Innate Immune Cells in Primary Sjogren Syndrome

Subjects: Allergy

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Primary Sjogren Syndrome (pSS) is an autoimmune exocrinopathy, characterized by xerophthalmia end xerostomia, and caused by a chronic inflammation of lacrimal and salivary glands. The interplay between innate immune cells and the inflammation prone microenvironment in Primary Sjogren Syndrome (pSS). pSS is a multifactorial rheumatic disease: environmental stimuli, in genetic susceptible subjects, may trigger Salivary gland epithelial cells (SGECs) to express ligands, receptors and cytokines, such as IL-22, that act in a paracrine and autocrine way when determining the activation of several innate immune cells like NKs, ILC3s, DCs and macrophages.

Sjogren syndrome innate immunity

1. Dendritic Cells (DCs)

DCs are antigen presenting cells and represent immunological sentinels that operate to detect dangerous insults to tissues rapidly. Their role in activating adaptive immunity leading to the production of antibodies is well known. This process requires the activation of both follicular (FDCs) and plasmacytoid dendritic cells (pDCs), which were actually found to be significantly increased in pSS salivary specimens [1]. As previously mentioned, pSS is an autoimmune disease characterized by the presence of autoantibodies that are produced in inflamed salivary tissue after the formation of ectopic germinal centers.

The precursor population of DCs in pSS displays an aberrant phenotype. In particular, their migration to salivary gland tissue seems to be related to the upregulation of chemokine receptor CCR5 and with an increased level of CCR5 ligands (CCL3 and 4) on saliva of pSS patients [2].

In addition, DCs altered genotype in pSS can cause their premature apoptosis in peripheral blood of patients [3]. These observations, taken together may explain DCs' increased number in pSS salivary glands and their reduction among circulating cells.

The activation of DCs in autoimmune epithelitis is related to exogenous triggers, such as viral infections accounting for the viral hypothesis in pSS pathogenesis. DCs react to dangerous stimuli via TLR activation, finally leading to secretion of type I IFN as well as other pro-inflammatory cytokines. Self-antigens, derived from epithelial cells apoptosis in a dysreactive immunity background, activate pDCs endosomal TLR-7 and 9, inducing the pro-inflammatory cascade [4][5].

In a minor way, other TLRs (2, 4 and 8) activated in inflammatory condition, were described on pDCs of pSS patients [6]. The key effector cytokine of pDCs stimulation, type I IFN, determines in autocrine and paracrine ways pDCs activation with a continuous reinforcing loop highlighting the importance of the IFN signature in pSS. Type I IFN activates monocyte circulating cells, inducing them to produce BAFF (B cell activating factor) that contributes to the production of pSS-autoantibodies, by linking pDC functions to autoimmunity outbreak [7][8].

FDCs are specialized reticular fibroblasts originating from local fibroblasts or fibroblast precursors activated in inflamed tissue. FDCs network plays a pivotal role in organizing the microarchitecture of ectopic GCs-like structure. In this milieu, FDCs are able to present immune-complexes (ICs), formed by Ag-Ab and complement, to B cells determining B cells activation and promoting B cell survival and proliferation. Differently from other APCs, FDCs can retain ICs long-term on their surfaces, constituting a persistent stimulus for memory B cells re-stimulation. Moreover, FDCs do not show phagocytic activity and lack lysosomes and lysozyme [9][10].

To conclude, as previously stated, pSS has a higher prevalence in women and interestingly, pDCs expression of TLR may depend on gender. TLR-7 coding gene (Tlr7) is located on the terminal region of the X-chromosome. In murine models of Systemic Lupus Erythematosus (SLE) the translocation of this region on the Y-chromosome constitutes the Y-linked autoimmune accellerating region (Yaa), that has been associated with severe renal manifestation of disease in male mice. In particular, the sole duplication of Tlr7 is sufficient to accellerate autoimmunity. This observation suggests the possible implication of Tlr7 and Yaa in autoimmune disease pathogenesis and deserves to be further elucidated [11].

TLR-7 expression may depend even on sex hormones levels. Particularly, androgens, both in blood and tissues, affect pDCs, causing a decrease in the expression of TLR-7 and -9. Androgens protect epithelial cells from apoptosis, reducing autoantigens release and preventing the upregulation of TLR. In women, a low level of such hormones, as seen during menopause or as a consequence of defective local production of androgens, determines a constitutional higher expression of TLR in pDCs predisposing their hyperactivation and a possible consequent loss of immunological tolerance [4].

