Medical Research Archives

European Society of Medicine

OPEN ACCESS

**Published:** October 31, 2023

**Citation:** CIE Smith, and P Bergman, 2023. The Yin and Yang of Plasmacytoid Dendritic Cells – SARS-CoV-2 Protection versus Susceptibility to Selected Autoimmune Diseases, Medical Research Archives, [online] 11(10) https://doi.org/10.18103/mra.v11i10.4552



**DOI**
https://doi.org/10.18103/mra.v11i10.4552

**ISSN:** 2375-1924

RESEARCH ARTICLE

# The Yin and Yang of Plasmacytoid Dendritic Cells – SARS-CoV-2 Protection versus Susceptibility to Selected Autoimmune Diseases

**Smith CIE[1,2,3,*] and Bergman P[3,4,5,*]**

1. Department of Laboratory Medicine, Biomolecular and Cellular Medicine, Karolinska Institutet, Stockholm, Sweden
2. Translational Research Center Karolinska (TRACK), Karolinska Institutet, Stockholm, Sweden
3. Department of Infectious Diseases, Karolinska University Hospital Huddinge, Stockholm, Sweden
4. Department of Laboratory Medicine, Clinical Immunology, Karolinska Institutet, Stockholm, Sweden
5. Department of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden

***Corresponding authors:** edvard.smith@ki.se
peter.bergman@ki.se

ABSTRACT

Dendritic cells can be subdivided into three major subsets. The conventional (classical) dendritic cells (cDCs), also known as myeloid DCs, can be further split into the cDC1 and cDC2 subpopulations. The third subpopulation is the plasmacytoid DC (pDC), which can be further divided into three subsets. The pDCs are unique because they constitute the leukocyte, which secretes the largest amount of interferon (IFN). Since IFNs are crucial in the defence against viruses, it could be hypothesized that reduced IFN production by pDCs could cause susceptibility to viral infections in general. However, this does not seem to be the case, since it was not until the SARS-CoV-2 pandemic that the essential role of pDCs in viral immunity was revealed. In this review we discuss the role of pDCs in the protection against Covid-19 and the mechanisms underlying susceptibility when these cells are malfunctioning as seen in haematological malignancies, exemplified by chronic lymphocytic leukemia (CLL). In contrast, overactive pDCs can lead to selected autoimmune diseases, where systemic lupus (SLE) is the premier example, demonstrating the yin and yang relationship. We also review pharmacological interventions related to pDCs.

## Introduction

The first description of pDCs may have been the report by Eckert & Schmid in 1989[1], although at this stage the nature of these cells remained elusive. Ten years later, pDCs were identified as the major cell in blood responsible for the secretion of type 1 IFNs [2,3]. Thus, in contrast to cDCs, which are essential antigen-presenting cells [4], pDCs have a very different physiological role.

These cells naturally produce IFN and are conserved across both humans and mice. Other functional, as well as key genetic features of pDCs, are shared between both species [5,6], demonstrating the evolutionary conservation of this immune cell type. Using gene inactivation experiments the authors concluded that all IFN-α and -β responses, whether systemic production in innate immunity, or local action of IFN from pDCs in adaptive immunity, are under the control of IFN regulatory factor 7 (IRF7) [7]. This research-group also demonstrated that the IFN-inducing Toll-like receptor 9 (TLR9) ligand, CpG oligodeoxynucleotide, together with the Myeloid differentiation primary response 88 (MyD88)–IRF7 complex, is specifically retained for long periods in the endosomal vesicles of pDCs. This spatiotemporal effect underlies the unique signalling scenario, which characterizes the extremely potent IFN induction by pDCs [8].

Plasmacytoid dendritic cells originate from the bone marrow and emerge as mature cells in the periphery. Here they remain non-proliferative and have a relatively short lifespan of days. Stimulation through TLRs will promote their survival [9]. In contrast to cDC, the pDC subset is known to require B-cell lymphoma-2 (BCL-2) to resist apoptosis. This pattern was maintained upon TLR stimulation. Hence, as expected, treatment with the BCL-2 selective inhibitor venetoclax (brandnames Venclexta® or Venclyxto®) primarily kills pDCs [10] and therefore this drug has also been used to treat blastic pDC neoplasms [11]. Furthermore, stimulation of precursors of pDCs results in the induction of three different subpopulations depending on the type of stimulus, the P1-pDC (Fig. 1), being found in SLE-patients [12].

