss. Other studies reported that tissue levels of IL-22 and IL-17 in vitiligo lesional skin were significantly higher in comparison with controls. IL-22 and IL-17 have been found to regulate IL-1β production via caspase-1 activation, resulting in pyroptosis in vitiligo keratinocytes (Dong et al., 2017; Zhou et al., 2018). However, whether IL-22 or IL-17 triggers the damage of MC though pyroptosis has yet been clear.

Pyroptosis is claimed to occur most frequently upon infection with intracellular pathogens. Actually, researches on scattered vitiligo accompanied with viral infection have revealed the relevance between vitiligo and viruses (Erf et al., 2001; Iverson, 2000). Therefore, the role of pyroptosis is predictable in virus-induced vitiligo. Nevertheless, this hypothesis was challenged, as Wang, S. et al. (S. Wang et al., 2015) found that cytosolic poly (dA:dT), an analog of viral non-CpG dsDNA, caused the cleavage of caspase-8 and caspase-3 in MCs, in contrast to the caspase-1 activation. However, recent researches have reported that caspase-8 and caspase-3 were able to active GSDMD, GSDME as well as IL-1β and trigger pyroptosis as alternative ways in some contexts (Sarhan et al., 2018; Y. Wang et al., 2017). Thus, further studies on viral infection in MCs, especially GSDMD and GSDME activation as well as the observation of morphological features are required.

In summary, pyroptosis may act as an alternative form of cell death in vitiligo MCs in some specific situation such as virus infection, which needs to be further validated.

3.3 | Ferroptosis

Ferroptosis is a newly identified form of regulated cell death, characterized by increased level of iron and initial lipid peroxidation without the activation of caspases (Dixon et al., 2012). Morphologically, ferroptotic cells mainly suffer the blebbing of the plasma membrane, reduction in or vanishing of mitochondrial cristae, with the normal size nucleus and lack of chromatin condensation (J. Li, Zou, et al., 2020), remarkably distinct from apoptosis, necroptosis, and autophagic cell death.

Among various inducers of ferroptosis, oxidative stress plays an extremely vital role, which was proved by the apparently increased ROS and lip-ROS level (Dixon et al., 2012; Zhu et al., 2019). Polyunsaturated fatty acids (PUFAs) were found to be more vulnerable to ROS than monounsaturated fatty acids and saturated fatty acids in ferroptosis. Labile iron pool is necessary for PUFA oxidation by lipoxygenases in ferroptosis. Acyl-CoA synthetase long-chain family member 4 (ACSL4) is an enzyme involved in PUFAs metabolism, activating PUFAs and affecting the transmembrane activity. It is now believed that ACSL4 act as an important node that determines sensitivity versus resistance to ferroptosis, because neither RSL3 nor erastin, the two classical ferroptosis inducers, can set off Acsl4-null cells death (Doll et al., 2017; Yuan et al., 2016). Meanwhile, GPX4 has been identified as a core regulator and biomarker in ferroptosis (Friedmann Angeli et al., 2014; Zou et al., 2019). As a member of GPX family, GPX4 is a selenium dependent enzyme, catalyzing lipid peroxide reduction, which prevents the oxidation of membrane lipid components (Herbette et al., 2007) and the ferroptotic process. RSL3 directly inhibits the catalytic selenocysteine in GPX4 to prevent elimination of PUFA hydroperoxides, while erastin disturbs System Xc- and prevents the transport of cysteine into cells (Robert et al., 2014), so as to inhibit the synthesis of glutathione (GSH). GSH depletion leads to inactivation of GPX4 and activation of lipoxygenase, finally resulting in ferroptosis (Seiler et al., 2008).

