

Insights into Autophagic Machinery and Lysosomal Function in Cells Involved in the Psoriatic Immune-Mediated Inflammatory Cascade

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Abstract

Impaired autophagy, due to the dysfunction of lysosomal organelles, contributes to maladaptive responses by pathways central to the immune system. Deciphering the immune-inflammatory ecosystem is essential, but remains a major challenge in terms of understanding the mechanisms responsible for autoimmune diseases. Accumulating evidence implicates a role that is played by a dysfunctional autophagy-lysosomal pathway (ALP) and an immune niche in psoriasis (Ps), one of the most common chronic skin diseases, characterized by the co-existence of autoimmune and autoinflammatory responses. The dysregulated autophagy associated with the defective lysosomal system is only one aspect of Ps pathogenesis. It probably cannot fully explain the pathomechanism involved in Ps, but it is likely important and should be seriously considered in Ps research. This review provides a recent update on discoveries in the field. Also, it sheds light on how the dysregulation of intracellular pathways, coming from modulated autophagy and endolysosomal trafficking, characteristic of key players of the disease, i.e., skin-resident cells, as well as circulating immune cells, may be responsible for immune impairment and the development of Ps.

Keywords

Autoimmune · Psoriasis · Skin-resident cells · Circulating immune cells · Autophagy-lysosomal pathway

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1. Introduction

In combination with autophagy, lysosomal compartments have been recognized as cellular hubs involved in both adaptive and innate immune functions, and thereby, when dysregulated, they contribute to inflammatory and autoimmune diseases. Thus, therapeutic strategies aimed at providing improvement (as for lysosomal storage and neurodegenerative diseases) or alleviation (as for cancer and autoimmune diseases) of abnormal lysosomal action, depending on the cellular context, are a focus (Figure 1).

Lysosomes as a cellular signaling platform are at the crossroads of various intracellular pathways, especially when considering the autophagy-lysosomal pathway (ALP), lysosome-to-nucleus cross-talk, and calcium signal transduction, with key roles played by mammalian target of rapamycin (mTOR; a regulator of cellular homeostasis and protein synthesis), transcription factor EB (TFEB; a regulator of lysosomal metabolism and autophagy function), nuclear factor of activated T cells (NFAT; a regulator of T lymphocytes activation, differentiation, and anergy), and nuclear factor κ B (NF- κ B; a regulator of proinflammatory responses) (Feske et al. 2003; Medina et al. 2015; Pastore et al. 2016;

Carroll and Dunlop 2017; Hogan 2017; Song et al. 2017; Brady et al. 2018; Hayama et al. 2018; Bonam et al. 2019; Schober et al. 2019; Ballabio and Bonifacio 2020; Deretic 2021; Kimura et al. 2022; Nabar et al. 2022). Although the underlying mechanisms are far from being fully deciphered, it has been seen that the dysfunction of lysosomes, their defects in fusion with cellular cargo vesicles, and autophagy deficiency related to these phenomena are all commonly observed abnormalities in autoimmune diseases (Ge et al. 2015; Monteleon et al. 2018; Klapan et al. 2021).

Psoriasis (Ps), a common noncommunicable skin and/or joint disease, is currently regarded as an autoimmune condition, sharing many features with other autoimmune diseases, such as chronicity of clinical symptoms and long-term inflammation (Hawkes et al. 2017; Hwang et al. 2017; Raharja et al. 2021; Noor et al. 2022). At the molecular level, the involvement of a genetic background is visible, with the Ps gene loci overlapping with those of other autoimmune diseases (Hwang et al. 2017; Peeters et al. 2017; Marzano et al. 2018; Kunz et al. 2019). Another key hallmark found in Ps is the occurrence of autophagic disturbances, also detected across several immune-mediated inflammatory diseases in the affected cells (Lee et al. 2011; Douroudis et al. 2012; Sil et al. 2018; Wang et al. 2019b, 2020; Hailfinger and Schulze-Osthoff 2021b; Klapan et al. 2022). Currently, Ps is considered the outcome of an imbalance between interactions of adaptive and innate immunity components, represented predominantly by skin-resident

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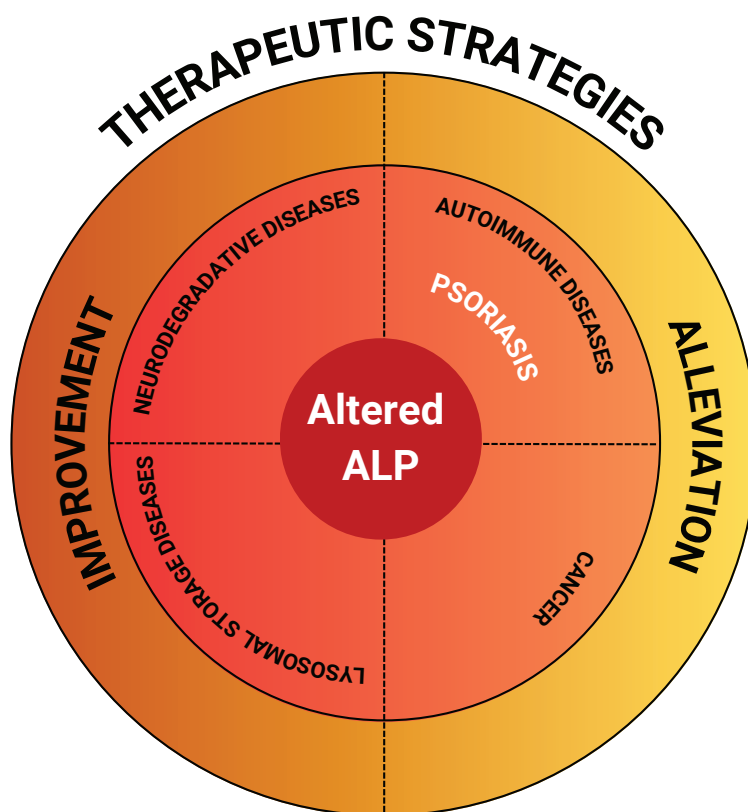


Fig 1. Therapeutic strategies targeting the dysfunctional ALP across different diseases. The figure serves as a comprehensive visual representation, elucidating the dual role of therapeutic approaches in modulating lysosomal action. The diversity of curative methods underscores the versatility and significance of targeting lysosomal functions in disease management. In lysosomal storage and neurodegenerative diseases, the goal is to improve lysosomal function, ensuring efficient cellular cleanup. In contrast, for cancer and certain autoimmune conditions such as Ps, the therapeutic objective is to alleviate or regulate heightened lysosomal activity that may contribute to disease pathology. ALP, autophagy-lysosomal pathway; Ps, psoriasis.

cells, systemic immune cells, and released cytokines. It must be taken into account that human skin maintains the immune cells passing through the tissue, named either recirculating/migrating memory cells or effector cells, as well as cells disconnected from the blood circulation, constantly remaining in the tissue and referred to as tissue-resident memory cells. This classification has been significantly advanced through research on Ps (Boyman et al. 2004; Gebhardt et al. 2009). In Ps, both skin cells, mainly epidermal keratinocytes (KCs) and skin-resident cells, as well as cells recruited from the circulatory system belonging to the acquired and innate immune systems, especially T lymphocytes (T cells), as predominant members of the Ps inflammatory loop are involved in complex feedback mechanisms (Lynde et al. 2014; Albanesi et al. 2018; Kunz et al. 2019; Moos et al. 2019; Abdallah et al. 2021; Ghoreschi et al. 2021). Successively appearing experimental findings, however, have referred to an altered suicidal fate in Ps mostly with respect to KCs, less often to immune cells, and are simultaneously trying to explain the contrasting results being reported between researchers (Mahil et al. 2016; Jeong et al. 2020; Yadati et al. 2020; Wang et al. 2021; Zhou et al. 2022). Meanwhile, discussion on impaired autophagic

machinery and lysosomal function is still missing in light of the complex condition of skin cells and the immune system. With a focus on this aspect, our review critically analyzes the recent research progress in clarifying the role of autophagic and lysosomal dysregulation in the Ps inflammatory cascade with both KCs and T cells as key players, as well as with other cells such as dermal fibroblasts (FBs), macrophages, dendritic cells (DCs), group 3 innate lymphoid cells (ILC3s), Langerhans cells (LCs), monocytes, natural killer cells (NKs), mast cells (MCs), vascular endothelial cells (VECs) and also B cells and neutrophils. Investigations into the possible effect of enhancing autophagic and lysosomal function on re-establishing the homeostasis of these cells in Ps have the potential to support novel treatment options for this immune-mediated inflammatory skin disease.

2. A snapshot on Autophagy and Lysosomal Changes

Autophagy is involved in maintaining cell homeostasis by removing or recycling non-functional components and reusing them for energy. Moreover, autophagy regulates the

secretory pathway of proinflammatory cytokines and cell development and activates the inflammasome (Harris et al. 2017; Ge et al. 2018). In this evolutionarily conserved catabolic process of intracellular material degradation, different from the ubiquitin–proteasome system (Dikic 2017), we can distinguish macroautophagy, chaperone-mediated autophagy, and microautophagy, which have different protein- and organelle-elimination pathways (Bento et al. 2016). The role of macroautophagy in inflammation and immunity is best understood and related to the subject discussed in this review, so it will be referred to as autophagy hereafter.

The autophagy process begins with the formation of a phagophore (also known as an isolation membrane), which sequesters the cytoplasmic components. The isolation membrane makes the platform for lipids required for phagophore elongation, which results in the formation of vesicles termed autophagosomes. Completed autophagosomes fuse with lysosomes to form autolysosomes, where the inner membrane and cargo are degraded by the enzymatic digestion pathway (Vega-Rubin-de-Celis et al. 2017).