2. Macrophages

Macrophages are tissue resident innate cells involved in early defence against pathogens and in principal mechanisms of tissue homeostasis. These cells are characterized by significant plasticity, as their polarization and activation are determined by a combination of several environmental stimuli. At the beginning of the century, two extreme functional phenotypes of macrophages were described: M1/M2. M1 $CD68^+$ promoted inflammatory response that was secondary to microbe attack, while M2 $CD163^+$ contributed to the repairing of tissue damage, as well as promoting angiogenesis and removing cell debris through phagocytosis [12]. M1 $CD68^+$ are drivers of a prevalent pro-inflammatory response, as they act as APC to T cells through the complex antigen-type II Major Histocompatibility Complex (MHC II) and directly produce inflammatory cytokines. On the other hand, the same cells are able to prevent dysreactive immunity by means of phagocyting impaired T-cells.

This dualistic function makes the understanding of the involvement of macrophages in inflammatory diseases such as pSS more complicated. It could be hypothesized that they rely on their ability to sense the environment and change consequently. As a matter of fact, these cells show a remarkable ability in shifting their functional phenotype from pro-inflammatory to protective, in relation to the microenvironment they are acting in. In the inflammatory setting, the expression of specific cytokines such as IFN, IL-12, IL-4 or IL-10 and the transcription factor HIF-1α (hypoxia-inducible factor 1 alpha) determine the polarization from one phenotype to another [12]. In conclusion, the biology of macrophages appears complex and dynamic due to the fact that these cells evolve in a heterogeneous continuum, resulting in high plasticity and reversibility so that any sort of strict categorization appears to no longer be suitable.

In pSS, salivary gland tissue macrophages appearance is an early occurrence; their number reflects the progression of the disease as it increases in later stages of this rheumatic condition [13].

Their function is related to the presence of IFNγ and IL-17 secreted by Th1 and Th17, respectively. These cytokines activate macrophages determining infiltration of salivary tissue, leading to exocrinopathy. Therefore, macrophages contribute to initiating and perpetuating the inflammatory epithelial damage.

Beside salivary glands, the epithelitis process may affect other epithelial barriers, as documented in eyes and kidneys. In particular, in ocular mucosa, immune cells infiltration occurs determining persistent inflammation. Chronic inflammation of eye epithelium determines the development of squamous metaplasia characterized by the keratinization of cornea surface, which represents the end stage of ocular involvement in pSS patients, who usually suffer from severe xerophthalmia. IL-1 secreted by activated macrophages has been demonstrated to play a crucial role in the development of squamous metaplasia. Experiments on eye tissue from murine models have demonstrated, not only the increase in number of macrophage in cornea and limbus, but also the aberrant network with $CD4^+$ T cells. The latter, once activated, evolves in autoreactive clones that may perpetuate the activation of macrophages, themselves sustaining a pro-inflammatory auto-maintained loop [14][15].

In kidney specimens of patients who suffer from tubule-interstitial nephritis macrophages have been observed. Particularly, in a recent paper, the increase of HIF-1α as well as M2 $CD163^+$ and M1 $CD68^+$ was highlighted in renal tissue of pSS patients presenting hypokalaemia. In normal conditions M2 $CD163^+$ cells and HIF-1α are not expressed in the tubule-interstitial space. This evidence may suggest a possible role for M2 in acute tubular injury and in the consequent restoration mechanism [16]. More studies should be conducted in order to clarify the protective action of these cells in renal damage during pSS and their possible use as therapeutic agents.

3. Mast Cells

Mast cells or mastocytes are cells rich in histamine and heparin granules that are usually found in the connective tissue. Their role in allergy and anaphylaxis has been extensively investigated. However, further research has underlined their possible involvement in tissue healing, angiogenesis and immune tolerance, as well as in defense against microbial insults.