Compared with keratinocyte and iron-rich hepatoma cell, MC expresses a relatively high level of bioavailable iron (Pelle et al., 2014). Upon external stimulation, such as UVB irradiation, the levels of ferrous iron and unsaturated fatty acids oxidation increase simultaneously in MCs (Jimbow, 1995; Memoli et al., 1997). Meanwhile, a spontaneous higher production of ROS and membrane lipoperoxidation was found in vitiligo MCs (Dell'Anna et al., 2007). VIT1/FBXO11, a vitiligo-related gene, alters the lipid content and composition in MCs (Y. Li et al., 2009), contributing to the lipid peroxides and cell death. Furthermore, it has been reported that System Xc- deficiency induced apparently ROS increase and appearance of lipid droplets in MCs, leading to non-apoptotic cell death (Zheng et al., 2016). Although the effect of GPX4 in vitiligo has yet been clear, a number of studies have shown that GPX is decreased both in serum and tissues of vitiligo patients (Xiao et al., 2016). Vitiligo MCs are thought to be more sensitive to oxidative stress due to their defects in antioxidant mechanisms, such as GPX (Yildirim et al., 2004). A research has reported that GPX1 polymorphism may be responsible for the decrease of GPX activity, which was involved in the susceptibility to vitiligo in Gujarat population (Em et al., 2007). Moreover, the analysis of the expression of GPX4 in different melanoma cell lines showed that the upregulation of GPX4 could protect melanoma cells from oxidative damage (Su et al., 2009).

Nrf2 is a widely known core factor involved in antioxidant response, as well as regulating cell proliferation and survival (Hirotsu et al., 2012; Paek et al., 2012). Hundreds of genes have been found to be involved in the pathophysiologic process of ferroptosis, most of which can thus far be transcriptionally regulated by Nrf2, including NQO1, solute carrier family 7 member 11 (SLC7A11), HO-1, ferritin heavy chain (FTH1), ferritin light chain (FTL), GCLC, GCLM, and GPX4 (Abdalkader et al., 2018; Bao et al., 2019; X. Li et al., 2020; H. Wang et al., 2019), making Nrf2 a critical modulator of ferroptosis. The proper activation of Nrf2 signal pathway also helps MCs to relieve the ROS and lipid peroxide (Jian et al., 2011; Mou et al., 2019). Conversely, impaired activation of Nrf2 and the downstream genes, such as NQO1, GCLC, GCLM, and HO-1, was thought to participate in the pathological process of vitiligo. Both tissue and serum levels of Nrf2 and its downstream proteins were found significantly lower in vitiligo, especially in lesions (Amin et al., 2013;

Natarajan et al., 2010). The presence of Nrf2/HO-1 usually ensures the timely removal of extra ROS and lack of HO-1 is thought to bring about poor tolerance for oxidative stress, which was claimed in vitiligo MCs (Jian et al., 2011) and certain ferroptotical cells (Adedoyin et al., 2017; X. Li et al., 2020). However, over-expression of HO-1 has been observed to promote oxidation reversely mainly through excessive formation of Fe2 + and thus result in ferroptosis (Villalpando-Rodriguez et al., 2019; Zukor et al., 2009). Considering that increased level of Fe2 + also causes ROS accumulation in MCs (Pelle et al., 2014), it is worthy of exploring whether HO-1 exerts bidirectional biological effects on MCs.

Taken together, the loss of MCs in vitiligo seems to be associated with ferroptosis. In view of the fact that selenium supplement is recommended as one of the treatment methods for vitiligo, which is consistent with the selenium dependence of GPX4 catalysis (Herbette et al., 2007), it is intriguing to investigate whether the level of GPX4 is altered and how ferroptosis may possibly be triggered in vitiligo MCs.

4 | SPECIAL FORMS OF CELL DEATH IN VITILIGO

4.1 | Anoikis

Anoikis is a distinctive type of apoptosis provoked specifically by loss of anchorage. Since firstly described by Schwartz (Meredith, Fazeli, & Schwartz, 1993), anoikis has proved to exit in various diseases, including cancer, neurodegenerative, and ischemic injury.