In addition, the lysosome is also involved in the endolysosomal pathway, the main route for the uptake, processing, and clearance of cargo collected from the extracellular area (Luzio et al. 2007; Bento et al. 2016; Cullen and Steinberg 2018). The endolysosomal pathway begins with endocytosis, where the cell's plasma membrane invaginates and forms vesicles called endosomes. Newly formed endosomes, also known as early endosomes (EEs), are characterized by the presence of receptors and ligands internalized during endocytosis. These EEs mature into late endosomes (LEs). LEs are more acidic due to the action of proton pumps present in their membranes. The interaction between LEs and lysosomes in eukaryotic cells can occur through two distinct pathways: kiss-and-run and direct fusion. In the kiss-and-run pathway, the LEs transiently fuse with the lysosomes to exchange materials without fully merging their membranes. In the direct fusion pathway, the LEs and lysosomes fully syndicate, combining their membranes to form a hybrid organelle called a late endolysosome. This process involves the merging of their membranes, resulting in the mixing of their contents, including lysosomal enzymes and endocytosed cargo (Luzio et al. 2007; Cullen and Steinberg 2018; Jeger 2020). The autophagy and endolysosomal pathways are interconnected, known as the ALP. Autophagy can deliver damaged organelles to LEs for degradation, and lysosomal enzymes from the endolysosomal pathway can be used in autophagy to degrade autophagosome contents during autolysosome formation. Monitoring of the ALP relies on specific markers that help to distinguish respective structures (Figure 2). Consequently, for EEs, they are EEA1, Rab4, Rab5, RhoB, and transferrin, and for LEs, Rab7, Rab9, LAMP1, LAMP2, and M6-PR. LAMP1, LAMP2, β -galactosidase, Rab7, and TM7SF1 are displayed on lysosomes, while ATG12, DiRas3, LC3A-II, and LC3B-II are on autophagosomes. Lysosomal-associated membrane proteins 1

and 2 (LAMP1 and LAMP2) are expressed on lysosomes and LEs, but lysosomes lack M6-PR. LC3 co-localization with LAMP1 indicates the formation of autolysosomes. Microtubule-associated protein 1 light chain 3 (LC3, MAP1-LC3s) are structural proteins of autophagosomal membranes with three members, LC3A, LC3B, and LC3C, existing in two forms, LC3-I and its proteolytic derivative LC3-II (He et al. 2003; Drake et al. 2010). LC3-I is localized in the cytoplasm and, during autophagy, becomes conjugated to phosphatidylethanolamine to form the LC3–phosphatidylethanolamine conjugate LC3-II (LC3A-II and LC3B-II, also LC3C-II, respectively), which is recruited to autophagosomal membranes (Kabeya et al. 2000). Reduced amounts of LC3-I and, conversely, enriched levels of LC3-II indicate an enhanced autophagic flux. LC3 levels are used as a marker for autophagic flux, along with p62, the first selective autophagy receptor to be characterized, also known as a multifunctional stress-inducible scaffold protein SQSTM1 (Sequestosome 1) (Bjørkøy et al. 2005; Pankiv et al. 2007). An LC3-interacting region is required for contact with p62, leading to the delivery of p62 and its cargo to the autophagosome. Upon binding to its ligands, p62 acts as a modulator of autophagy, inducing autophagosome biogenesis, resulting in the formation on phagophore marked with LC3-II, NBR1, optineurin (OPTN), and p62 (Wang et al. 2017). Overall, the p62 protein serves as a multifunctional signaling hub with diverse roles in cellular processes. It can influence molecular pathways involved in inflammation, oxidative stress, cell proliferation, and cell survival. The versatility of p62 in autophagy regulation and cellular signaling makes it a critical player in maintaining cellular homeostasis and responding to stress and damage. Lysosomes are central to the regulation of cell death, operating at multiple levels. In unfavorable conditions, they initiate autophagy, which helps avoid cell death by breaking down factors that promote death, such as p53 upregulated modulator of apoptosis and receptor-interacting protein kinases-1 (RIPK1), and by maintaining mitochondrial balance. However, under extreme stress, lysosomal membrane permeability (LMP) increases, leading to the release of cathepsins, reactive oxygen species (ROS), and iron ions ($\text{Fe}^{2+/\beta+}$) (Serrano-Puebla and Boya 2018; Wang et al. 2018; Ballabio and Bonifacio 2020; Holland et al. 2020). This release can trigger various cell-death forms, including apoptosis, necrosis, pyroptosis, ferroptosis, and lysosome-dependent cell death (LDCD). For instance, cathepsins escaping from lysosomes can trigger apoptosis by activating BID proteins or BAX channels, while high levels of lysosomal cathepsin activities can cause cell necrosis by rapidly breaking down critical cell components. LDCD, as classified by the Nomenclature Committee on Cell Death, is characterized by initial LMP and catalyzed by cathepsins, with or without caspase involvement and mitochondrial outer membrane permeabilization. While autophagy is often a cell-protective process, it can also contribute to lethal signaling. For example, selective autophagy is known to promote ferroptosis by degrading ferritin and intracellular lipid droplets, leading to

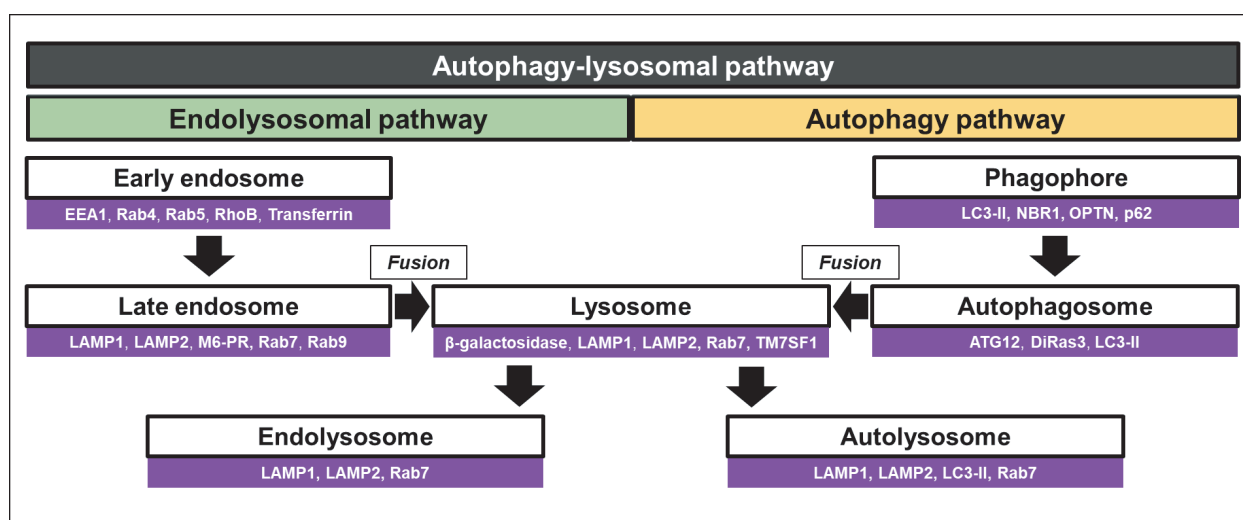


Fig 2. Schematic representation of the ALP, detailing its main stages and highlighting key structural markers. The diagram begins with the endolysosomal pathway and the initiation of autophagy, progressing through the phases of EE and phagosome formation, leading to their respective maturation into an endolysosome and autolysosome, and culminating in the degradation phase within those structures. This visual representation underscores the intersection and the interconnection between the endolysosomal and autophagic pathways, illustrating the complex interplay and convergence of these two critical cellular processes. Each stage is meticulously annotated with relevant markers, which are presented against a distinct purple background for easy identification. ALP, autophagy-lysosomal pathway; ATG12, autophagy-related protein 12; DiRas3, distinct subgroup of the Ras family member 3; EEA1, early endosome antigen 1; EE, early endosome; LAMP1, lysosomal-associated membrane protein 1; LAMP2, lysosomal-associated membrane protein 2; LC3, microtubule-associated protein1A/1B-light chain 3; M6-PR, mannose-6-phosphate receptor; NBR1, neighbor of BRCA1 gene 1, autophagy cargo receptor; OPTN, optineurin; p62, autophagy receptor protein, also known as a multifunctional stress-inducible scaffold protein SQSTM1 (Sequestosome 1); Rab4, Rab5, Rab7, Rab9, members of the Ras superfamily of small Rab GTPases; RhoB, Ras homolog gene family, member B; TM7SF1, transmembrane 7 superfamily member 1 protein.

iron buildup and lipid peroxidation (Galluzzi et al. 2018; Zhou et al. 2020). Although there are aspects yet to be fully understood, it is evident that lysosomes play a pivotal role in both preventing and inducing cell death, as well as in the final clearing stage of the cell death process (Amaravadi et al. 2016; Napoletano et al. 2019). Cross-talk between autophagy and apoptotic cell death is complicated and observed in various cell types, where regulators of apoptosis also function as regulators of autophagic activation and *vice versa*. Recent reports showed that the restriction of autophagy by the treatment of specific inhibitors for autophagic regulators or suppression of autophagy-regulatory pathways may promote apoptosis in corresponding cell and animal experiments (Fimia and Piacentini 2010; Mariño et al. 2014; Jiang et al. 2022). On the other hand, intervention by autophagy activator rapamycin or inhibitor 3-MA, both targeting at mTOR, accordingly induced activation or inhibition of apoptosis; intervention by MK-3903 or dorsomorphin, activator or inhibitor of 5'AMP-activated protein kinase (AMPK), received similar results (Chen et al. 2023). One of the main regulators of autophagy, BECLIN-1 may interact alternatively with either BCL-2, thus allowing apoptosis, or PI3KC3, thus promoting autophagy (Salwa et al. 2023). Dysregulation of UNC-like autophagy activating kinase 1 (ULK1) has been implicated in numerous diseases via regulation of autophagy. The level of this

key initiator of autophagy that induces the nucleation of the immature autophagosome, by phosphorylating the downstream BECN1 complex, and its phosphorylation at Ser556 were distinctively decreased in the epidermis from the lesional skin of Ps patients and in *in vitro* studies. ULK1 impairment by siRNA and SBI0206965, a selective ULK1 inhibitor, arrested cell proliferation and promoted apoptosis of KCs. Treatment with autophagy inhibitors chloroquine (CHQ) and 3-MA efficiently inhibited the proliferation of KCs as evidenced by the lower percentage of cells in the S phase (Qiu et al. 2021). Alterations and malfunctions in lysosomes have significant implications for the development of a wide range of human diseases. These lysosomal changes can disrupt normal cellular processes and contribute to disease progression. Targeting various aspects of lysosomal function, such as lysosomal acidification, cathepsins, membrane permeability and integrity, calcium signaling, mammalian target of rapamycin complex 1 (mTORC1) signaling, degradation of immune signals, TFEB, noncanonical autophagy, and vesicle movement, presents promising therapeutic strategies. Some drugs that focus on these targets have already been clinically tested and found to be effective and safe.