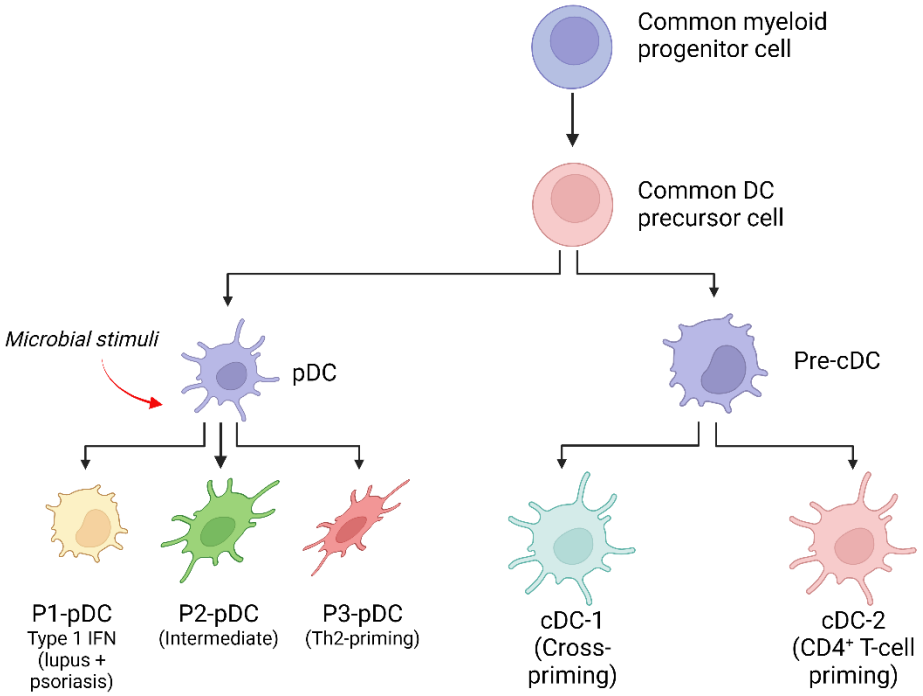


**Figure 1.** The development and diversification of plasmacytoid dendritic cells (pDCs). Modified from [12]. Accordingly, the pDC subsets have the following characteristics: P1-pDC, PD-L1$^{+}$CD80$^{-}$; P2-pDC, PD-L1$^{+}$, CD80$^{+}$, P3-pDC, PD-L1$^{-}$CD80$^{+}$.

Both cDCs and pDCs carry the cytokine receptor FMS-related tyrosine kinase 3 (FLT3, also known as CD135) and are strictly dependent on its ligand FLT3L for development. In fact, FLT3 alone in the absence of other signals, is sufficient to drive the development of pDCs and cDCs [13].

Plasmacytoid dendritic cells may not always be protective against infections but increased numbers have instead been shown to occasionally correlate with disease severity. Thus, in mice susceptible to cutaneous leishmaniasis, the presence of larger numbers of pDCs is associated with more protracted infection, suggesting a complex and important role for pDCs in this condition [14].

Recently, a novel interferonopathy was discovered, where deletions of the 3' end of the RELA (also known as p65 in the NF-kB pathway) mRNA cause a dominant negative effect on the gene product [15]. Autoinflammation and autoimmunity in these patients was driven by an upregulation of TLR7 and MyD88 transcripts in pDCs, but also in classical and nonclassical monocytes and in myeloid DCs (mDCs). Although the exact contribution of the pDC is not yet defined, it demonstrates that excessive IFN production causes disease.

In this review, we will describe conditions where pDCs are impaired with potential implications for viral infection susceptibility. In contrast, overactive pDCs may also lead to disease, which can be exemplified by SLE. Finally, we discuss whether pDCs can be directly targeted by drugs to modulate immune responses in different disorders.

## LOSS AND IMPAIRMENT OF pDCs DURING INFECTION WITH HIV

Already in 1994, Feldman et al. showed that the number of IFN-producing cells in peripheral blood is reduced in HIV-infected patients [16]. Seven years later the same group reported that such IFN-producing cells corresponded to the pDC population [17]. The authors concluded that deficient production of IFN-α by pDCs from HIV-infected patients results from both loss of these cells in number, as well as their qualitative dysfunction. Patterson et al., 2001 reported that while both pDCs and mDCs express CD4, as well as, low levels of C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4), pDCs are more readily infected by HIV [18]. Treatment with highly active antiretroviral therapy (HAART) regimens did not fully restore the pDC compartment, while the correlation with CD4 counts varied among the studies [19,20]. Collectively, this demonstrates that HIV impairs pDC activity at different levels and points to the importance of pDCs in the immune defence response against this infection. Given the profound immunological defect in untreated HIV, even if pDCs have a unique capacity to produce IFN, because they are just one of many cell types affected by a retroviral infection, their impairment only explains part of the enhanced susceptibility to infections among these patients (Fig. 2). More recently, it was found that upon TLR stimulation, pDCs show augmentation of activation-marker levels, IFN-related genes, HIV-1-restriction factors and cytokine levels [21]. The T-cell response appeared in parallel with upregulation of HIV-1-restriction factors and IFN-α production by pDCs.