According to melanocytorrhagy hypothesis, detachment of living MCs from the basal membrane (BM) may result in the loss of MCs (Gauthier, Cario Andre, & Taïeb, 2003). One study suggested that adhesion to LM-1 through integrin α6β1 can represent a protective mechanism for MCs to withstand UVB damage, indicating that the impaired ability of biding to LM-1 via integrin may result in an altered UV vulnerability in vitiligo MCs through anoikis(Krengel et al., 2005). Later on, a comparative study of MC adhesion in stable and unstable vitiligo showed that in patients with unstable vitiligo, MCs were poorly attached to type IV collagen along with increased caspase-3 and greater Annexin V staining, whereas stable vitiligo MCs and control MCs were firmly adhered to type IV collagen (Kumar et al., 2011). Another study showed that NSV MCs had an intrinsic defect, which limited their adhesion in a reconstructed epidermis and increased their sensitivity to stimuli (Kumar et al., 2012). Meanwhile, one research found that the BM disappeared at some points in the biopsy specimens from stable vitiligo patients, suggesting altered microenvironment for difficult MC adhesion(Panuncio & Vignale, 2003). Moreover, either use of caspase inhibitors (Ivanova, van den Wijngaard, Gerzer, Lamers, & Das, 2005) or increasing adhesion (Krengel et al., 2005) has been claimed to reduce the death of vitiligo MC with adhesion defects in vitro.

TABLE 1 Different Types of MCs death in Vitiligo

Cell Death Pathway	Evidence in Vitiligo	Authors Comments	Vitiligo Literature Citations
Apoptosis	Low ratio of Bcl−2/Bax and elevated level of Fas in vitiligo MCs; Elevated expressions of IFN-γ, TNF-α and CXCL10 in vitiligo lesional skin	Supports intrinsic cell death and autoimmunity hypothesis	Kumar et al., 2012; Jimbo et al., 2019; Birol et al., 2010; L. Yang et al., 2015; Tulic et al., 2019.
Necrosis	MBEH-induced necrotic MCs death	Supports autoimmunity hypothesis	Hariharan et al., 2010
Autophagy and autophagic cell death	Aberrant autophagy level in vitiligo MCs	Supports degenerative theory and oxidative stress theory	Yu et al., 2019; X. Li et al., 2013; Raam et al., 2018.
Necroptosis	To be further validated		
Pyroptosis	Aberrant NLRP1 expression in vitiligo MCs; HVT involved in the SL vitiligo	Supports autoimmunity hypothesis	Jin et al., 2007; Marie, Kovacs, Pain, Jouary, & Dermatology, 2014; Erf et al., 2001.
Ferroptosis	Decreased GPX in serum and tissues of vitiligo patients; Lipoperoxidation of membrane in vitiligo MCs	Supports oxidative stress theory	Xiao et al., 2016; Em et al., 2007; Dell'Anna et al., 2007.
Anoikis	Limited adhesion ability of vitiligo MCs	Supports cell detachment theory	Krengel et al., 2005; Kumar et al., 2011; Kumar et al., 2012.
Phagoptosis	Elevated CRT expression in vitiligo lesional skin	Supports oxidative stress theory and autoimmunity hypothesis	Y. Zhang et al., 2014

Abbreviations: CRT, cell surface calreticulin; GPX, glutathione peroxidase; HVT, turkey herpesvirus; IFN-γ, interferon-γ; MBEH, mono-benzyl ether of hydroquinone; MCs, melanocytes; NLRP1, pyrin domain-containing protein 1; SL, smyth line; TNF-α, tumor necrosis factor-α.

Taken together, Anoikis is likely to play a role in the loss of vitiligo MC especially at the active phase, although not usually, namely noted in published articles.

4.2 | Phagoptosis

Phagocytosis used to be regarded as the secondary process after apoptosis or necrosis. Therefore, it was thought that phagocytes only ate dead cells or cells doomed to death. However, it is now clear that phagocytosis can execute death of viable cells, which has been referred to as primary phagocytosis, later called phagoptosis. The reversible exposure of "eat-me" signals, and/or the loss of "don't-eat-me" signals on the surface of a viable cell lead to phagoptosis and inhibition of phagocytosis prevents cell death (Brown & Neher, 2012). Up to know, phagoptosis has been claimed to be involved in various diseases, especially in neuronal loss. Imaging of inflamed glial–neuronal cultures illustrated microglia phagocytizing large numbers of apparently healthy neurons (Neher et al., 2011).