Lysosomal acidification impairment in the immunopathogenesis may offer new insights into the complex mechanisms underlying this autoimmune skin disorder. Targeting lysosomal

dysfunctions, particularly those affecting lysosomal acidification, has emerged as a potential therapeutic strategy for autoimmune diseases (Wang and Muller 2015; Bonam et al. 2019). The acidic nature of lysosomes is fundamental to both their structure and function. This low pH environment is essential for cancer cells to sustain their heightened metabolic activity and is linked to the excessive activation of immune cells in autoimmune disorders. Conversely, the cells in neurodegenerative and cardiovascular diseases often display compromised lysosomal acidification and autophagic processes. Accordingly, therapeutic approaches can be tailored based on the specific state of lysosomal acidification present in different diseases. Impaired acidification of lysosomes has been identified as a critical factor contributing to the development of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Lo and Zeng 2023). This impairment is often linked to genetic factors that affect the function of vacuolar-type ATPase and ion channels present on the membranes of these organelles. This issue is not only found in genetic cases but also in sporadic instances of neurodegeneration, although the exact mechanisms behind these sporadic cases are not yet fully understood. Recent research has shown that problems with lysosomal acidification can start early, even before the noticeable onset of neurodegenerative symptoms. The research group of Lo and Zeng (2023) highlights the importance of defective lysosomal acidification as an early sign of neurodegeneration, emphasizing the urgent need to develop advanced technologies for monitoring lysosomal pH for both research and clinical use. It also reviews emerging pharmacological treatments in the preclinical stage that can influence lysosomal acidification, including various small compounds and nanotechnology-based medicines, and their potential for being developed into treatments that specifically target lysosomes. The early detection of lysosomal dysfunction and the creation of treatments that can reinstate normal lysosomal function are seen as revolutionary steps in addressing neurodegenerative diseases. In addition, reduced autophagic processes and lysosomal functions are key contributors to age-related changes in cells, as identified by Cuervo et al. (2005). A particularly relevant area of study is the impact of lysosomal acidification dysfunction on the aging, or senescence, of mesenchymal stem cells (MSCs). As cells age, their lysosomal acidification is often compromised, resulting in an increased pH within the lysosome's lumen. Additionally, there is a decline in mitophagy, the process of autophagic degradation of mitochondria, which is crucial for cellular health. This decline is accompanied by an increase in the production of ROS. The accumulation of ROS further exacerbates cellular aging. ROS can induce LMP, resulting in the leakage of cathepsins, a type of protease normally confined within lysosomes. The release of these enzymes into the cell cytoplasm can trigger cellular senescence and apoptosis, a form of programmed cell death (Zhang et al. 2022a). Thus, the control of lysosomal acidification is emerging as a key factor in developing effective therapies

using MSCs, a concept underscored in Ruckenstein et al.'s (2014) study. Recognizing that an appropriate acidic environment in the lysosomes is essential for MSCs to function at their best and provide maximum therapeutic benefits, various approaches are being explored. They include genetic engineering, applications of traditional Chinese medicine, the use of nanomaterials, and the development of small molecule compounds, each offering a unique strategy to augment lysosomal acidification as a therapeutic intervention. These methods focus on targeting lysosomal proteins to improve the health and therapeutic potential of MSCs, especially to combat the effects of aging in these cells. Moreover, impaired lysosomal acidification, leading to reduced autophagic activity and diminished cellular function, plays a role also in nonalcoholic fatty liver disease and type 2 diabetes (Assali et al. 2019). This dysfunction in lysosomal acidification disrupts essential cellular processes and contributes to the development and progression of these conditions. Utilizing acid-activated acidic nanoparticles as a means to target lysosomal acidity presents an innovative approach to enhance lysosome function and autophagic activity in liver cells. This strategy shows promise for treating conditions where lysosomal dysfunction and impaired autophagic flux are contributing factors to the disease process in hepatocytes.

3. Impact of Autophagy and the Endolysosomal Apparatus on Ps

Unique autophagy and lysosomal machinery likely exist in human nonimmune skin cells, skin-resident immune cells, and those immune cells transmigrating between the blood and the skin (Feng et al. 2019; Hailfinger and Schulze-Osthoff 2021b; Klapan et al. 2022). A recent study has shown that impaired autophagy and dysfunctional lysosomal signaling may be involved in the immunopathogenesis of Ps (Bocheńska et al. 2019; Hailfinger and Schulze-Osthoff 2021b). Various stimuli, including starvation, hypoxia, calcium ions (Ca^{2+}), environmental stress, or pathogen-derived molecules, can induce autophagy (Harris et al. 2011; Leidal et al. 2018). Moreover, interleukin (IL)-2, IL-6, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α , involved in the pathogenesis of Ps, are also inducers of autophagy. This multistep process is regulated by autophagy-related (ATG) proteins encoded by autophagy-related (ATG) genes (Botbol et al. 2015; Vega-Rubinde-Celis et al. 2017). An extensive visual depiction elucidating the intricate molecular signaling pathways implicated in the autophagy machinery and lysosomal biogenesis within Ps-affected human cell is provided in Figure 3. The master regulator of autophagy function and lysosomal metabolism is TFEB, controlled by the intracellular level of Ca^{2+} and the activity of mTORC1, calmodulin (CaM), and calcineurin (CaN). mTORC1, a master controller of cell growth and metabolism, and mTORC2, which

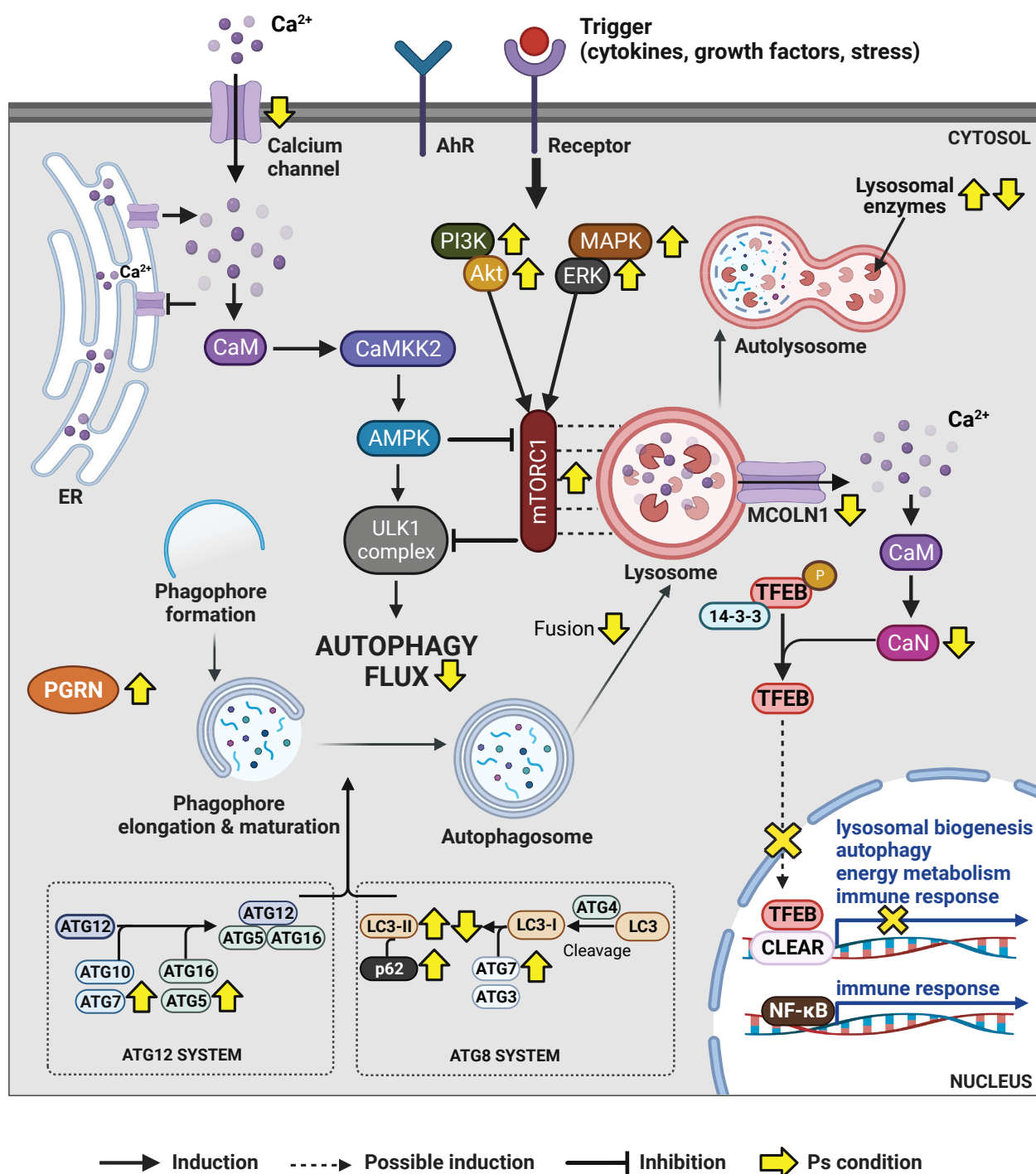


Fig 3. Molecular signaling involved in autophagy machinery and lysosomal biogenesis in Ps-affected human cell, particularly well known in KCs, and possible implications in Ps. Ca^{2+} is a prominent cell signaling mediator driving diverse cellular processes; it is absorbed from the extracellular space and/or mobilized from intracellular stores, such as the ER or lysosomes. Due to the ability to release the ions via dedicated channels, i.e., MCOLN1, in response to environmental cues, the lysosome is a key regulator of the cellular signaling pathway through mechanisms involving AMPK, mTORC1, CaM, and TFEB. Upon extracellular and ER Ca^{2+} flux, AMPK, transiently activated by CaM, partially inhibits mTORC1 in physiological conditions. Consequently, the mTORC1 effect on MCOLN1 and TFEB inhibition is diminished. MCOLN1 releases Ca^{2+} from the lysosome and activates CaM, which in turn triggers CaN. Activated CaN dephosphorylates TFEB, causing TFEB translocation to the nucleus, where it binds in the promoter region of genes encoding proteins with lysosomal and autophagy function (CLEAR element). Deregulation of molecular mediators, i.e., Ca^{2+} influx and intracellular