It is also known that TLR7-driven type I IFN-production in pDCs is higher in women owing to cell-intrinsic actions of oestrogen and escaped X-chromosome inactivation leading to increased TLR7 protein levels [22,23]. The effect of this sex-difference on the outcome of an HIV-infection is, however, complex [24]. In contrast, as described elsewhere in this report, the sex difference enhances the development of autoimmune disease, with females having a greater propensity to such disorders [25].

## LOSS AND IMPAIRMENT OF pDCs IN HEMATOLOGICAL MALIGNANCIES

Another group of conditions where pDCs are impaired are the hematological malignancies. We have previously pointed out [26] that pDCs are lost and functionally impaired in chronic lymphocytic leukemia (CLL), a B-cell malignancy, both in the human disease [27-30], and in the T-cell leukemia/lymphoma-1 (TCL1) mouse model of CLL [29]. Interestingly, treatment with Bruton tyrosine kinase (BTK) inhibitors, which selectively block B-cell receptor-mediated NF-kB signalling [31], restores pDC numbers [28,30,32]. In Smith et al., 2022 [26], we also proposed that the severe Covid-19 observed in CLL [33] and in other hematological malignancies may be caused by lack of pDC activity, in particular due to reduced pDC numbers.

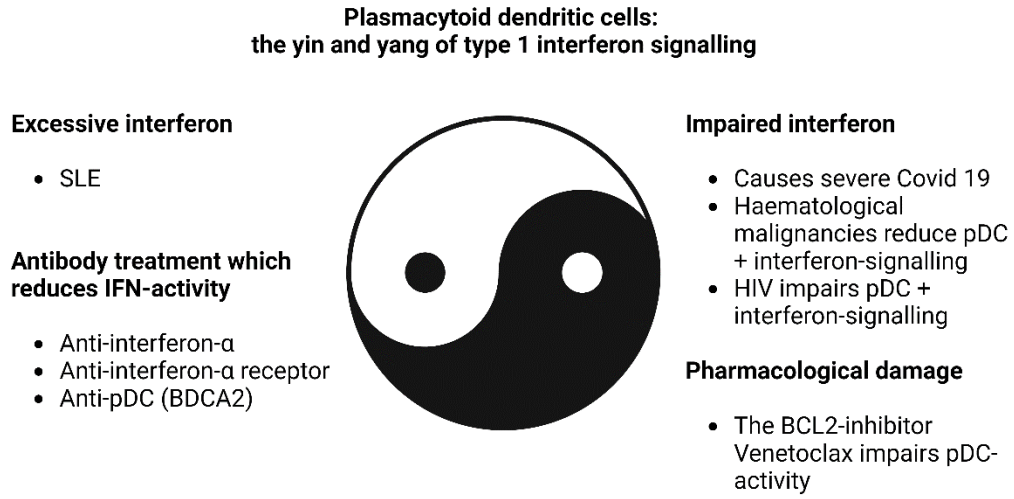


**Figure 2.** Plasmacytoid dendritic cells (pDCs) impact human health in different ways corresponding to a *yin* and *yang* scenario. Excessive pDC effects seem to induce susceptibility to Systemic Lupus Erythematosus (SLE), whereas reduced effects predispose to severe Covid-19.

We have now found additional evidence for this notion in the literature. However, as mentioned, apart from reduced numbers, the pDC population in CLL also frequently seems to be functionally impaired [27]. In other hematopoietic malignancies both reduced pDC numbers and activity have also been reported. Boissel et al., 2004 demonstrated that bloodborne pDCs in chronic myeloid leukemia (CML) show altered gene expression, which correlates with high plasma levels of Vascular endothelial growth factor (VEGF), and that reduced numbers of pDCs are not completely normalized by treatment with imatinib mesylate, a tyrosine kinase inhibitor [34]. Wysocka et al., 2002 reported that $CD123^+$ DCs, major producers of IFN-α, are significantly diminished in patients with cutaneous T cell lymphoma (Sézary syndrome) regardless of the level of tumour burden [35]. Thus, pDCs appear to be reduced both in number and function in various haematological malignancies (Fig. 2), which could increase the risk for infectious complications in this patient-group.