The best-characterized "eat-me" signal is the cell surface exposure of the phosphatidylserine (PS) (Dias-Baruffi et al., 2003). In healthy cells that are not activated, PS is found almost exclusively on the inner leaflet of the plasma membrane. Under oxidative stress, PS exposure was found to be activated in MCs (F. Yang et al., 2000). Cell surface calreticulin (CRT) is the second major "eat me" signal inducing phagocytosis of both apoptotic and viable cells via activation of lipoprotein receptor-related protein (LRP) on the phagocyte (Chao et al., 2010). Disruption of "don't-eat-me" signals, such as CD47 also results in phagoptosis of viable cells. One study found there was a positive relationship between the expression of CRT and lesion area in vitiligo patients, and CRT presented at higher levels in the active phase than in the stable phase (Y. Zhang et al., 2014). In vitro, they observed that CRT was markedly increased on MC surface after H2O2 stimulation and CD47-positive cells decreased simultaneously. Meanwhile, mononuclear cell and macrophage infiltration has been observed around the damaged MCs at the border between depigmented and normal skin (Panuncio & Vignale, 2003).

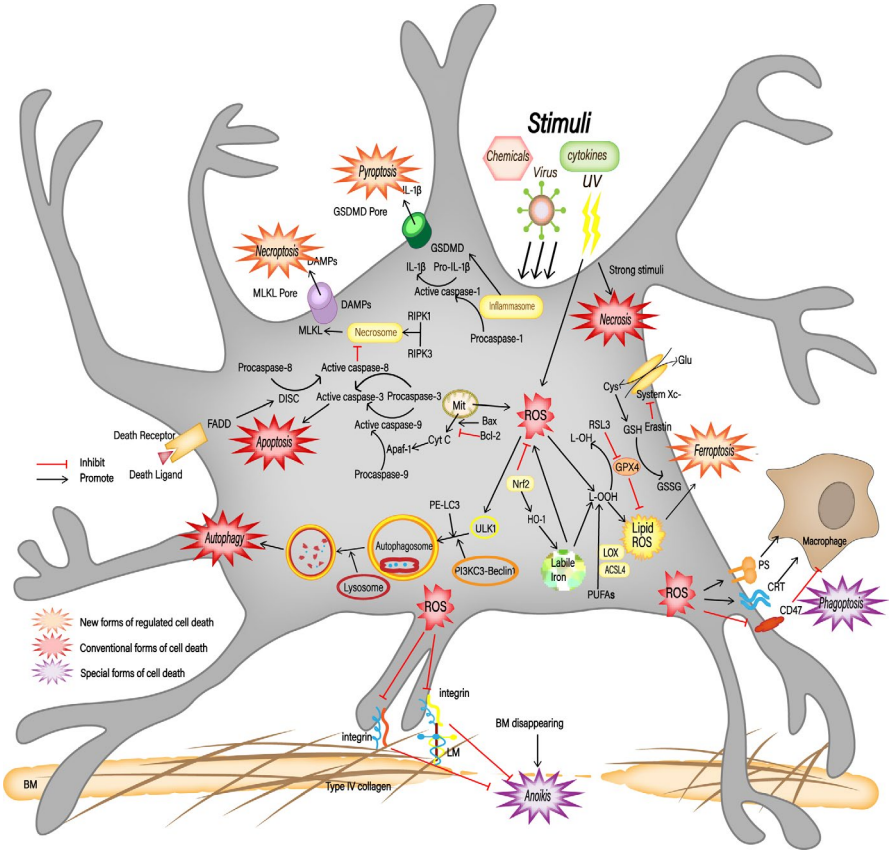

FIGURE 1 **Forms of MC death in vitiligo**. Seven forms of death, including apoptosis, necrosis, autophagy, necroptosis, pyroptosis, ferroptosis, phagoptosis, and Anoikis, are likely to participate in the pathogenesis of vitiligo. Mit, mitochondrion; ROS, reactive oxygen species; UV, ultraviolet; GSDMD, propyroptotic protein gasdermin