continued

Fig 3. Continued

signaling reflected in Ps and upon the Ps inflammatory cascade, affects the majority of cellular processes, especially well known in KCs. These alterations in Ps KCs amplify the inflammatory immune feedback loop that initiates and sustains chronic inflammation in Ps. The disturbed Ca^{2+} level in KCs diminishes AMPK action, transiently activates mTORC1, inhibits ULK, impairs an autophagic flux and reduces the fusion of autophagosomes with lysosomes. In addition, during Ps inflammation, cells are continuously activated in response to a strong admission of cytokines and growth factors on the PI3K/Akt and MAPK/ERK pathways, promoting the active form of mTORC1. The downstream mediators in these cellular signaling pathways that inhibit autophagic flux and the exact target in the autophagic process remain unknown. Autophagy is a multistep process of a phagophore elongation, an autophagosome creation (with the conjugation of ATG12 to ATG5 and the conversion of LC3 I to LC3 II), proceeded by an autophagosome fusion with lysosomes to form autolysosomes, where the degradation of intracellular content and the recycling of macromolecule components appear. It seems that the transiently active mTORC1 facilitates the induction of autophagy in an initial phase. However, it reduces the lysosomal metabolism and levels and enzymatic activities in later periods, resulting in autophagy inhibition. This latter inhibition may be related to mTORC1-dependent TFEB nuclear translocation reduction, causing downregulation of genes involved in lysosomal biogenesis, autophagy machinery, immune responses, and metabolism. In parallel, NF- κ B continuous activation associated with Ps inflammatory status determines the expression of immune response factors. Although the triggers and mediators, as well as the exact locations of their action during autophagy in Ps, are unknown, modulation by these factors of the autophagy process can contribute to immune-mediated inflammation and initiate or worsen the disease, with possible effects on proliferation and differentiation of KCs, epithelial barrier dysfunction, and inflammation. Created using BioRender.com. AhR, aryl hydrocarbon receptor; Akt, protein kinase B; AMP, antimicrobial peptide; AMPK, 5'AMP-activated protein kinase; ATG, autophagy-related protein; Ca^{2+} , calcium ion; CaM, calmodulin; CaMKK2, Calcium-calmodulin-dependent protein kinase 2; CaN, calcineurin; CLEAR, coordinated lysosomal expression and regulation; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; KC, keratinocyte; LC3, microtubule-associated protein 1A/1B-light chain 3; MAPK, mitogen-activated protein kinase; MCOLN1, mucolipin-1; mTORC1, mammalian target of rapamycin complex 1; NF- κ B, nuclear factor κ B; p38MAPK, p38 mitogen-activated protein kinase; PGRN, progranulin; PI3K, phosphoinositide 3-kinase; Ps, psoriasis; TFEB, transcription factor EB; ULK1, UNC-like autophagy activating kinase 1.

plays an important role in controlling cell proliferation and survival, are two protein complexes containing the mTOR catalytic subunit. While limited knowledge is available on the mTORC2 mechanistic action, extensive studies have shown that mTORC1 is a central signaling node with a dual role in controlling cell growth and metabolism, i.e., promoting anabolic pathways and inhibiting catabolic routes. In physiological conditions, upon intracellular and endoplasmic reticulum (ER) Ca^{2+} flux, AMPK, transiently activated by CaM, partially inhibits mTORC1. Consequently, the mTORC1 effect on the major lysosomal calcium channel of mucolipin transient receptor potential cation channel 1 (MCOLN1) and TFEB inhibition is somehow diminished (Wu and Eisenman 2021). MCOLN1 releases Ca^{2+} from the lysosome and activates CaM, which in turn triggers CaN. Activated CaN dephosphorylates TFEB, causing TFEB translocation to the nucleus, where it binds in the promoter region of the genes encoding proteins with lysosomal and autophagy functions (a transcriptional network of genes named coordinated lysosomal expression and regulation [CLEAR] element) (Hailfinger and Schulze-Osthoff 2021b). In turn, as for autophagy induction under environmental stress, low energy, starvation, hypoxia, Ca^{2+} , infection, and also in the case of the Ps inflammatory cascade, AMPK is even more activated and inhibits the mTORC1 via phosphorylation of tumor-suppressor proteins 2 and regulatory associated protein of mTOR. Thus, the level of mTORC1 is reduced, and its effect on MCOLN1 and TFEB markedly weakens. This promotes the release of calcium ions by MCOLN1, activating local CaM, and then CaN, which dephosphorylates TFEB (Wu and Eisenman 2021). Nuclear translocation of dephosphorylated TFEB initiates signal transduction pathways involved in many metabolic processes such as lysosomal

biogenesis and exocytosis, autophagy, lipid catabolism, energy metabolism, and immune responses (Settembre et al. 2011, 2013; Medina et al. 2015; Pastore et al. 2016; Slade and Puliniikunnil 2017; Brady et al. 2018; Scotto Rosato et al. 2019). This situation, associated with autophagy induction, persists for a certain period in the cell; however, in the long term, the deregulation of molecular mediators, i.e., Ca^{2+} influx and intracellular signaling, reflected among other things, upon Ps inflammatory cascade, affects the majority of the cellular processes. An abnormal Ca^{2+} metabolism via decreased capacitive Ca^{2+} influx (e.g., decreased MCOLN1 channel levels in Ps) and an increased cytosolic Ca^{2+} response to ATP, as well as enhanced secretion of antimicrobial peptides (AMPs), apparently upregulated at least in part as a result of epigenetic changes (e.g., hypomethylation of the S100A9 gene) are observed in Ps vs. the normal cell status. These alterations amplify the inflammatory immune feedback loop that initiates and sustains chronic inflammation in Ps. The disturbed Ca^{2+} level in the cell diminishes the AMPK action, activates mTORC1, inhibits ULK1, impairs an autophagic flux, and reduces the fusion of autophagosomes with lysosomes. In addition, during Ps inflammation, the triggered cells are continuously activated in response to a strong admission of cytokines and growth factors on the signaling pathways, promoting the active form of mTORC1 (Werner and Grose 2003; Belleudi et al. 2007; Mitra et al. 2012). Active mTORC1 is found on the surface of the lysosomes and inhibits the flux of Ca^{2+} from the lysosome into the cytosol through MCOLN1 and directly phosphorylates and inhibits the TFEB nuclear translocation. Inactive, i.e., phosphorylated TFEB interacts with 14-3-3 protein and becomes suspended in the cytoplasm. Thus, it has been concluded that the activity of

TFEB is regulated by mTORC1-mediated phosphorylation, defined recently as noncanonical mTORC1 signaling (Napolitano et al. 2022), which controls its nucleocytoplasmic shuttling. Certain stimuli that modulate guanosine triphosphatase Rag activity (Rag GTPase) induce selective mTORC1 regulation, reported as RagA/B-GTP and RagC/D-GDP active configuration of the signaling axis responsible for TFEB phosphorylation. Besides mTORC1, other kinases, including protein kinase B (Akt), extracellular signal-regulated kinase 2 (ERK2), serine/threonine protein kinase 3, protein kinase C β , and the cyclin-dependent kinases (CDKs) 4/6, are also known to be involved in the regulation of TFEB subcellular localization (Palmieri et al. 2017; Li et al. 2018; Puertollano et al. 2018; Yin et al. 2020). However, how the cell integrates and coordinates the roles of these protein kinases in the control of TFEB remains obscure. Referring to the above, the transcriptional network CLEAR controlled by the TFEB factor varies in different tissues and diseases and, in addition to genes involved in lysosomal biogenesis and autophagy, includes genes involved in lipid degradation and the control of immune and inflammatory responses. It appears that the transiently active mTORC1 facilitates the induction of autophagy in the initial phase. However, in later periods, it reduces the lysosomal metabolism and the levels and enzymatic activities of cathepsin (CAT)-D and CAT-L, resulting in autophagy inhibition. This later inhibition may be related to mTORC1-dependent TFEB nuclear translocation reduction, causing downregulation of genes involved in lysosomal biogenesis, autophagy machinery, immune responses, and metabolism (Vega-Rubin-de-Celis et al. 2017). In parallel, NF- κ B's and NFAT's continuous activation associated with the Ps inflammatory status determines the expression of immune response factors (Al-Daraji et al. 2002, 2009; Goldminz et al. 2013). Although the triggers, mediators, and the exact locations of their action during autophagy in Ps are unknown, modulation of the autophagy process by these factors can contribute to immune-mediated inflammation and initiate or worsen the disease, with possible effects on the proliferation and differentiation of KCs, epithelial barrier dysfunction, and inflammation (Dai and Hu 2015; Li et al. 2016; Sil et al. 2018; Yin et al. 2018; Jeong et al. 2020; Wang et al. 2020; Klapan et al. 2022). However, whether the regulation of other TFEB- and/or NFAT-mediated transcriptional programs (e.g., lysosomal metabolism, autophagy, and inflammation) also contributes to the Ps phenotype, resulting from changes in particular tissues and cells of the Ps body, i.e., nonimmune skin cells and skin-associated immune cells, as well as those recirculating, has yet to be determined in detail. However, accumulating evidence implicates the appearance of a modulated autophagic niche and endolysosomal trafficking in the immune-inflammatory ecosystem of Ps.

4. Epidermal KC and Dermal FB Fate with Respect to Autophagy and Lysosomal Administration in Ps

Most of the work to study the pathomechanisms of Ps, as well as analyzing autophagy and lysosome function, has been focused on nonimmune cells, especially on KCs and, to a lesser extent, on FBs. These respective nonimmune epidermal and dermal skin cells are considered cells with immune properties and functions, often named nonprofessional immune cells, and moreover, are no longer considered passive protection barriers but true innate immune cells (Pivarcsi et al. 2004; Bernard et al. 2012; Chieosilapatham et al. 2021). Indeed, they are capable of secreting cytokines, ILs, colony-stimulating factors, TNFs, and growth factors and are increasingly being recognized as an important part of the immune system. Still, in this review, they are consistently discussed as a separate group from immune cells.