In blood malignancies, pDCs are not the only cell type affected, rather in such malignancies haematopoietic progenitors in general are impacted. As an example, bone marrow of untreated CLL shows a significantly lower proportion of CFU-GM (colony forming unit of granulocyte-macrophage), BFU-E (burst-forming unit-erythrocyte), and of CFU-GEMM (granulocyte, erythrocyte, monocyte, megakaryocyte) compared to normal controls [36]. CLL cells were also reported to block hematopoiesis by TNF and other cytokines, among them IL-3 [37]. In addition, disturbed T and B cell interactions may cause defects of the immune system observed in patients suffering from CLL [38]. Moreover, CLL cells influence their microenvironment by producing cytokines and chemokines, and by subverting normal accessory cells to promote tumour cell survival and escape from immune detection [39,40].

## pDCs ORCHESTRATE THE TYPE 1 INTERFERON RESPONSE DURING SARS CoV-2 INFECTION

The Covid-19 pandemic has swept over the world during recent years. Early in the pandemic, it was clear that older people had a much higher risk of dying from Covid-19. In addition, underlying conditions such as obesity, lung disease and severe immunosuppression also increased the risk of succumbing to the disease [41]. Interestingly, male sex appears to be a risk-factor as well, which could be related to X-linked traits [42].

However, some young and previously healthy people also had a very severe disease course. This fact prompted a deeper analysis of the underlying cause in these unexpected cases [43]. Several research-teams across the world found genetic variants in the type 1 IFN pathway that turned out

to explain parts of this susceptibility [44]. Notably, many of these genes are highly expressed in pDCs, and indeed dysfunctional pDCs were shown to be involved [45]. For example, patients with deleterious variants in the genes encoding TLR7 and IRF7, which profoundly impair pDC function, are highly susceptible to severe Covid-19 [46,47].

Notably, these genetic variants do not seem to confer an increased risk to other viral infections, since most of the affected individuals in the SARS CoV-2 studies appeared to have handled influenza, varicella, and other viral infections in a normal way. This narrow immunological gap to SARS CoV-2, is intriguing and deserves further investigations before the next pandemic arrives. Nevertheless, the lessons learned from the studies on these inborn errors of immunity have been immense and contributed to an increased understanding of the essential role that pDCs play in the immune response and as master controllers of the type 1 IFN responses in humans [48].

Collectively, this suggests that there are at least 3 pDC-related mechanisms causing susceptibility to severe SARS-CoV-2 infection (Fig. 2): 1. inherited defects, affecting *TLR7* and *IRF7* genes, resulting in impaired activity of pDCs, 2. crowding-out activities by which leukemias and lymphomas impair the development of normal hematopoietic cells, including pDCs, by the synthesis of cytokines and possibly by other means and, less substantiated, 3. pharmacological effects caused by treatment with BCL-2 inhibitors because pDCs are highly sensitive to BCL-2 inhibition. In addition, all the mechanisms underlying susceptibility in the general population, such as age, sex and impairment of interferon (outside of TLR7 and IRF7) synthesis may also impact disease course and severity, but these are not specific pDC-mediated effects.

## EXCESSIVE pDC-ACTIVITY CAN LEAD TO DISEASE: SYSTEMIC LUPUS AS AN EXAMPLE.

Women have a more rigorous immune response to infectious agents, while at the same time have an increased risk for autoimmune diseases. This can partly be explained by sex hormones, such as estrogen and progesterone [23], but recent knowledge indicates that the control of immunity is directly linked to the number of sex chromosomes. A key gene, that is highly expressed in pDCs, is *TLR7*, the corresponding protein of which is a sensor of double stranded RNA. *TLR7* is X-linked and thus undergoes inactivation in most female cells, thereby avoiding gene dosing effects. However, in several immune-cell subsets, *TLR7* escapes inactivation, which subsequently leads to increased amounts of TLR7 transcript and protein and thereby an excessive immune response after receptor activation.