D; DAMPs, damage-associated molecular pattern; BM, basal membrane; MLKL, lineage kinase domain-like protein; RIPK1, receptor-interacting protein 1; RIPK3, receptor-interacting protein 3; DISC, death-inducing signaling complex; FADD, death domain; Apaf-1, apoptotic protease activating factor-1; Cyt C, cytochrome c; PE-LC3, microtubule-associated protein 1 light chain 3 complex with phosphatidylethanolamine; ULK1, unc-51-like autophagy activating kinase 1; PI3KC3, class III phosphatidylinositol 3-kinase; HO-1, heme oxygenase-1; Nrf2, nuclear factor E2-related factor 2; LOX, lipoxygenases; ACSL4, Acyl-CoA synthetase long-chain family member 4; PUFAs, polyunsaturated fatty acids; Glu, glutamic acid; Cys, cysteine; GSH, glutathione; GSSG, glutathione (oxidized form); LM, laminin; PS, phosphatidylserine; CRT, cell surface calreticulin; System Xc-, glutamate/cysteine antiporter

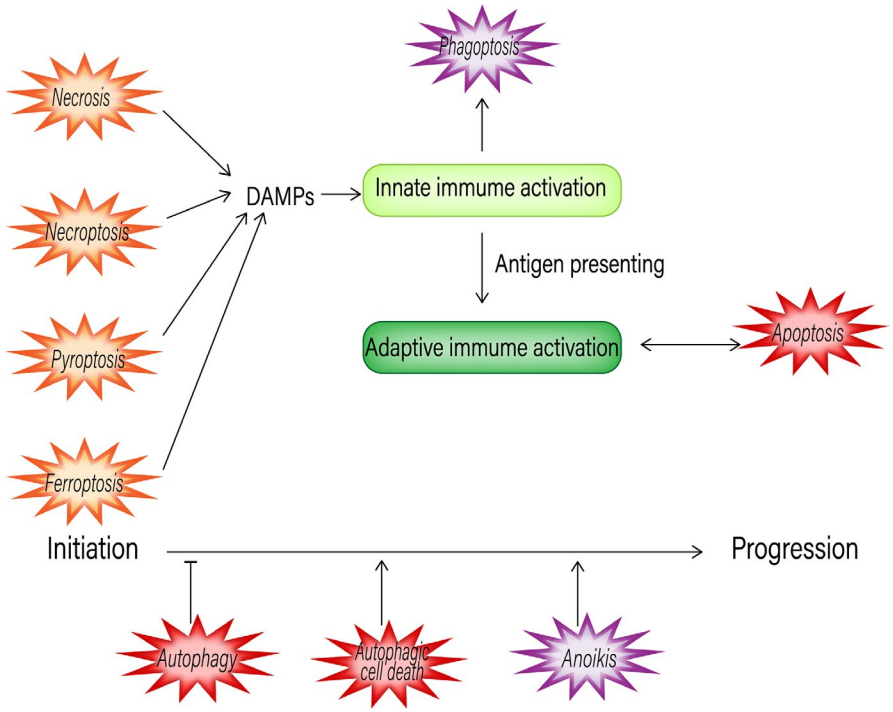

FIGURE 2 Hypothesis: roles of different forms of MC death in the initiation and progression of vitiligo. Necrosis, necroptosis, pyroptosis, and ferroptosis of MCs activate innate immune cells through the release of DAMPs. Autophagy facilitates the breaking of immune tolerance by working as autoantigen. Innate immune cells then present antigens and triggers adaptive immunity. With the recruitment of T lymphocytes, more MCs are induced to apoptosis during the progression of vitiligo. The infiltration of macrophages makes it possible for MC phagoptosis. Anoikis could occur in the active phase of vitiligo. MC, melanocyte; DAMPs, damage-associated molecular patterns