The research group of Lee et al. (2011) first discovered that autophagy abnormalities in KCs lead to increased inflammatory cytokine production and cell proliferation, contributing to Ps development. They found that stimulating Toll-like receptor (TLR) 2/6 or TLR4 triggers the autophagy pathway and increases p62 expression in KCs through NADPH oxidase (NOX)-dependent generation of ROS. The induction effect of TLR2/6 on p62 expression and autophagy requires the involvement of two components in the TLR signaling pathway, i.e., myeloid differentiation primary response protein 88 and TNFR-associated factor 6 (TRAF6). These adapter proteins play critical roles in transducing signals from TLRs and other immune receptors to activate downstream molecular pathways, including NF- κ B. Inhibiting autophagy further enhances the expression of cathelicidin/LL-37 and p62 accumulation. Additionally, suppressing p62 *via* RNA interference reduces NF- κ B activation, inflammatory cytokine production, cathelicidin expression, and KCs proliferation. This study emphasized the importance of autophagy and p62 in managing cutaneous inflammation in Ps. However, the report highlights that the results should not be taken at face value, and the role of p62 in autophagy regulation requires careful examination. Overexpression of p62 does not necessarily imply autophagy induction alone; it could also indicate autophagy inhibition, which needs to be verified by concurrent upregulation of LC3-II, another autophagy marker (Lee et al. 2011; Li et al. 2016). Indeed, a potential link between Ps and autophagy marker LC3 with lower skin expression in patients than in control was reported (Nada et al. 2020). Likewise, it was shown to be absent from all the epidermal layers in the skin of Ps patients (Akinduro et al. 2016). In contrast, a recent study showed increased levels of two LC3 isoforms, LC3A and LC3B, in the Ps epidermis. Moreover, LC3B was present and distributed through all layers of the epidermis in both lesional and nonlesional normal skin of Ps

subjects (Klapan et al. 2021; Wang et al. 2021). Therefore, whether LC3 is upregulated or downregulated in inflammatory skin diseases remains unclear. Interestingly, the report by Sun and collaborators showed that the overexpression of psoriasin (S100A7) reversed the increase of LC3-II production in the presence of lipopolysaccharide in KCs, suggesting the inhibitory effect of S100A7 on autophagy, which might be somewhat relevant to the promotion of inflammation by psoriasin (Sun et al. 2014). Subsequently, newer data have indicated that the increased epidermal expression of p62 in KCs results in the upregulation of the potent proinflammatory cytokine IL-36 in these cells and promotes neutrophil infiltration (Yin et al. 2018; Salazar et al. 2020). High expression of the essential proteins for autophagosome elongation, including ATG5 and ATG7, was also found in Ps skin. However, KCs from the same tissue had decreased expression of lysosomal proteases. Altered levels of lysosomal enzymes and ATG proteins confirm that autophagy can be dysregulated during inflammation, as the short-term treatment of KCs with TNF- α increased their autophagic capacity (Klapan et al. 2021). In addition, according to this report, in Ps biopsies as well as KCs with long-term exposure to TNF- α , not only a reduced level and activity of cathepsins, i.e., CAT-D and -L, but also decreased fusion of autophagosomes with lysosomes together with increased autophagy flux were observed. The accumulation of p62 in these conditions indicated that the cargo handling was impaired despite the augmented initiation of autophagosome formation. In other words, while autophagosomes could form and capture the cellular cargo, the clearance and degradation of that cargo in the lysosomes were hindered or delayed. It was concluded that this impaired autophagic flux can lead to the buildup of p62 and its associated cargo, which can be detrimental to cellular homeostasis. In addition to p62 function as a cargo receptor for autophagy, the protein can also activate proinflammatory transcription factors, such as NF- κ B and nuclear factor erythroid 2-related factor 2 (NRF2) (Sánchez-Martín et al. 2019). Therefore, the increased stabilization of p62 owing to impaired lysosome-dependent autophagy, as observed by the Klapan group (2021), can promote the activation of proinflammatory transcription factors such as NF- κ B and NRF2 in Ps. This activation can trigger the production of proinflammatory cytokines, which are a hallmark of Ps (Klapan et al. 2021). In turn, Mahil et al. (2016), in their contribution, have already reported a connection between skin inflammation and autophagy, as evidenced by the lack of functional autophagy regulator AP1S3, a component of the activator protein 1 (AP-1) complex, in pustular Ps (Mahil et al. 2016). The genetic variants of *AP1S3* that lead to defective autophagy and elevated p62 in KCs resulted in an inflammatory cascade with increased NF- κ B activation and the secretion of IL-1 β and IL-36 proinflammatory cytokines. It is worth noting that a study by Douroudis et al. (2012) had linked the single nucleotide

polymorphisms in the *ATG16L1* gene, coding for another KC autophagy regulator, to Ps susceptibility. Wang et al. (2021) demonstrated a significant positive correlation between functionally active autophagy and Ps severity. They showed that an autophagy-dependent unconventional secretory pathway (autosecretion) involving ATG5 and Golgi reassembly stacking protein 2 increases psoriasiform KC inflammation (Wang et al. 2021). These events might contribute to disturbances in the epithelial barrier and parakeratosis (Hailfinger and Schulze-Osthoff 2021b; Klapan et al. 2021). The work of the Monteleon group and that of others demonstrated that the compromised nucleophagy due to defective ALP in differentiating KCs might be linked to the development of parakeratosis in Ps skin (Akinduro et al. 2016; Monteleon et al. 2018). In addition, Ps skin revealed reduced expression of the *PPP3CA* and *PPP3CB* genes (encoding CaN subunits) and overexpression of the *mTORC1* gene in most Ps patients (Balato et al. 2014; Bocheńska et al. 2019). In physiological conditions, lysosomal acidification influences the localization and activity of mTORC1. The skin-specific deletion of *MTOR* and subsequent disruption of mTOR signaling demonstrate the importance of this pathway in various aspects of skin morphogenesis and maintenance (Monteleon et al. 2018). In the Ps inflammatory environment, the mTORC1 cascade was aberrantly activated in all the epidermal layers (Buerger 2018). Continuous kinase mTORC1 hyperactivity contributed to abnormal proliferation in the basal layer, defective maturation and differentiation of the suprabasal KCs, senescence-like growth arrest, and resistance to apoptosis. The mechanisms of how mTORC1 signaling controls skin homeostasis and contributes to inflammatory skin diseases, such as Ps, are broadly discussed in the literature (Mitra et al. 2012; Buerger 2018; Patel et al. 2018; Varshney and Saini 2018; Mahanty et al. 2019; Jeong et al. 2020). Special attention has been drawn to the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK)/ERK molecular pathways, with their involvement in the pathogenesis of this disease through autophagy dysregulation and induction of the transcription of anti-apoptotic genes via NF- κ B (Tang et al. 2021). Both PI3K/Akt and MAPK/ERK signaling pathways are upregulated in Ps (Johansen et al. 2005; Yu et al. 2007; Zhang and Zhang 2019; Mercurio et al. 2021; Li et al. 2022). Studies have shown that the aryl hydrocarbon receptor (AhR)-modulated autophagy in human KCs can trigger molecular pathways, such as p65NF- κ B and p38 mitogen-activated protein kinase (p38MAPK), and this, in turn, affects the inflammatory response in the skin (Kim et al. 2020). Several other reports have shown that the Ps skin differs from normal skin in the activity level of lysosomal hydrolytic enzymes and membrane proteins (Johansen et al. 2007; Dombrowski et al. 2011; Salskov-Iversen et al. 2011). It has been reported that modulation of autophagy and lysosomal function can affect the intensity of inflammation in Ps, as

increased expression of progranulin (PGRN), encoded by the *GRN* gene and being under the control of TFEB, was noted in Ps patient's serum and lesions (Huang et al. 2015; Paushter et al. 2018; Farag et al. 2019). PGRN plays an important role in lysosomes, as it binds directly to and acts as a chaperone of at least two lysosomal enzymes, i.e., CAT-D and β -glucocerebrosidase (Valdez et al. 2017; Zhou et al. 2017, 2019). Thus, it can be both anti-inflammatory and proinflammatory. In mouse inflammatory arthritis models, PGRN antagonizes TNF- α and exhibits anti-inflammatory activity (Tang et al. 2011; Liu and Bosch 2012; Lan et al. 2021). Patients with Ps showed a negative correlation between the PGRN/TNF- α ratio and disease severity (Huang et al. 2015). Further, another research aiming to investigate the relationship between serum levels of PGRN and TNF- α in relation to the activity of *Ps vulgaris* was announced (Sheir et al. 2022). In turn, the study reported by Tian et al. (2016) focused on exploring how PGRN influences inflammation and autophagy in HaCaT cells. Their findings revealed that PGRN is significantly overexpressed in Ps lesions and in HaCaT cells under inflammatory conditions. They observed that suppressing PGRN led to increased levels of inflammatory cytokines such as COX-2, IL-1 β , IL-6, iNOs, and MCP-1. Additionally, the silencing of PGRN resulted in elevated levels of the autophagy-related genes coding for p62 and decreased levels of LC3-II and Atg7 in HaCaT cells (Gunes et al. 2022). Interestingly, these elevated levels of PGRN did not show a significant correlation with various clinical characteristics of Ps, such as the presence of joint and nail involvement, the Psoriasis Area and Severity Index scores, the duration of the disease, or the age at which the disease onset occurred. The specifics of the relationship regarding PGRN and autophagy, particularly in the context of specific conditions such as Ps, is however not fully understood or extensively studied yet. Further studies to explore these relationships more in depth are therefore highly recommended. This might include experimental research to directly investigate how PGRN influences autophagy in Ps, as well as clinical studies to understand the implications of this relationship for disease treatment and prognosis. Furthermore, Ps subjects had elevated levels of CAT-S, the main protease that cleaves and activates IL-36 γ , a potent inflammatory cytokine strongly associated with Ps (Schönefuß et al. 2010). The modulation of the ALP in immune cells may thus lead to the augmentation of inflammation in Ps. The outcomes of all this research are, however, generally contradictory as sometimes the activity of these enzymes and membrane protein levels increase, whereas a decrease was observed in other studies. While our recent study reported an increase in LAMP1 protein levels in Ps skin lesions (Bocheńska et al. 2019), the research of Xue et al. (2022) has shown a downregulation of LAMP1 protein in psoriasis-treated normal human KCs or immortal HaCaT cells. The discrepancy in these findings could be attributed to several

factors, i.e., Ps models, proinflammatory milieu, detection methods, disease stage, and tissue source. It is assumed that modular synthesis or altered activity of some lysosomal enzymes in the epidermal cells can lead to hyperproliferation, followed by a decrease in KC differentiation and changes in the cells of the dermis, which is typical for Ps. This results in the modulation of the inflammatory response (Li et al. 2016; Hailfinger and Schulze-Osthoff 2021a).

While the study of autophagy and lysosome function in Ps has predominantly focused on KCs, virtually no research is dedicated to understanding these mechanisms in dermal FBs. The cells are important regulators in Ps skin (Arasa et al. 2015; Gubán et al. 2016; Gęgotek et al. 2020), and some of the latest results indicated that their enhanced inflammatory phenotype depends on altered zinc finger protein 36 (ZFP36) family levels (Angiolilli et al. 2022). The study showed that reduced expression of ZFP36 members in Ps dermal FBs contributed to their inflammatory phenotype. ZFP36 proteins are RNA-binding proteins with mRNA-degrading properties encoded by immediate-early genes downstream of MAPK and mTORC1/2 signaling, otherwise involved in the ALP in Ps. Generally, considering the role of FBs in the skin and their potential involvement in immune regulation and inflammation, it becomes crucial to explore the mechanisms of autophagy-lysosomal signaling in these cells in the context of Ps. Investigating how altered autophagy and lysosome function in FBs may impact the inflammatory microenvironment can provide a more comprehensive understanding of Ps pathogenesis.