In chronic inflammatory processes, mast cells contribute as key players and the first description of this subset in pSS dates back to 1998 [17]. Mast cells were demonstrated to promote fibrosis and fatty infiltration of salivary glands because of their interaction with fibroblasts and their contribution to collagen synthesis. Moreover, enzymes produced by mast cells can cleave and consequently activate matrix metalloproteinases (MMPs), which are considered as important mediators of tissue destruction and are produced by epithelial cells. Mast cells interact directly with the epithelium by releasing their activating enzymes after an early damage of epithelial barrier, as in the case of loss of basal lamina anchorage and the consequent altered cell adhesion. Therefore, the activity of these enzymes does not dependent on the lymphocyte infiltration but it precedes this phenomenon. Specifically, while analyzing salivary biopsies from pSS patients, increased levels of MMP-9 and -3 were detected; higher enzyme levels correlated with more structurally and functionally impaired glands were found as well, thus evidencing a more severe disease activity [18].

Recently, mast cells, identified using anti-tryptase antibodies, were observed in pSS salivary glands. However, a direct correlation between their number, angiogenesis and fibrosis was not established [19].

4. Salivary Gland Epithelial Cells (SGECs)

Salivary gland epithelial cells (SGECs) compose the ductal excretory structure and were considered classical non-immune cells in the past. Nowadays, thanks to several advances in understanding their functions, they are regarded as both the principal target of autoimmune responses and important players in the initiation of autoimmunity in pSS. In details, SGECs in pSS favor the inflammation process as a result of subverted cell architecture, cytokines production and immune cell recruitment; they simultaneously boost adaptive response, as they are the major source of pSS autoantigens, therefore acting as immunogenic elements [20].

In pSS, the onset of the inflammation process starts with the loss of polarity of SGECs [21]. Tight junction maintains cell polarity and in pSS several studies evidenced a dysfunctional expression of this molecules in SGECs. In particular, a decrease of occludin and Zo-1 and redistribution of claudin were described. This architectural disorganization has been linked to IFN and TNF levels thus suggesting a causative role for these cytokines. Clinically, the expression of the dysfunctional tight junctions could account for the reduced saliva production, one of the main symptoms in this disease [22][23]. At the beginning of the inflammatory process, they express and secrete different chemiotactic factors for lymphocytes such as CXCL12, CXCL13, CCL19 and CCL2 as well as adhesion molecules (ICAM-1), costimulatory molecules (CD80–CD86) and MHC II [24][25]. This complex interplay determines the recall, adhesion and activation of T and B cells at the inflammation site.

SGECs determine the maturation of naive $CD4^+$ T-cells in T-follicular helper cells and are essential in the maintenance of germinal centers, as pre-clinical studies have demonstrated [26]. Moreover, they directly secrete cytokines (IFN, IL-1, IL-6, IL-7 and BAFF) involved in the constitution of a pro-inflammatory environment that finally leads to epithelitis [27][28].

Several hypotheses have been proposed to assess their role in pSS, but the most fascinating regards the involvement of the endoplasmic reticulum stress model [29]. In fact, SGECs have extended ER in order to produce fluids such as saliva and its proteins as typical secretory cells, found also in lachrymal glands, bronchioles, bile ducts and renal tubules. However, when the request of protein production is huge, the ER system undergoes a severe metabolic stress, evidenced by the dilatation of its lumen [30]. At this point, different mechanisms such as unfolded protein response (URP), autophagy and apoptosis emerge. In particular, the activation of URP, a process that needs high energy levels, determines the subsequent arrangement of autophagy-genes. Doing so the cell can obtain the metabolic support to maintain the URP process active [31][32]. When the stress trigger continues, it overcomes the possibility of the cells to survive causing apoptosis. Hence endoplasmic reticulum's (ER) stress in SGECs can trigger the immune cascade. In particular, several products of the ER stress can activate immune response such as IL-6, produced during URP activation; MHC expressed during autophagy process; and nucleic acid exposed on cell surfaces into apoptotic blebs [33].

In addition, clarification about the link between ER stress and the expression of pSS autoantibodies (anti-Ro and anti-La) was provided [34]. During ER stress, in the course of apoptosis, cytoplasmic antigens (Ro and La), move into the cell membrane and in the final stage of this process are exposed outside the cell into apoptotic blebs. Therefore, the interruption of autophagy and the consequent aberrant cell death represent the trigger for an immune stimulation, finally determining the exposure of pSS self-antigens.

Hence, the apoptosis can no longer be considered as a "silent" process, since the discharge of self-antigens by apoptotic cells activates pathological autoimmune responses [35].

