Innate lymphoid cells (ILC) are a heterogeneous group of immune cells characterized by lymphoid morphology and cytokine profile similar to T cells but which do not express clonally distributed diverse antigen receptors. These particular cells express transcription factors and cytokines reflecting their similarities to T helper (Th)1, Th2, and Th17 cells and are therefore referred to as ILC1, ILC2, and ILC3. Other members of the ILC subsets include lymphoid tissue inducer (LTi) and regulatory ILC (ILCreg). Natural killer (NK) cells share a common progenitor with ILC and also exhibit a lymphoid phenotype without antigen specificity. ILC are found in low numbers in peripheral blood but are much more abundant at barrier sites such as the skin, liver, airways, lymph nodes, and the gastrointestinal tract. They play an important role in innate immunity due to their capacity to respond rapidly to pathogens through the production of cytokines. Recent evidence has shown that ILC also play a key role in autoimmunity, as alterations in their number or function have been identified in systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis. Here, we review recent advances in the understanding of the role of ILC in the pathogenesis of autoimmune diseases, with particular emphasis on their role as a potential diagnostic biomarker and as therapeutic targets.

Keywords: innate lymphoid cell (ILC), autoimmune diseases, autoimmunity, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, ANCA-associated vasculitis, NK cell

INTRODUCTION

Innate lymphoid cells (ILC) are lymphocytes that lack somatically diversified antigen receptor expression (1). So far, different subtypes of ILC have been described, depending on their specific functional features mirroring CD4+ T helper (Th)1, Th2, and Th17 cells. In 2013, they were classified as group 1 (including NK cells), group 2, and group 3 ILC (1, 2); however, following further research, a new description was proposed in 2018 which classifies ILC into five categories, namely, NK cells, ILC1, ILC2, ILC3, and lymphoid tissue inducer (LTi) cells (Table 1) (3).

ILC in humans and mice originate from a common lymphoid precursor (CLP), which is able to give birth to all lymphocyte subsets (37). Studies in murine models have shown that CLP initially differentiates into the common innate lymphoid progenitor (CILP) which serves as a common precursor for both NK cells and ILC. CILP then evolves into the common helper innate lymphoid progenitor (CHILP), which is common to LTi and ILC (6, 38). CHILP finally differentiates into innate lymphoid cell precursors (ILCP) that will give rise to ILC1, ILC2, and ILC3 (3, 12). Of note, in
mice, lymphoid progenitors (which have the potential to differentiate into all ILC lineages, including NK cells) were identified as inhibitor of DNA binding 2 (ID2) positive (5). ID2 is a transcription factor required for organogenesis of lymphoid tissues, and its loss was shown to disrupt the generation of ILC precursors (14, 15). In humans, the differentiation steps that lead to the development of ILC are less well known even though they are considered to be similar (19). Similarities and differences between human and murine ILC have been excellently reviewed elsewhere (19).

Many phenotypic markers have been used to characterize mature ILC subsets, but no definitive marker universally defining ILC has been identified so far. This is notably due to the fact that their phenotype depends on the tissue they populate and that ILC represent very heterogeneous populations (20, 21). Despite tremendous variability in their definition, ILC can be roughly defined as CD3-negative lymphocytes that express IL-7 receptor (CD45^+CD3^−CD127^+), although in many tissues ILC do not express CD127 (20, 21).

NK cells were initially included in group 1 ILC, together with ILC1, because of important similarities such as the expression of the transcription factor T-bet and the production of interferon γ (IFN-γ) (3, 7). However, subsequent studies indicated that NK cells and ILC1 belong to distinct lineages and represent two separate cell types (6, 13, 17, 21). Indeed, while ILC are mainly tissue-resident cells, NK cells are principally found in blood circulation, constituting 5%–20% of circulating lymphocytes, and are capable of being rapidly recruited to inflammation sites (20, 39, 40). Moreover, NK cells have an important cytotoxic function with high expression levels of perforin and granzyme B, whereas ILC1 are in general noncytotoxic or only weakly cytotoxic. Interestingly, recent evidence in murine models shows that CD160^+ ILC1-like NK cells are able to kill cells infected with murine cytomegalovirus (3, 18, 22, 39). NK cells play a special role in antitumor surveillance and in antimicrobial defense against intracellular pathogens and viruses (39). In addition, compared with ILC1, they follow a specific differentiation pathway that requires the expression of the T-box transcription factor Eomes for their development, and the induction of CD122 with subsequent IL-15 responsiveness (8, 13, 16).