5. Immune Cell Fate with Respect to Autophagy and Lysosomal Administration in Ps

Dermal resident immune cells, such as DCs, LCs, macrophages, MCs and T cells, as well as immune cells circulating and recruited from blood and lymph vessels to the skin during Ps inflammation, such as T cells, macrophages, DCs, ILC3s, LCs, monocytes, NKs, MCs, VECs, B cells, and neutrophils, matter in Ps immunopathology. Therefore, it is worth paying attention to the impact of impaired autophagy and dysregulated lysosomal function in these groups of immune cells.

Initiation of potent adaptive or innate immune response is based on an intricate interplay between autophagy and cytokines effect (Saitoh et al. 2008; Deretic and Levine 2009). Even though T helper cells (Th)2-associated IL-4 and IL-13 inhibit autophagy, IL-1 released, i.e., by KCs, provokes this process (Harris et al. 2007; Shi and Kehrl 2010). Autophagosomes, in turn, regulate the processing and release of IL-1 β , which induces IL-23 secretion by DCs (Harris et al. 2008, 2011) and prompts the differentiation of Th17 cells (Stockinger et al. 2007; Chung et al. 2009), which might be crucial for the Th1/Th17 balance disturbance in inflammatory disorders, indicating a connection between

dysregulated processing and release of IL-1 cytokines with alterations in the autophagic process. Consideration of the role of autophagy in T cell differentiation is based on studies revealing the role of proinflammatory cytokines, including IFN- γ , IL-1, IL-2, IL-6, and TNF- α , in the induction of autophagy, and anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, in autophagy inhibition (Li et al. 2006; Kiyono et al. 2009; Liang et al. 2012; Harris 2013; Deretic and Levine 2018). The degree to which CD4⁺ T cells exploit this process for differentiation and function varies between each subset but is possibly associated with cytokine signaling pathways and individual lineage metabolic phenotypes. Th1 cells lacking autophagy activity display defects in IL-2 and IFN- γ production (Hubbard et al. 2010) without reported T cell receptor (TCR) signaling deficiencies. This suggests that autophagy may be required for T cell function and differentiation capacity. On the contrary, autophagy seems to have an inhibitory effect on the proliferation and differentiation of Th2 and Th9 cells (Kabat et al. 2016; Benoit-Lizon et al. 2018).

Signaling through mTORC1 and mTORC2 specifically regulates the differentiation of CD4⁺ T cells. Th1, Th9, and Th17 lineage development is regulated positively by mTORC1, while Th2 development requires mTORC2 activity (Lee et al. 2010; Delgoffe et al. 2011). Both mTORC1 and mTORC2 negatively regulate regulatory T (Treg) cell differentiation. Suppression of mTOR with rapamycin favors the generation of Treg cells *in vitro*, even in the presence of Th17-polarizing cytokines (Kopf et al. 2007). Loss of mTORC1 in T cells increases the production of Treg but not Th1, Th17, or Th9 cells upon activation (Delgoffe et al. 2009). At the same time, overactivation of mTORC1 impairs the suppressive function of Tregs, which revokes naïve T cell quiescence and promotes Th9 lineage development. Overactivation of mTORC2 promotes Treg instability and impairs the Treg-mediated suppression of Th1 differentiation, while loss of mTORC2 does not affect Treg function but reduces Th1 differentiation (Wei et al. 2016). Th17 subset development requires the Ca²⁺/CaM-dependent protein kinase IV, which induces IL-17 expression by interacting with Akt and enhancing Akt/mTORC1 activity (Koga et al. 2014). Kovacs et al. (2012) observed that Beclin-1 deficiency in CD4⁺ T cells results in defective autophagy, which preferentially promotes Th1 apoptosis compared to Th17 cells, and the blockade of autophagy can suppress cell death in the Th2 lineage. Considering Ps as a disease characterized by a Th cell imbalance, autophagy might be a significant process since it also decreases Th17 differentiation. It is unlikely that Ps is caused primarily by an autophagy defect or that lysosomal interferences are the result of Ps. However, Hirai et al. (2013) indicated the meaning of a lysosomal enzyme, i.e., CAT-K, in the immunopathogenesis of Ps and its role in the development of Ps lesions by the activation of Th17 cells. The magnitude of steps involved in the autophagy machinery and its regulatory mechanisms are evolutionary conserved

across eukaryotic cells. Commonly, an enhanced mTORC1 kinase activity results in a reduction in autophagy. On the other hand, it is known that T cells become activated even if both mTORC1 kinase and the level of autophagy are increased simultaneously, suggesting that autophagy in T cells also must be generated independently of mTORC1 (Botbol et al. 2015; Park et al. 2023). Indeed, some studies documented that autophagy can be induced in CD4⁺ T cells *via* the pathway of the common cytokine receptor γ -chain, also known as the IL-2 receptor subunit γ (Jonchère et al. 2013; Botbol et al. 2015). It is worth emphasizing the role of IL-2 as one of the cytokines produced as a result of T cell activation that is crucial for sustained T cell proliferation and survival. This pathway of autophagy promotion is not well understood. Still, it is likely mediated by Janus kinase 1/3 and signal transducer/activator of transcription proteins, and it might operate independently of active mTOR kinases (Dowling et al. 2018). Given that CD4⁺ and CD8⁺ T cells are the most prevalent subpopulations of lymphocytes in the pathogenesis of Ps, it is interesting that the stimulation of the TCR in these cells results in an increased level of autophagy (Li et al. 2006; Matsuzawa et al. 2015; Mocholi et al. 2018; Murera et al. 2018). Although not described in the context of Ps, it is worth noting that several studies have reported that pharmacological or genetic inhibition of autophagy affects proliferation in CD4⁺ T cells (Pua et al. 2007; Hubbard et al. 2010). T cells lacking essential autophagy genes, i.e., *ATG3*, *ATG5*, *ATG7*, *Beclin-1*, or *VPS34*, showed reduced proliferative responses to TCR stimulation that could not be overcome by CD28 or IL-2 receptor signaling (Li et al. 2006; Pua et al. 2007; Kovacs et al. 2012; Willinger and Flavell 2012). Deletion of *ATG3*, *ATG5*, or *ATG7* genes also resulted in increased apoptosis (Hubbard et al. 2010), which confirmed the concept of autophagy-controlled T cell stability and function (Wei et al. 2016) and, therefore, its significance in the development of autoimmune and inflammatory disorders. Moreover, the deletion of *ATG3*, *ATG5*, or *ATG7* caused the expansion of ER compartments with increased calcium stores that could not be adequately depleted, resulting in defective calcium influx inside cells (Jia and He 2011; Jia et al. 2011). Th lymphocytes in a mouse model with *ATG7* deletion showed a decreased level of autophagy, impaired IL-2 and IFN- γ production, and defective proliferation after T cell activation (Hubbard et al. 2010). Studies in mouse models deficient in *Vps34* or *ATG* proteins displayed reduced numbers of T cells, presumably due to the regulation of cell survival and apoptosis following autophagy-related alterations (Pua et al. 2007; Willinger and Flavell 2012; Parekh et al. 2013). The expression of LC3 was also increased after TCR stimulation (Botbol and Macian 2015; Bronietzki et al. 2015). Autophagy deficiency in T lymphocytes contributes to the selective degradation of CDK inhibitors (such as CDKN1B) and protein tyrosine phosphatase nonreceptor type 1, which decrease TCR responses and inhibit cell cycle progression (Jia and He 2011; Jia et al. 2015; Mocholi et al. 2018). In relation to $\gamma\delta$ T cells, autophagy deficiency in

psoriasiform KCs ameliorated imiquimod (IMQ)-induced skin lesions in *Krt14Cre/+ -atg5^{ff}* mice accompanied by a reduction in the number of IL17A-producing $\gamma\delta$ T cells (Wang et al. 2021). Studies with a HeLa^{TFEB-GFP} cell line showed that FK506 and cyclosporin A (CaN inhibitors) reduce TFEB nuclear translocation during starvation. In the same model, constitutive CaN activation induced TFEB translocation in normally nourished cells and encouraged the expression of TFEB-dependent genes. Both cell starvation and CaN overexpression promoted NFAT nuclear translocation (Medina et al. 2015). Furthermore, TFEB binds to CaN at a similar region as NFAT, but the binding of NFAT to CaN is stronger than that of TFEB (Song et al. 2017; Schober et al. 2019).

Macrophages are among the major immune cells that penetrate Ps skin and are present in the peripheral blood of affected people. They accumulate in the dermis and epidermis, contributing to the inflammatory infiltrate observed in Ps (Marble et al. 2007; Fuentes-Duculan et al. 2010; Golden et al. 2015; Nguyen et al. 2018). Macrophages in Ps adopt a proinflammatory phenotype (M1-like phenotype), characterized by the production of various cytokines such as IL-1, IL-23, TNF- α and inflammatory mediators, i.e., ROS, which drive the inflammatory response and contribute to the maintenance of Ps lesions (Wang et al. 2019a; Kamata and Tada 2022). Autophagy was shown to promote the polarization of macrophages toward the M2 phenotype, also known as the anti-inflammatory or tissue-repairing phenotype. M2 macrophages are involved in tissue remodeling, immune regulation, and the resolution of inflammation (Jacquel et al. 2012; Liu et al. 2015; Germic et al. 2019). The involvement of macrophage autophagy in Ps inflammation is unknown.

DCs, representatives of antigen-presenting cells (APCs), produce pivotal proinflammatory cytokines, i.e., IL-12, IL-22, and TNF- α and are the key regulators for the IL-23/Th17 pathway (Jariwala 2007). Numerous studies suggest that autophagy in APCs is involved in regulating T cell responses via major histocompatibility complex (MHC) I and II pathways (Dengjel et al. 2005; Schmid et al. 2007; Kasai et al. 2009; Wenger et al. 2012; Mintern et al. 2015; Loi et al. 2016; Merkley et al. 2018). Merkley et al. (2018) described that autophagic defects in APCs may induce the secretion of IL-1 β and IL-23, reinforcing the process of naïve T lymphocyte differentiation into Th17 cells (Merkley et al. 2018; Feng et al. 2019). In response to IL-1 β and IL-23, ILC3s are also activated, which are important sources of proinflammatory cytokines (Bernink et al. 2013; Villanova et al. 2014; Ward and Umetsu 2014; Bugaut and Aractingi 2021).