IFN acts as a major player among the cytokines produced by SGECs, even if the exact mechanism of IFN production is still unknown. The higher and dysfunctional expression in several autoimmune diseases, such as pSS, of Viral-like Long Interspersed Nuclear Element-1 (LINE-1, L1) that are highly repetitive DNA sequences, leading to the production of a huge amount of Type I IFN, has been suggested [36]. Human L1 contains two reading frames encoding for L1 ORF1p and L1 ORF2p proteins. The latter, physiologically expressed in germinal and somatic cells, has enzymatic activities that are essential for L1 functions [37]. The increased level of L1 ORF2p in ductal salivary cells may account for L1 hyperactivity with a consequential intensified production of IFN [38].

Another important finding is the lack of L1 ORF2p in high lymphocytic focus score biopsies of pSS patients and the increased expression of L1 ORF1p in high-grade B cell lymphomas, meaning that the reduction of ORF2p in pSS could be considered an alert for lymphomas development [39].

Instead, in low grade focus score a positive correlation with L1 ORF2p level and negative correlation with APOBEC3B, an inhibitory enzyme acting directly on L1, was found, suggesting a dysfunction in the inhibitory mechanism [38]. Conversely, SGECs apoptosis could expose L1 ORF1p and ORF2p to the immune system through the creation of ICs that, as mentioned above, directly activate pDCs and determine the production of type I IFN [36].

Taken together, these findings suggest a complicated mechanism beneath the immunogenic role of SGECs, which needs to be further investigated. At present, we can assume that chronic inflammation in a specific genetic background, could lead to an unbalanced antigens expression and cytokine profile in SGECs that may contribute to pSS development as well as to proliferative disease occurrence. In fact, SGECs may exert a pro-oncogenic role contributing to the development of lymphoepithelial sialadenitis (LESA), a pre-cancerous lesion associated with a high risk of developing MALT lymphomas. LESA constitution is due to the aberrant cross-talk with localized lymphocytic aggregates, but its exact mechanism is at the moment under investigation [40]. The complete knowledge of this process can lead to the development of new therapeutic intervention and may give physicians tools to interfere in this pathological feed-back in pSS.

5. Endothelial Cells

Endothelial cells, expressing CD31, constitute blood and lymphatic vessels. High endothelial venules represent the highways through which immune cells arrive at the inflammation sites, while the lymphatic vessels promote the arrival of antigens and APCs by the drainage of interstitial fluid into the tertiary lymphoid sites (TLSs), typically found in pSS salivary glands. These latter, differently from secondary lymphoid organs (SLOs) such as lymph nodes, spleen, tonsils and Peyer's patches, lack in T and B cells organization, capsulation and vascularization [41].

The activated endothelium expresses adhesion molecules such as ICAM-1, VCAM-1 and E- and P- selectins necessary for the interaction with lymphocytes. In pSS patients the activation of endothelial cells is increased allowing an important migration of immune cells in inflamed tissues [42][43]. Moreover, the expression of ICAM-1 positively correlates with focus score of salivary biopsy [44]. Furthermore, in pSS, as well as in other chronic inflammatory diseases, an increased neoangiogenesis is observed. The leading cause relies on the overexpression of vascular endothelial growth factor (VEGF), that determines chaotic neoangiogenesis. Dysfunctional vessels lead to persistent extravasation of immune cells [45]. In addition, defective lymphatic vessels, characterized by over expression of CCL21, together with a dysregulation in chemokine gradient, increase the arrival and permanence of lymphatic cells into the TLSs [46].

6. Mucosa-Associated Invariant T (MAIT) Cells

Mucosa-associated invariant T (MAIT) cells are described as a specific subset of non-conventional/innate like T cells and represent a bridge between innate and adaptive responses [47].

As conventional T cells, MAIT cells originate from thymus, but differ by expressing an arranged TCR composed of Vα7.2 and Jα33 segments. Furthermore, they share with NK cells the expression of CD161 marker ($CD161^{high}$/$TCRV\alpha7.2^{+}$ MAIT cells).