In addition, ILC1 also share similarities with Th1 cells, as they react to intracellular pathogens, mainly secrete IFN-γ and depend on the transcription factor T-bet for their differentiation (1, 3, 6). Although they can be detected in peripheral blood or cord blood, they are primarily tissue-resident cells (20). In humans, ILC1 are mainly found in the tonsils, gut, lung, liver, adipose tissue, skin, lymph nodes, and spleen (4, 9, 20, 40). They show significant differences in the
expression of surface markers and transcription factors linked to the microenvironment of the tissue they populate (20).

ILC2, like Th2 cells, produce high levels of interleukin (IL)-4, IL-5, and IL-13 in response to epithelial-cell-derived IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) (1, 10, 41). They express high levels of the transcription factors GATA3 and RORα (3, 11). Phenotypically, they are characterized in mice, by the expression of suppression of tumorigenicity (ST2, also known as IL-1RL1) (23, 24), CD161, and inducible T-cell COStimulator (ICOS), whereas in human peripheral blood, they are described as chemoattractant-homologous receptor expressed on Th2 cells (CRTH2+), ST2+, and/or CD161+ (20, 41). ILC2 are involved in allergies and parasite elimination (3).

In mice, they are abundant in the airways, lungs, skin, and gut, especially in models of asthma (1, 41, 42). In humans, ILC2 represent the main population of ILC that inhabit peripheral blood, skin, lungs, and adipose tissue, but they are little or not present in adult gut (20, 41, 43). Furthermore, the presence of ILC2 has also been described in liver, lymph nodes, spleen, and adenoids (20).

ILC3 are the innate counterpart of Th17 cells. They play a role in innate immunity against fungi and extracellular microbes and depend on the transcription factor RORγt (1, 3). Like other ILCs, they require IL-7 for their development. More specifically, they secrete IL-22 and certain subsets can produce IL-17A, in response to IL-23 and IL-1β (3, 44). In mouse models, ILC3 participate in the secondary antibody response by promoting the survival of CD4+ T cells through the expression of OX40 ligand and CD30 ligand (44). They are also able to express antigen-presenting molecule major histocompatibility complex-II (MHC-II) and present processed antigens to CD4+ T cells (44).

In humans, ILC3 and notably NKp44+ ILC3 are particularly found in mucosal tissues such as the gut (20, 45). However, they may also be found in blood, spleen, lymph nodes, tonsils, skin, and lung (20). Phenotypically, in humans, they were notably described as Lin−CD56+CD127+CRTH2+CD117−NKp44−/− (46) or Lin−CD45+CD127+Killer RNase+CRTH2+NKp44− or NKp44+/− (47).

LTi were previously included in the group 3 ILC because of their capacity to produce IL-17 and IL-22. They undergo differentiation from a specific progenitor, the lymphoid tissue inducer progenitor (LTiP) and depend on RORγt for their differentiation (3). However, now considered a specific population, LTi have a specific role as mesenchymal organizer cells in the formation of secondary lymphoid structures during embryonic development (3). According to data from studies in mice, the crosstalk between LTi and lymphoid tissue stromal cells continues postnatally, as it has been demonstrated that LTi cells contribute to the restoration of lymphoid tissue architecture following infection with LCMV (48).

In humans, LTi express neuropilin-1, produce IL-17, IL-22, GM-CSF, TNF-α, TNF-β, and IL-8, and play possibly a role in the Th1 and Th17 immune response (49, 50).

Lately, another ILC subpopulation was described, which harbors a regulatory phenotype, and hence named regulatory ILC (ILCreg) (51). These cells, phenotypically defined as Lin−CD45+CD127−IL-10+, were initially described in mouse and human intestine secrete high amounts of IL-10 and TGF-β and are devoid of CD4 and Foxp3 expression (51). They show a distinct gene expression profile compared with other ILC and play an important role in the resolution of innate intestinal inflammation through the suppression of ILC1 and ILC3 via IL-10 secretion, in a mouse model of colitis (51). In addition, the secretion of TGF-β acts in an autocrine way to support the expansion of ILCreg during gut inflammation (51). Of note, the existence of IL-10-producing ILCreg as a distinct population of ILC remains controversial. From this point of view, in various mice models, the main source of IL-10 in the gastrointestinal tract comes from activated populations of ILC2, which expresses KLRG1, IL-25R, and the transcription factor GATA-3 (52).