LCs are predominant DCs in the epidermis, characterized by the expression of langerin (CD207), a lectin receptor involved in antigen presentation to T cells (Hunger et al. 2004), exposed only in skin-resident LCs (Valladeau et al. 2000). Diverse data declare the association of monocyte-derived Langerhans-like cells (MoLCs) and monocyte-derived dermal DCs (MoDCs) with Th17 expansion in Ps (Singh et al. 2016).

In MoLCs activated by IL-1 β and MoDCs activated by CHQ, an antimalarial drug and autophagy inhibitor, secretion of IL-23 and IL-6, respectively, was enhanced. Moreover, CHQ augmented the release of IL-17A by CD4⁺ T cells, potentially shifting the T cell response from Th1 to Th17. Intriguingly, bafilomycin A, another late-stage autophagy inhibitor, induced secretion of levels of IL-23 comparable to treatment with CHQ, contrary to no effect observed for the early-stage autophagy inhibitor, PI3K inhibitor 3-methyladenine (3-MA), indicating that the restriction of cytokine release is associated with the late phase of autophagy or inhibition of lysosomal activity. This result was supported by the increased levels of autophagy marker LC3A-positive vesicles after CHQ treatment and the decreased levels when treated with 3-MA in MoLCs and MoDCs. The presence of CHQ-upregulated levels of p62 in MoLCs was also observed. p62 partakes in IL-1 β signaling through TRAF6, with an increased expression upon CHQ treatment. TRAF6 regulates numerous signaling molecules, i.e., MAPK with enhanced phosphorylation in MoLCs cultured with CHQ; this late-stage autophagy inhibitor regulates IL-23 release, which occurs in a p38-dependent manner (Said et al. 2014). Administration of the nonselective beta-adrenoceptor (ADRB) antagonists (β -blocker) with lysosomotropic nature propranolol is associated with the induction, maintenance, and aggravation of Ps-like skin inflammation (Tsankov et al. 2000; Brauchli et al. 2008), and it was identified as a critical inducer of IL-23A release in MoLCs and to a minor extent in MoDCs (Müller et al. 2020). This process was mediated by NFkB/NF- κ B and p38MAPK on ADRB-independent pathways. Propranolol increased lysosomal pH, resulting in a late-stage block in autophagy and prompted ROS production, crucial for IL-23A secretion, in Langerhans-like cells. Markedly, those outcomes were more significant in MoLCs, causing extensive cytokine secretion compared to MoDCs. p62 expression was substantially increased in IL-1 β -activated MoLCs, but not in MoDCs. Propranolol administered separately was insufficient to increase IL-1 β expression in both DC subtypes, but IL-1 β -induced IL-1 β upregulation was subsequently magnified by propranolol in MoLCs and negatively regulated in MoDCs (Müller et al. 2020). Ps is often associated with dyslipidemia, and epidermal LCs of affected patients are characterized by a higher level of neutral lipids than the LCs of healthy individuals. Epidermal LCs from murine IMQ-induced Ps-like dermatitis demonstrate enhanced phagocytosis and excessive secretion of IL-23, tightly correlated with elevated neutral lipid levels, resulting from impaired autophagy of these macromolecules rather than altered lipid engulfment (Zhang et al. 2022b). Apart from experiments conducted on MoLCs and MoDCs, monocytes were not considered subjects of extensive and profound studies on lysosomal nature and autophagy course in Ps.

The role of NK cells in Ps is still being actively investigated. NK cells were found to infiltrate Ps skin lesions, particularly

in the dermis (Ottaviani et al. 2006). NK cells can produce various cytokines, including IFN- γ , TNF- α , and transforming growth factor β , which suggests their potential involvement in the local immune response within Ps skin. Previous research suggested that the systemic cytokine profile related to NK cell function may not drastically differ in Ps patients compared to healthy controls (Dunphy et al. 2017). Although research on autophagy in NK cells is still relatively limited, the evidence points to the impact of autophagy on NK cell development and survival (Wang et al. 2016).

Derived from bone marrow precursors, MC cells form a peculiar bridge between adaptive and innate immunity. As local tissue sentries, they are at the front line, frequently activated by external environmental stimuli or pathogen invasion. Their complex communication with other cells is not only involved in the maintenance of barrier function and immune homeostasis, but also in the initiation, development, and progression of Ps, i.e., MCs interaction with T cells was followed by the recruitment of neutrophils into the skin (Ghoreschi et al. 2007). Mature MCs can synthesize cytokines and chemokines *de novo*, but their cytoplasm also contains numerous granules that store a variety of chemical mediators, leukotrienes, proteoglycans, and proteases. Autophagy is crucial for the process of these factors' degranulation, which sustains the inflammation, leading to the proliferation of KCs and endothelia (Ushio et al. 2011). The amount of resting MCs is mostly diminished in Ps skin, contrary to the excessive MCs activation (Zhang et al. 2021). Moreover, the quantity and degranulation of MCs are greater in the initial phases of Ps lesions, especially in the newly formed rather than in the mature ones (Toruniowa and Jabłońska 1988). Furthermore, the number of MCs in Ps lesions is reduced by successful treatment (Zhang et al. 2021).

The Ps-involved skin is characterized by expanded blood vessels and angiogenesis. An *in vitro* model consisting of human umbilical vein endothelial cells (HUVECs) treated with the M5 proinflammatory cytokines (IL-1, IL-17, IL-22, TNF- α , oncostatin M) was created to evaluate autophagy contribution in Ps VECs upon rapamycin, an inhibitor of mTORC1, administration (Zhou et al. 2023). M5 cytokines significantly increased mRNA expression levels for *IL-6*, *IL-8*, and *CCL20* in HUVEC culture, whereas induction of autophagy with rapamycin lowered the expression levels to levels comparable to that of the controls. Rapamycin treatment markedly increased the ratio of LC3-II/LC3-I, while decreasing p62 expression. Moreover, the results of this study indicated that rapamycin-induced autophagy negatively regulates inflammation elicited by cytokines in HUVECs through the p38MAPK/mTOR pathway. Simultaneously, it was demonstrated that autophagy improves the function of inflamed endothelial cells *via* inhibition of p38MAPK (Zhou et al. 2023). While the exact functions of B cells in Ps are not fully understood, they seem to play a significant role in

influencing the inflammatory processes occurring in Ps skin lesions, thereby contributing to the development of the condition acting both as regulators and effectors of the disease. Skin-resident B cells have been found to produce various inflammatory cytokines such as IL-4, IL-6, GM-CSF, and IFN- γ , which could enhance the inflammatory response seen in Ps (Shen and Fillatreau 2015; Grän et al. 2020). Interestingly, studies have reported reduced numbers of regulatory B cells (Bregs) in both the blood and skin of Ps patients compared to healthy individuals (Hayashi et al. 2016; Lu et al. 2016; Mavropoulos et al. 2017; Kahlert et al. 2019). Notably, the levels of IL-10 $^{+}$ B cells were decreased and were inversely correlated with the presence of IL-17A $^{+}$ and IFN- γ $^{+}$ T cells and with the severity of the disease (Hayashi et al. 2016; Mavropoulos et al. 2017). By producing IL-10, Bregs may potentially control the activity of these proinflammatory T cell subsets, particularly Ps-related Th1 and Th17 cells. In B cells, autophagy is involved in cell activation, development, differentiation, metabolic homeostasis, antigen presentation, and immune tolerance (Weindel et al. 2015; Arnold et al. 2016; Sandoval et al. 2018; Arbogast et al. 2019; Raza and Clarke 2021). Dysregulation of autophagy in B cells has been associated with autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis (Dai and Hu 2015; Qi et al. 2019; Vomero et al. 2019; Jang et al. 2021). Further research is necessary to fully comprehend the precise mechanisms through which B cells, including Bregs, impact Ps.

Ps skin lesions are characterized by a significant infiltration of granulocytes, represented mainly by neutrophils. They are recruited to the skin in response to inflammatory signals and can release various proinflammatory mediators, including cytokines (such as IL-6, IL-8, and IL-17), chemokines, and ROS in the local microenvironment (Hoffmann and Enk 2016; Chiang et al. 2019; Germic et al. 2019; Wang and Jin 2020). Neutrophils in Ps can undergo a process called NETosis, leading to the release of neutrophil extracellular traps (NETs). NETs are web-like structures composed of chromatin, AMPs, and proteases. While NETs are important for microbial defense, their excessive formation in Ps can contribute to tissue damage and amplification of inflammation (Pinegin et al. 2015; Hoffmann and Enk 2016; Delgado-Rizo et al. 2017; Mutua and Gershwin 2021). Neutrophils isolated from the blood of Ps patients are more susceptible to undergo NETosis, which is the process of releasing NETs, compared to neutrophils from healthy individuals. This indicates an aberrant neutrophil response in Ps, leading to increased NET formation. The level of spontaneous NETosis in Ps patients correlates with the severity of the disease. This suggests that NETs may play a role in the pathogenesis and progression of Ps. Ps serum, which contains various factors and mediators associated with the disease, can induce NETosis in neutrophils from healthy individuals. This indicates that the

factors present in the Ps microenvironment contribute to the activation of NETosis in neutrophils. The formation of NETs in Ps is likely dependent on the generation of ROS (Hu et al. 2016; Glennon-Alty et al. 2018). It is worth noting that autophagy has been implicated in regulating NETosis, both in terms of promoting NET formation and ensuring the degradation of released NETs to prevent excessive tissue damage (Gemic et al. 2019). Moreover, autophagy influences the production of cytokines by neutrophils. It regulates the secretion of proinflammatory cytokines, such as IL-1 β , by controlling the processing and release of cytokine precursors (Iula et al. 2018). Studies showed changes in the levels or activity of lysosomal enzymes, such as CAT-G, elastase, and lysozyme in Ps neutrophils. Dysregulated lysosomal enzyme activity may contribute to proteolytic enzyme accumulation and perpetuate inflammation in Ps (Gliński et al. 1984; Henry et al. 2016; Guo et al. 2019).