Considering no cell corpses are left to confirm the presence of phagocytes and phagoptosis in vivo and studies in vitro are usually conducted in the absence of phagocytes, whether phagoptosis participated in the loss of MCs in vitiligo is still unclear. Nevertheless, MCs seem to have the potential of altering "eat-me" and "don't-eat-me" signals. Further study with phagocyte–MC co-culture and phagocytosis inhibition is required to clarify the possible involvement of phagoptosis in the pathogenesis of vitiligo.

5 | CONCLUSIONS

At the very beginning, cell death instances can be operationally classified into "accidental" and "regulated," usually referring to necrosis and apoptosis. In recent years, various new types of RCD have been discovered, such as necroptosis, pyroptosis, and ferroptosis, which are thought to be the main players in the RCD subroutine during pathological processes (Galluzzi et al., 2015). Apoptosis has been most widely studied in vitiligo, yet the unique role of apoptosis is being challenged owing to the presence of dead MCs varied in shape and biomarkers. Moreover, histological studies have demonstrated the presence of inflammatory cells in vitiliginous lesions and marginal areas (Sharquie, Mehenna, Naji, & Al-Azzawi, 2004), inconsistent with the concept that the process of apoptosis was not accompanied by inflammation. Interestingly, features of dead MCs in certain published studies actually matched the new forms of RCD rather than apoptosis which was formerly claimed to be. In light of recent recognition of non-apoptotic forms of regulated cell death in vitiligo, it is conceivable that some, if not to say the majority, of these conditions may proceed through other non-apoptotic cell death paradigms (Table 1). Considering that oxidative stress plays a unique role in vitiligo, ferroptosis might take an unexpected role in MC loss, in spite that relevant research is still unavailable. Anoikis, as a special form of apoptosis, may help to optimize melanocytorrhagy hypothesis. Meanwhile, in view of the macrophage infiltration in perilesional area, phagoptosis may reinforce the mechanism of MC destruction in vitiligo. Coming to autophagy, it may either function as a catabolic process which prevents cell damage and promotes survival or kill MCs, namely autophagic cell death (Figure 1).

During the initiation and the progression of vitiligo, different forms of cell death may play varied roles. It is probable that intrinsic abnormalities and environmental stress induce NCD of MCs at the very beginning, which activates innate immune cells through the release of DAMPs. In contrast, autophagy may help to defend the exogenous stress, and however, when unsuccessfully, it may work as autoantigen to facilitate the breaking of immune tolerance. Innate immune cells might then present antigens and triggers adaptive immunity, accelerating the progress of vitiligo (Figure 2).

Research on different types of death in vitiligo MCs can be difficult. Firstly, very few MCs are present in specimens biopsied from depigment lesions, meaning that it will be extremely hard to capture the essence of MCs loss. Meanwhile, cells from normally pigmented skin of vitiligo patients showed reduced initial seeding and proliferation capacity compared to healthy adult human skin, making culturing of vitiligo epidermal MCs a tough task. Secondly, the dominant form of MC death may vary under different contexts, as vitiligo has proved to be a syndrome with multi-factorial etiology rather than a single entity and can be divided into different types clinically. Last of all, different forms of cell death may share similarities and be closely connected thus contribute to the outcome through their integrated effects.

Although arduously, it is vital to identify various forms of cell death that MCs undergo during vitiligo. Further researches delineating the mechanisms of above cell death forms will shed light on the mechanisms of MC loss and more importantly, pave the way for treatments not only to rescue MCs from death but also to reach durable repigmentation. Last but not least, it is noteworthy that MC death is disastrous for vitiligo but favorable for melanoma treatment. Extensive understanding of the multifaceted mechanisms of cell death and survival will help to identify resistance processes of melanoma and improve the tumor response to current therapy.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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