In another context, ILCreg were also described in mouse and human kidney, where they play a protective role in ischemia-reperfusion injury (53). Another regulatory population of ILC, named follicular regulatory ILC, has been described in human tonsils and lymph nodes and secretes high amounts of TGF-β (54).

Interestingly, ILC have been recently shown to exhibit plasticity, similarly to T cells. They have the ability to coexpress lineage-determining transcription factors in response to signal from their microenvironment (23). This is especially true for CD127+CD117+ ILC precursors, a cell subset which expresses CD45RA and CD62L and shows similarities to naive CD4+ T cells (23). Their differentiation depends on cytokines present in the tissue they populate (23). Balance between ILC1 and ILC3 changes in the presence of inflammatory stimulations, with ILC1 numbers increasing and ILC3 decreasing in the intestine in pathological conditions such as Crohn’s disease (45). This process occurs through a differentiation of ILC3 to ILC1, which depends on exposure to IL-12. In addition, this differentiation has been shown to be reversible, as the presence of IL-23 and IL-1β favors the differentiation of ILC1 to ILC3 (45). Recently, ILC3–ILC1 intermediate subsets were identified in human tonsils and intestinal mucosa, describing ILC3 and ILC1 as the ends of a spectrum, with the cells closest to ILC1 having the maximal ability to produce IFN-γ in vitro (4).

Another study showed that human ILC3 that are transferred to humanized mice acquire ILC1-like features in the spleen more than in the liver (5). These results support the hypothesis that tissue specific triggers cause local transdifferentiation of ILC (23).

Since their discovery, numerous studies suggest that ILC play a key role in the pathogenesis of systemic autoimmune conditions such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and antineutrophil cytoplasm antibody (ANCA)-associated vasculitides. In this review, we discuss the latest advances on the role of ILC in the pathogenesis of human autoimmune diseases and their potential use as diagnostic biomarkers and/or therapeutic targets.

**ILC IN AUTOIMMUNE CONDITIONS**

**Systemic Sclerosis**

Systemic sclerosis (ScS) is an autoimmune connective tissue disease characterized by vasculopathy and fibrosis in multiple
organs. Ssc prototypically causes Raynaud phenomenon, arthralgias, fingertip lesions, skin thickening, hypertensive renal crisis, lung fibrosis, and pulmonary arterial hypertension (55–57). The pathophysiology of Ssc is unclear but involves genetic and environmental factors (i.e., silica solvents, epoxy resins, breast implants, skin microbiota), leading to chronic inflammation, endothelial injury, vascular dysfunction, fibroblast activation, and tissue fibrosis (58, 59). Numerous immune cells, antibodies, and cellular pathways contribute to the processes that lead to tissue fibrosis. In particular, dysregulation of interferon α (IFN-α) is an important alteration in patients with antitopoisomerase I antibodies (58, 60). This dysregulation is characterized by an IFN-α overproduction by plasmacytoid dendritic cells in response to the activation of toll-like receptors (TLR) 7 and 9 by immune complexes generated by endothelial cell death (60). Constitutive fibroblast activation driven by mediators such as tumor growth factor β (TGF-β) also represents a key process, which leads to tissue fibrosis (58).

Few studies have examined the role of ILCs in the pathophysiology of human Ssc (Figure 1). A study published in 2015 by Wohlfahrt et al., including 69 Ssc patients, showed that ILC2 number is elevated in the skin and peripheral blood of patients with Ssc compared with healthy controls (34). There was also a positive correlation between the number of ILC2 in the skin and the modified Rodnan Skin Score. In addition, patients with extensive pulmonary fibrosis showed the highest numbers of circulating ILC2 (34). Of note, ILC2 were defined using two different marker panels, both including ST2 (ICOS+ ST2+CD3-CD11b- or ST2+IL-17RB+KLRG1+), with consistent results (34). These data suggest a potential pathogenic role of ILC2 in Ssc, although the mechanism is still unclear. As it was shown that type 2 cytokines such as IL-4 and IL-13 can increase TGF-β production in bronchial epithelial cells in diseases such as asthma (61), one could hypothesize that ILC2, which secrete such cytokines, could thus induce TGF-β secretion from fibroblasts or other epithelial cells such as keratinocytes, and therefore, increase fibrosis (62). Moreover, in murine models, TGF-β is required for the development of ILC2, suggesting a potential crosstalk between fibroblasts and ILC2 (63). However, data are still missing in Ssc, and this hypothesis needs to be investigated.