Formerly, this subset of cells was considered as $T\text{-}CD8^{+}$, able to recognize vitamin B related peptides, expressed on pathogens through MHC class I molecules [48][49]. But subsequently the capacity of diversification in different T cell subsets was evidenced; this was underlined by the ability of MAIT cells in expressing both CD4 or CD8 co-

receptors in order to respond to different stimuli [50]. In fact, the expression of CD8 enables MAIT cells to recognize intracellular peptides, meanwhile the CD4 receptor orchestrates a fast response to extracellular attacks [51][52].

Physiologically, MAIT cells are “natural memory” cells and promptly produce Th1, Th2 and Th17 cytokines under microbial insults [53]. Moreover, they represent potent regulatory cells able to maintain self-tolerance and homeostasis. Among MAIT cells, a specific subpopulation named $CD161^{dim}$/TCRVα7.2^{+} T cells was initially described. They resembled MAIT cells without the CD161 receptor and were characterized by a reduced ability in cytokine production, compared to classical MAIT cells [54].

MAIT cells in pSS are involved in the dysregulation of the mucosal environment beneath the autoimmune epithelitis development.

In the first study describing the pathogenetic role of MAIT cells and $CD161^{dim/}$TCRVα7.2^{+} T cells in pSS, the decreased number of both subpopulations in peripheral blood was evidenced, while their presence was observed in salivary gland tissue, due to the homing process [55]. Moreover, the altered function of remaining circulating MAIT cells has been revealed. MAIT cells and $CD161^{dim}$/TCRVα7.2^{+} T cells detected in peripheral blood from pSS patients were mainly $CD4^{+}$ and naïve, in contrast with controls. This might justify their reduced anti-microbial properties and their altered function determining the dysregulation of mucosal environment. In fact, both MAIT cells and $CD161^{dim}$/TCRVα7.2^{+} T cells share a decrease in the expression of activation markers CD154 and CD69, as well as a reduction in TNF and INFγ production.

In conclusion, the functional role of $CD161^{dim}$/TCRVα7.2^{+} T cells needs to be further elucidated in order to clarify their possible role in pSS aetiology, as they have been claimed to be an autonomous cell group independent from MAIT cells [56][57].

7. Natural Killer Cells (NKs) and Natural Killer T Cells (NKTs)

Natural Killer cells (NKs) represent the link between innate and adaptive immune system through their crosstalk with DCs and the interaction with epithelial cells. They are mainly involved in antiviral and anti-tumoral responses. In particular, classical NKs express the NKp30 receptor recognized by DCs with consequent production of IFN and IL-12. To date, contrasting evidence shows a possible pathogenetic role of these cellular groups in pSS. In mouse models, their activation appears protective towards pSS development and even helps in mitigating sicca symptoms. On the other hand, in pSS patients the presence of NK in salivary gland is correlated to local inflammation. The reason for this difference seems to depend on an increased NKp30 receptor expression. In support of this evidence, genetic mutation of the promoter of NKp30 gene, with a reduced transcription and transduction of the relative protein, determines the amount of protection from pSS [58].

The over-expression of NKp30 and its ligand (B7H6) on SGCE membranes at salivary level in pSS patients may explain the hyperactivity of NKs in the early phases of the disease, causing their aberrant cross-talk with SGECs and DCs [58]. The hyper-expression of B7H6 may determine the homing of these cells in pSS target tissue and

could justify the decreased number of these cells in a pSS patient's circulation. The NKs isolated from pSS blood patients, moreover, showed a dysfunctional phenotype with a lowered killing activity and a reduction in the expression of activating receptors [59].

NK functions may possibly be related to the inflammatory milieu in which they act in, and even depend on the stage of the disease.

An interesting review of our group described the pathogenetic role in pSS of a specific subset of NK cells named Natural Killer T cells (NKTs), focusing in particular on invariant NKT (iNKTs). iNKTs have been described as potential therapeutic agents or possible predictors to response to treatment in pSS. An attempt to use iNKTs as cellular therapy has already been reported in Systemic Sclerosis, and this evidence should encourage researchers to investigate iNKTs functions in pSS [60].

In conclusion, a former subset of NKs named NK22, characterized by the production of high amount of IL 22, has been recently recognized as a completely different cell group belonging to Innate Lymphoid Cells (ILCs), which are described in another section of this article [61]. The pathogenetic role of IL-22 in pSS patients has clearly emerged in the last few years; the overexpression of genes implicated in the production of this cytokine and its receptor (IL-22R) expressed on SGECs has been demonstrated and a positive correlation between salivary inflammation and level of IL-22 has been described [62].

8. Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) belong to a relatively new subsets of cells that seem to play a crucial role in the pathogenesis of several chronic inflammatory diseases [63][64]. Three different subsets of ILCs have been described so far. Each group is characterized by the expression of specific surface markers, cytokine production and depends on different transcription factors to develop and acquire functions. Specifically, T-bet, Gata3 and RoRγt are the master regulators of ILC1, ILC2 and ILC3, respectively [65]. Effector cytokines produced from each subset are IFNγ for ILC1; IL-4, IL-5, IL-9, IL-13 and GMCSF for ILC2; IL-17A/F, IL-22, IFNγ and GMCSF for ILC3 [66][67]. It shows clearly that ILCs share common feature, especially considering cytokine production, with their adaptive counterpart belonging to the T helper family, namely Th1, Th2, Th17 [68][69].

ILC cells can switch their transcriptional program on specific environmental stimuli gaining effector functions of a different ILC group. This phenomenon described as ILC plasticity deserves a deeper investigation to better understand ILC activity [70][71].

These cells are involved in protective processes against pathogens as viruses, bacteria and parasites as well as in granting tissue homeostasis [72]. However, their unbalanced activation in a pro-inflammatory milieu strongly participates in the dysreactive process beneath autoimmune diseases. In particular, there have been different reports accounting for a possible role of ILCs in inflammatory bowel diseases, rheumatic diseases, asthma and allergy [73][74].

In rheumatology, the analysis of synovial fluid from rheumatoid arthritis and psoriatic arthritis patients has revealed an increase in ILC1 and ILC3. ILC3 in particular are a major source of IL-17 and IL-22 [75]; these cytokines drive inflammation in spondyloarthritis and an increase of ILC3 was documented in psoriatic arthritis, as well as in ankylosing spondylitis [76].

ILCs are scarcely detected in blood, they can be depicted as “tissue resident cells”, mainly localized at epithelial barriers. Most of the evidence on their activity derives from studies conducted at the gut level that have extensively explored ILCs interaction with other immune cells and their response to microbiota stimulation [77][78].

In pSS, a marked disequilibrium between IL-22 and IL-22BP was demonstrated. Moreover, an aberrant expression of IL-22R1 on hematopoietic cells was described in both peripheral blood and salivary gland tissue. In addition, the IL-22 axis, the aberrant and hyperexpression of IL-22R1 were shown to be related to the presence of high amount of IL-18, a cytokine produced via inflammasome activation. Taken together, these observations point out that, at a salivary gland epithelial site, in a pro-inflammatory milieu as in pSS, IL-22 producing cells may play a pivotal role in amplifying a dysreactive immune response that causes final tissue damage [79]. The IL-22 network induces STAT3, AKT and MAPK pathways activation; these mechanisms will be overviewed in detail in a special section in this review.

However, the production of IL-22 from ILC3 does not justify their implication in the formation of GCs-like structure. ILC3 appear as a powerful link between adaptive and innate immunity. A more extensive analysis on their chemokine production has revealed that ILC3 secrete CCL20. This molecule displays a strong chemotactic activity on immune cells, particularly lymphocytes and DCs, giving rise to the formation of mucosal lymphoid tissue in the area surrounding the epithelial barrier where inflammation occurs in earlier stages of the disease. Furthermore, ILC3 produce a B-cell-activating factor (BAFF) that stimulates B-cells to proliferate, survive and organize in GCs-like structures where in situ antibodies production takes place [80][81].

The role of ILC3 in determining this inflammatory-prone microenvironment appears of paramount importance, but further studies are required in order to clearly outline their activity [82].

Aspects that deserve to be clarified are mainly related to the migration of ILC3 in salivary gland tissues, their role in forming TLS and their interaction with epithelial cells [83]. Specifically, ILCs express the NKp30 receptor on their surface, the same receptor can be found on NK cells. In pSS an increased expression of NKp30 has been evidenced. It recognizes the B7H6 ligand expressed on epithelial cells; this underlines how complex the interaction at epithelial barrier sites could be [58].

Defining the exact aetiology of pSS remains a great challenge. Innate immunity, with a particular focus on ILC3, IL-22 production and the consequent activated pathways should be regarded with special attention in order to better clarify disease pathogenesis.

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