6. Remarks and Future Perspectives

Extensive studies with innovative and rigorous methodologies have broadened our knowledge of complex immune-mediated inflammatory diseases in general and autophagic machinery and lysosomal function in cells. Recently, marked progress has been made in our understanding of these aspects in relation to Ps, a unique disease where both autoimmune and autoinflammatory responses co-exist, with the balance between the two being critical in shaping the fairly broad Ps spectrum in terms of clinical manifestations. The impaired ALP is only a part of the Ps pathomechanism; however, it is essential for understanding the issue. The question of whether inhibiting either canonical (such as autophagosome formation) or non-canonical (such as LC3-associated phagocytosis and chaperone-mediated autophagy) autophagy could serve as an effective treatment for Ps in clinical settings is an intriguing area of exploration. The role of autophagy in Ps is multifaceted. On one hand, autophagy helps regulate inflammation and immune responses, which are the key elements in Ps pathology. On the other hand, it is involved in cell survival and proliferation – processes that are dysregulated in Ps lesions. Inhibiting canonical autophagy might potentially reduce the hyperproliferation of skin cells in Ps. However, since autophagy also aids in clearing damaged cells and controlling inflammation, inhibiting it could have unintended consequences, potentially exacerbating the condition. Noncanonical autophagy, less understood than its canonical counterpart, could play unique roles in the skin's immune environment. Inhibiting these pathways might offer new therapeutic avenues, but understanding their specific functions in Ps is crucial before pursuing this strategy. The complexity of autophagy in skin health and disease suggests that any therapeutic approach targeting these pathways must be finely balanced.

According to recent data, it is becoming more evident that the disease affects specific interactions of different cellular players within the skin and immune system. Their interactome in relation to subcellular autophagic machinery and the endo-lysosomal degradation system orchestrates the choreography of Ps (Table 1). Nonetheless, these data on the regulation of autophagy and the lysosomal layout in the context of Ps are incomplete and require further research. Moreover, immunometabolic reprogramming may be worth further exploring to comprehend its therapeutic potential in this disease. The clinical detection of autophagic and lysosomal dysfunction as a potential method for diagnosing autoimmune diseases may potentially involve a multifaceted approach that combines advanced histological and molecular techniques. To begin with, obtaining tissue samples through minimally invasive procedures such as skin punch biopsies can be an effective starting point. This technique is particularly useful as it allows for the direct examination of affected tissue, which is crucial in autoimmune diseases that often manifest with skin abnormalities. Once the tissue samples are collected, they can be subjected to detailed histological analysis. Techniques such as immunohistochemistry and electron microscopy are invaluable in this regard. Immunohistochemistry allows for the visualization of specific proteins and enzymes associated with autophagy and lysosomal functions by using antibodies that bind to these targets. Electron microscopy provides a more detailed view, enabling the visualization of cellular structures such as autophagosomes and lysosomes at a microscopic level. In addition to histological analysis, molecular techniques such as polymerase chain reaction and Western blotting are essential. Furthermore, monitoring changes in autophagic and lysosomal activities over time through sequential biopsies, or even better by tape stripping could offer insights into the disease progression and response to therapy. This approach could be particularly valuable in personalized medicine, where treatment strategies are tailored based on individual patient profiles. Exploring alternative methods beyond skin biopsies for the clinical detection of autophagic and lysosomal dysfunction in autoimmune diseases involves blood tests and serum biomarkers. Certain proteins or enzymes that are released into the bloodstream during autophagy or lysosomal dysfunction can serve as indicators. Techniques such as enzyme-linked immunosorbent assay can be employed to measure these biomarkers accurately. Advanced imaging methods such as positron emission tomography scans or magnetic resonance imaging can be adapted to observe metabolic changes in tissues that might result from altered autophagy or lysosomal activities. While these techniques are more commonly used for other purposes, ongoing research is exploring their potential in detecting cellular dysfunction. Similar to blood tests, urine analysis can reveal the presence of specific compounds that

Table 1. Overview of autophagic machinery and lysosomal function in cells, both structural (i.e., skin nonimmune cells) and immune (i.e., skin-associated and recirculating immune cells) cells, involved in the immune-mediated inflammatory cascade in Ps

Cell type		ALP alterations in Ps	Possible effects of autophagy disturbances leading to the development of the Ps phenotype	References
Structural cells (skin nonimmune cells)	KCs	Upregulation of ATG5, ATG7, MAPK/ERK, mTORC1, NF- κ B, NRF2, p62, and PI3K/Akt; Downregulation of AP1S3, CaN, and MCOLN1; Altered levels of LAMP1, LC3, TFEB, and lysosomal enzymes	Cytokine production growth, inflammatory activation, hyperproliferation, differentiation disturbances, cathelicidin/LL-37 expression enhancement, PGRN expression increase	Akinduro et al. 2016; Balato et al. 2014; Bocheńska et al. 2019; Buerger 2018; Dombrowski et al. 2011; Douroudis et al. 2012; Farag et al. 2019; Huang et al. 2015; Johansen et al. 2007; Klapan et al. 2021; Lee et al. 2011; Li et al. 2016; Mahil et al. 2016; Mercurio et al. 2021; Monteleon et al. 2018; Nada et al. 2020; Paushter et al. 2018; Salazar et al. 2020; Salskov-Iversen et al. 2011; Sánchez-Martín et al. 2019; Schönefuß et al. 2010; Sun et al. 2014; Wang et al. 2019b; Xue et al. 2022; Yin et al. 2018; Yu et al. 2007; Zhang and Zhang 2019
	FBs	Downregulation of ZFP36	Cytokine production growth	Angiolilli et al. 2022
Immune cells (skin-associated and recirculating immune cells)	T cells	Increased level of autophagy upon TCR stimulation; Reduced level of autophagy upon enhanced mTORC1 kinase activity	Cytokine production growth, hyperproliferation, differentiation disturbances, Th population imbalance, TCR activation increase, apoptosis augmentation, cytokine secretion by multiplied DCs	Benoit-Lizon et al. 2018; Botbol and Macian 2015; Bronietzki et al. 2015; Chung et al. 2009; Delgoffe et al. 2009, 2011; Deretic 2021; Dowling et al. 2018; Harris et al. 2008; Hirai et al. 2013; Hubbard et al. 2010; Jia et al. 2015; Kabat et al. 2016; Kiyono et al. 2009; Koga et al. 2014; Kopf et al. 2007; Kovacs et al. 2012; Lee et al. 2011; Liang et al. 2012; Matsuzawa et al. 2015; Mocholi et al. 2018; Murera et al. 2018; Parekh et al. 2013; Pua et al. 2007; Stockinger et al. 2007; Wei et al. 2016; Willinger and Flavell 2012
	Macrophages	Autophagy induction	Polarization to M2 phenotype activation	Germic et al. 2019; Jacquet et al. 2012; Liu et al. 2015
	DCs	Autophagy inhibition	Cytokine production growth, inflammatory activation, Th17 differentiation increase, Th population imbalance, T cells responses via MHC I and MHC II pathways regulation	Chung et al. 2009; Dengjel et al. 2005; Feng et al. 2019; Kasai et al. 2009; Loi et al. 2016; Merkley et al. 2018; Mintern et al. 2015; Schmid et al. 2007; Stockinger et al. 2007; Wenger et al. 2012
	LCs	Autophagy inhibition	Cytokine production growth, Th17 differentiation increase, Th population imbalance	Müller et al. 2020; Said et al. 2014; Zhang et al. 2022b
	NKs	n.d.	Development and survival defect	Wang et al. 2016
	MCs	n.d.	Degranulation increase, KC hyperproliferation	Ushio et al. 2011
	VECs	Autophagy induction; Downregulation of p38MAPK/ mTOR pathway	Cytokine production growth	Zhou et al. 2023
	B cells	n.d.	Inflammatory activation, differentiation disturbances, development defect, autoantigen presentation, immune tolerance disturbances, metabolic homeostasis fault	Arbogast et al. 2019; Arnold et al. 2016; Raza and Clarke 2021; Sandoval et al. 2018
	Granulocytes	Altered lysosomal enzymes levels and activity	Cytokines production growth, NETosis rise, proteolytic enzyme accumulation	Germic et al. 2019; Gliński et al. 1984; Guo et al. 2019

Akt, protein kinase B; ALP, autophagy-lysosomal pathway; AP1S3, component of the activator protein 1 (AP-1) complex; ATG, autophagy-related protein; CaN, calcineurin; DC, dendritic cell; ERK, extracellular signal-regulated kinase; FB, fibroblast; KC, keratinocyte; LAMP1, lysosomal-associated membrane protein 1; LC3, microtubule-associated protein1A/1B-light chain 3; LCs, Langerhans cells; MAPK, mitogen-activated protein kinase; MCOLN1, mucolipin transient receptor potential cation channel 1; MCs, mast cells; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; n.d., no data; NET, neutrophil extracellular trap; NF- κ B, nuclear factor κ B; NRF2, nuclear factor erythroid 2-related factor 2; p38MAPK, p38 mitogen-activated protein kinase; p62, autophagy receptor protein, also known as a multifunctional stress-inducible scaffold protein SQSTM1 (Sequestosome 1); PGRN, progranulin; PI3K, phosphoinositide 3-kinase; Ps, psoriasis; TCR, T cell receptor; TFEB, transcription factor EB; Th, T helper cell; VECs, vascular endothelial cells; ZFP36, zinc finger protein 36.

are indicative of autophagic or lysosomal dysfunction. This method has the advantage of being noninvasive and can be particularly useful for monitoring disease progression or response to treatment. Genetic tests can identify mutations or variations in genes known to be involved in autophagy and lysosomal pathways. This approach is especially relevant in cases where autoimmune diseases have a known genetic component or predisposition. For more detailed analysis, the cells extracted from patients can be cultured and observed under laboratory conditions. This allows for the direct observation of autophagic and lysosomal activities in a controlled environment, providing insights into how these processes are altered in autoimmune diseases. Finally, various functional assays can be employed to assess the efficiency and integrity of autophagic and lysosomal processes. These might include tests for enzyme activity, acidification of lysosomes, or the turnover rate of autophagic substrates. Combining these methods can provide a comprehensive overview of autophagic and lysosomal function in the context of autoimmune diseases. Each technique offers distinct advantages and can contribute valuable information to the diagnosis, understanding, and management of these complex conditions. As research advances, these methods are continually refined and improved, enhancing their accuracy and utility in clinical settings.

In future studies, it will be quite intriguing to define more precisely the interplay between the cellular factors and metabolic

regulators of affected tissues to update perspectives regarding a systemic and holistic approach, allowing clinicians to institute targeted and personalized medicine, leading to the maximization of efficacy and minimization of toxicity, and allowing us to overcome the most significant challenge we face in achieving long-term and stable remission in patients with Ps. We believe that the data collected in this review shows that expanding this area may prove valuable in better understanding Ps and facilitating progress in therapeutic development.

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Original draft preparation, review, and editing: MK, MM, MGC; supervision, funding acquisition: MM, MGC. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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