On the other hand, a study published in 2016 by Roan et al. showed that a subset of ILC1, defined as CD4+ ILC1, and NKp44+ ILC3 were increased in the peripheral blood of Ssc patients compared with healthy subjects (25, 26). An interesting point is that the CD4+ ILC1 expressing IL-6Rα were decreased in Ssc, suggesting that these cells are overactivated and contribute to the amplification of the inflammatory response that characterizes SSc (25, 26). In another study, the authors showed that KLRG1low ILC2 are increased in the fibrotic skin from SSc patients. This population is activated by TGF-β and produces lower levels of IL-10 compared with KLRG1high ILC2. These KLRG1low ILC2 cells fail to negatively regulate collagen production by dermal fibroblasts, a process which is physiologically IL-10 dependent, thus enhancing skin fibrosis (35). Despite these interesting findings on the role of ILC1 and ILC2 in Ssc pathogenesis and fibrosis development, data are still missing to fully understand the importance of ILC in the pathogenesis of Ssc.

**Systemic Lupus Erythematosus**

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease affecting mainly young women of childbearing age. Its pathophysiology is complex, involving loss of self-tolerance with an imbalance between apoptotic cell abundance, extracellular exposition of nuclear antigens, and disposal of this apoptotic material. The free nuclear antigens will activate TLR notably on plasmacytoid dendritic cells (pDC),

![FIGURE 1](https://example.com/figure1.png)
with secretion of type I IFN (known as the “interferon signature”) and other cytokines that drive B-cell differentiation, and the production of autoantibodies (64). These antibodies directed against self-antigens then form immune complexes that deposit in the tissues, leading to chronic inflammation and tissue damage (27, 64).

The role of ILC in SLE pathogenesis is poorly understood, particularly in humans (Figure 2). In 2019, a study by Guo et al. examined circulating ILC in the peripheral blood of 49 SLE patients and showed an increase in ILC1 (defined as Lin−CD127−CRTH2−CD117−) compared with healthy controls, while ILC2 (Lin−CD127−CRTH2+) and ILC3 (including 2 subpopulations, defined as Lin−CD127−CRTH2−CD117+NKp44− or NKp44+) were decreased (28). Moreover, the greatest increase in ILC1 and decrease in ILC2 and ILC3 were observed in patients with moderate and severe disease activity, with a positive correlation of ILC1 numbers to systemic lupus erythematosus disease activity index (SLEDAI) (28). This altered distribution of ILC in active SLE with lupus nephritis was reversed after initiation of treatment (steroids and cyclophosphamide), suggesting that ILC1 may represent a biomarker of disease activity (28). Recently, a study by Jiang et al. examined the number of ILC in the peripheral blood of SLE patients (29). They also found an increase in ILC1 and a decrease in ILC2 in patients with active SLE, but, in contrast to Guo et al., they found an increase of ILC3 in the blood of patients with active SLE compared with inactive (SLEDAI<5). Interestingly, there was a positive correlation between ILC3 absolute numbers in the peripheral blood and the SLEDAI score. This discrepancy between the two studies might be due to differences in gating used to define ILC subsets, as the markers used to distinguish between ILC1 and ILC3 were similar. Heterogeneity of SLE patients might also contribute to such differences. An interesting point in the research by Jiang et al. is a positive correlation between ILC3 and serum anti-dsDNA titers, and a decrease in ILC1/ILC3 and ILC2/ILC3 ratio in SLE patients with arthritis compared with patients without arthritis (29).