Notably, *TLR7* activation induces downstream activation of the type 1 IFN system, which is implicated in the pathogenesis of SLE. The ligands of TLR7 originate from several sources, including foreign viral RNA and endogenous retroviral RNA [49]. In addition, pDCs can be activated by endogenous DNA via additional nucleic acid sensors, such as cGAS (cyclic guanosine monophosphate–adenosine monophosphate [cGAMP] synthase) [50]. In fact, it seems that excessive nucleic acid sensing can break tolerance in B-cells and drive development of autoreactive antibodies in SLE [51]. Thus, excessive TLR7-signaling in both pDCs (Fig. 2) and B-cells is a central theme in SLE pathogenesis. Another piece of evidence for the involvement of B-cells is the recent report on chimeric antigen receptor (CAR) T-cells directed against CD19 as a treatment in SLE [52].

Only selected autoimmune disorders are dependent on pDCs for their pathological manifestations. Apart from SLE, Systemic sclerosis, a systemic inflammatory disease, also seems to be dependent on pDCs [53].

## FUTURE PERSPECTIVES: CAN pDCs BE TARGETED AS A NOVEL TREATMENT OF IMMUNOLOGICAL DISORDERS?

There is solid evidence that IFN-α is a key driver of the pathogenic process in SLE [54]. Thus, several attempts have been carried out to block this cytokine [55]. The strongest evidence stems from work in mouse models, where depletion of IFN-α ameliorates [56], whereas elevation of endogenous IFN-α production worsens disease [57]. Recently, a monoclonal antibody directed against the IFN-α receptor showed beneficial effects in subgroups of lupus patients [58]. However, the precise target population and clinical use is still discussed.

More recently, antibody-mediated pDC depletion has been suggested as one option to reduce IFN-α signalling in lupus (Fig. 2). Again, solid evidence has been produced in two mouse models where pDC-depletion reduced disease scores [59]. In particular, the target has been BDCA (blood dendritic cell antigen), a pDC marker for which there is a monoclonal antibody. Results from cynomologous monkeys have shown that this drug could inhibit IFN signalling in blood cells [60]. Notably, results from two Phase 2 trials have been published where litifilimab, an IgG1 monoclonal antibody directed against the BDCA2 cell surface antigen, was evaluated against cutaneous and systemic lupus

erythematosus, respectively [61,62]. Both trials showed beneficial effects on the primary endpoints. However, an increased incidence of herpes virus infections occurred in a few patients.

Following the same concept, an antibody directed against the pDC-specific marker immunoglobulin-like transcript 7 (ILT7) has been tested in two Phase 1 clinical trials and demonstrated promising results. A detailed analysis of the results revealed that response was better in those with high baseline type 1 IFN activity, which lends further support for pDC depletion in systemic lupus [63]. The BCL-2 inhibitor, venetoclax has also been used to treat SLE, but the clinical benefit remains elusive [64]. To this end, the blastic pDC neoplasm is an aggressive neoplasm, which frequently responds to venetoclax [11]. A majority of these tumours seems to lack expression pf PD-L1/CD274 [65], suggesting that at least some of them belong to the P3-pDC subpopulation characterized as PD-L1$^{-}$CD80$^{+}$ [12], Fig. 1. For these reasons we propose that the BCL-2 dependency may not exist for all the three pDC subsets, including the P1-pDC population implicated in the pathogenesis of SLE.

Combined, there are several promising approaches to block IFN-α signalling in lupus, including inhibition of the cytokine directly, receptor blocking as well as depletion of the pDC number and function. However, careful monitoring of adverse events, such as viral infections (specifically SARS CoV-2) are warranted, and real-world data are still scarce.

## Conclusion

Here we have reviewed different aspects of pDCs in relation to loss-of-function or excessive activity. First, we can conclude that pDCs are central components of the type 1 IFN responses to viral infections and are crucial for protection against SARS CoV-2. This is clearly shown by patients with genetic variants in the type 1 IFN signaling system mainly affecting pDC responses, who unexpectedly had very severe Covid-19 infection. Secondly, it seems that pDC numbers and function can be suppressed also in other conditions, for example due to haematological malignancy or drug treatment, where the BCL-2-inhibitor venetoclax seems to be particularly efficient in depleting pDCs. However, whether this dependency is valid for all the three pDC subsets remains elusive. Thirdly, excessive type 1 IFN activity is implicated in the pathogenesis of lupus. Consequently, several attempts to block type 1 IFN signaling have been tried with various success. Recently, pDCs have been directly targeted in SLE by using anti-BDCA2-antibodies, which resulted in beneficial outcomes for patients in Phase 2 clinical trials. However, an increased frequency of viral infections was observed. Thus, pDCs can be described as the yin and yang of the type 1 IFN system and emerge as a promising therapeutic target for selected autoimmune diseases, given that the risk for susceptibility to viral disease is considered.