In a study by Blokland et al., which also included patients with primary Sjögren’s syndrome (pSS) patients, ILC1 were increased in the peripheral blood of SLE patients (27). In pSS, the abundance of total ILC did not differ from healthy donors but was associated with disease activity as measured by the EULAR Sjögren’s syndrome disease activity index (ESSDAI). The
patients (SLE and pSS) showing an interferon (IFN) signature (defined by an elevated IFN score) had an increased FAS expression, with a decrease in ILC2 and ILC3 frequency (27).

Finally, a study including 51 SLE patients also showed an increase in ILC1 in the peripheral blood. They also identified a positive correlation between increased ILC1/ILC3 count and disease activity (30). These data suggest that ILC1 may participate in constituting a response to the inflammatory process, while ILC3 may play a role in the development of the autoantibody response in SLE. However, further studies are warranted to explore these hypotheses and understand the role of the altered abundance of ILC in the peripheral blood of SLE patients. Moreover, in humans, ILC1 definition is still controversial (65), and no data are currently available on ILC phenotype in the organs and tissue from SLE patients. This would be of paramount importance to shed light on the role of these cells at the epithelial barrier sites in SLE.

Antineutrophil Cytoplasm Antibody-Associated Vasculitis

ANCA-associated vasculitis (AAV) encompasses three distinct entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (66).

These inflammatory diseases are all characterized by small- and medium-vessel inflammation, but with relatively distinct clinical presentations, specific biologic features, and ANCA serotype. Anti-PR3 are mainly associated with GPA, while anti-MPO are more frequently associated with EGPA and MPA (67). GPA often manifests as granulomatous inflammation of the upper and lower airways and ear/nose granulomatous inflammation and kidney damage. MPA is characterized by necrotizing glomerulonephritis and pulmonary capillaritis. EGPA is prototypically associated to eosinophilia, pulmonary infiltrates, and asthma (68).

The pathogenesis of AAV relies on the production of antibodies that target myeloperoxidase and proteinase 3 (67). These two proteins are abnormally overexpressed on the surface of neutrophils, and, subsequently to antibody binding, neutrophils are activated and produce cytokines, reactive oxygen species, and neutrophil extracellular traps (NETosis) (67). Overactivation of B and T cells is also involved in the pathogenesis of AAV and leads to the production of ANCA (67).

As ILC have been shown to play particularly a role in tissue homeostasis at mucosal sites, and especially at the level of airways epithelia, examination of their role in AAV is of particular interest (Figure 3). From this point of view, one study examined the frequencies of ILCs in the peripheral blood of AAV patients (26 GPA and 15 MPA subjects) compared with healthy controls (31). Samples were collected during acute phase, defined by Birmingham vasculitis activity (BVAS) score >3, before any treatment, or during remission phase, defined as BVAS 0. Total ILCs, defined as Lin−CD127+, were decreased during acute phase in AAV patients compared with controls. More precisely, ILC2 and ILC3 were decreased while ILC1 were increased when compared with healthy controls or AAV patients.
in remission (31). Even if these data are of interest, it remains difficult to draw any definitive conclusion on the role of ILC in the pathogenesis of AAV. Further studies are warranted to address this point.

**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is an autoimmune disease affecting the joints with synovial inflammation and cartilage/bone destruction (69). The pathogenesis is complex and involves the development of auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which can be detected years before the onset of clinical disease (70). Development of ACPA and/or RF is triggered by a complex interplay between genetic, epigenetic, and environmental factors (smoking, pathogens, obesity, dysbiosis, toxic substances) (69, 71, 72). Innate immunity is central to the pathogenesis of RA, with the presence of macrophages, mast cells, and NK cells in the synovial membrane, and neutrophils in the synovial fluid (69). NK cells are also increased in the synovial fluid of RA patients (73).

The humoral immune response plays also an essential role in the pathogenesis of RA, and B cells, plasmablasts, and plasma cells are very abundant in the inflamed synovium (69). ACPA promote the production of TNF-α by macrophages, a cytokine that is the cornerstone of RA joint damage, by activating fibroblasts and chondrocytes (69). Additionally, cytokines involved in the Th17 response, including IL-6, IL-21, IL-17, IL-23, and IL-1β, are also elevated in the peripheral blood and synovial fluid of patients with RA (71, 74).

Some recent studies evaluated the role of ILC in RA patients (Figure 4). In 2017, Rodriguez-Carrio et al. showed that ILC distribution differed in lymph nodes (LN) of RA patients compared with at-risk patients (defined as patients with RF and/or ACPA positivity, and arthralgia without arthritis) or healthy controls (32). LTi cells were shown to be decreased in RA patients, while ILC1 were increased in RA and at-risk patients. ILC3 were increased in RA patients compared with healthy controls and at-risk patients. A positive association of LTi frequency with VCAM expression on LN endothelial cells was also shown, suggesting a potential crosstalk between ILC and the stromal cell compartment (32). In 2019, Takaki-Kuwara et al. found that a subset of CCR6+ ILC3 was increased in the synovial fluid of RA patients compared with osteoarthritis controls, and positively correlated with RA clinical activity (36). Moreover, a positive correlation was established between the number of CCR6+ ILC3 cells and CCL20 concentration in synovial fluid of RA patients, suggesting that CCR6+ILC3 may play a role in RA pathogenesis through the production of Th17 cytokines such as IL-17 and IL-22 (36). Finally, Yang et al. described that RA patients with stable disease depicted decreased ILC1 and

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**FIGURE 4** | Role of ILC in rheumatoid arthritis (RA). ACPA, anticitrullinated protein antibodies; TNF-α, tumor necrosis factor α; IL, interleukin; DC, dendritic cell; MMP, metalloproteinase; ILC, innate lymphoid cell; IL, interleukin; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; Th, T helper CD4+ T cell.
increased ILC2 proportion in the peripheral blood compared with healthy controls and with patients with active disease, while both active and stable RA patients had a decreased percentage of ILC3 (33). A positive correlation between disease activity and ILC1 proportion was also found, while there was a negative correlation between ILC2 percentage and disease activity (33). This suggests that ILC2 may counterbalance the proinflammatory effect of ILC1 through the production of IL-13 (75, 76), which has been shown to have anti-inflammatory effect on synovitis in rheumatoid arthritis (77).

**DISCUSSION**

Since their initial description 10 years ago, ILC have been increasingly recognized as important players in the immune response, but their role in human autoimmune diseases remains controversial. Currently available data suggest that they could be useful as biomarkers of disease severity or response to treatment.

A major limitation to identify the role of ILC in human diseases is related to the fact that ILC are tissue-resident cells. Access to barrier sites requests invasive biopsies, which are not easy to be routinely performed. Therefore, most studies are limited to the examination of cells from the peripheral blood, where ILC are only present at low abundance and where they display a phenotype that might differ from their tissue-resident counterpart. Technically, examination of restricted subpopulations of ILC may be difficult due to the important number of markers needed to identify these populations. Recent advances in single cell mass cytometry and flow cytometry that allow the examination of high amount of parameters in limited biological samples should facilitate future studies on the subject.

Therapeutic approaches targeting ILC are challenging, because ILC are highly heterogeneous. Moreover, no specific markers for ILC have been identified to date, making it difficult to develop a drug that specifically targets ILC or ILC subsets. Accordingly, the border between pathogenic versus beneficial role of ILC is not always obvious. ILC2, for example, seem to be pathogenic in atopic dermatitis, but in a mouse model of RA, they foster the resolution of inflammation (1, 78). Since ILC exhibit an important plasticity that depends on their microenvironment, targeting cytokines or soluble factors involved in their differentiation and maintenance would likely affect ILC subpopulation distribution and alter diseases course. Recent evidence, for example, showed that patients with inflammatory bowel disease exhibit an altered distribution of ILC subsets in the gut and blood during active disease. This anomaly is partly restored after treatment with the anti-IL12/23 monoclonal antibody ustekinumab (79). Overall, future studies are warranted to explore the role of ILC in human diseases, because currently available data remain largely descriptive and functional data are lacking.

**AUTHOR CONTRIBUTIONS**

AC, MH, NF, MK, and DC researched the data for the article. AC, MK, and DC wrote the manuscript. AC, MH, NF, MK, and DC reviewed the manuscript. All authors accepted the final version of the manuscript.

**FUNDING**

This study received funding from the Swiss National Science Foundation (Ambizione PZ00P3_173950 to DC) and a grant from the Novartis Foundation for Medical-Biological Research (to DC). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

**ACKNOWLEDGMENTS**

All figures included in the present manuscript were created with BioRender.com.

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