## Acknowledgements

We are grateful to Dr. Lindsay Davies for constructive comments on the text. BioRender was used to construct the figures.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## Funding statement

This work was supported by the Center for Innovative Medicine (CIMED), the Swedish Cancer Society and the Swedish Research Council.

## References


1. Eckert, F. & Schmid, U. Identification of plasmacytoid T cells in lymphoid hyperplasia of the skin. *Arch Dermatol* 125, 1518-1524 (1989).
2. Cella, M. *et al*. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat Med* 5, 919-923, doi:10.1038/11360 (1999).
3. Siegal, F. P. *et al*. The nature of the principal type 1 interferon-producing cells in human blood. *Science* 284, 1835-1837, doi:10.1126/science.284.5421.1835 (1999).
4. Banchereau, J. & Steinman, R. M. Dendritic cells and the control of immunity. *Nature* 392, 245-252, doi:10.1038/32588 (1998).
5. Crozat, K. *et al*. Comparative genomics as a tool to reveal functional equivalences between human and mouse dendritic cell subsets. *Immunol Rev* 234, 177-198, doi:10.1111/j.0105-2896.2009.00868.x (2010).
6. Guilliams, M. *et al*. Unsupervised High-Dimensional Analysis Aligns Dendritic Cells across Tissues and Species. *Immunity* 45, 669-684, doi:10.1016/j.immuni.2016.08.015 (2016).
7. Honda, K. *et al*. IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature* 434, 772-777, doi:10.1038/nature03464 (2005).
8. Honda, K. *et al*. Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. *Nature* 434, 1035-1040, doi:10.1038/nature03547 (2005).
9. Zhan, Y. *et al*. Plasmacytoid dendritic cells are short-lived: reappraising the influence of migration, genetic factors and activation on estimation of lifespan. *Sci Rep* 6, 25060, doi:10.1038/srep25060 (2016).
10. Carrington, E. M. *et al*. Prosurvival Bcl-2 family members reveal a distinct apoptotic identity between conventional and plasmacytoid dendritic cells. *Proc Natl Acad Sci U S A* 112, 4044-4049, doi:10.1073/pnas.1417620112 (2015).
11. Jain, A. & Sweet, K. Blastic Plasmacytoid Dendritic Cell Neoplasm. *J Natl Compr Canc Netw* 21, 515-521, doi:10.6004/jnccn.2023.7026 (2023).
12. Alculumbre, S. G. *et al*. Diversification of human plasmacytoid predendritic cells in response to a single stimulus. *Nat Immunol* 19, 63-75, doi:10.1038/s41590-017-0012-z (2018).
13. Sathe, P., Vremec, D., Wu, L., Corcoran, L. & Shortman, K. Convergent differentiation: myeloid and lymphoid pathways to murine plasmacytoid dendritic cells. *Blood* 121, 11-19, doi:10.1182/blood-2012-02-413336 (2013).
14. Baldwin, T. *et al*. Dendritic cell populations in Leishmania major-infected skin and draining lymph nodes. *Infect Immun* 72, 1991-2001, doi:10.1128/IAI.72.4.1991-2001.2004 (2004).
15. Moriya, K. *et al*. Human RELA dominant-negative mutations underlie type I interferonopathy with autoinflammation and autoimmunity. *J Exp Med* 220, doi:10.1084/jem.20212276 (2023).
16. Feldman, S. B. *et al*. Viral induction of low frequency interferon-alpha producing cells. *Virology* 204, 1-7, doi:10.1006/viro.1994.1504 (1994).
17. Feldman, S. *et al*. Decreased interferon-alpha production in HIV-infected patients correlates with numerical and functional deficiencies in circulating type 2 dendritic cell precursors. *Clin Immunol* 101, 201-210, doi:10.1006/clim.2001.5111 (2001).
18. Patterson, S., Rae, A., Hockey, N., Gilmour, J. & Gotch, F. Plasmacytoid dendritic cells are highly susceptible to human immunodeficiency virus type 1 infection and release infectious virus. *J Virol* 75, 6710-6713, doi:10.1128/JVI.75.14.6710-6713.2001 (2001).
19. Chehimi, J. *et al*. Persistent decreases in blood plasmacytoid dendritic cell number and function despite effective highly active antiretroviral therapy and increased blood myeloid dendritic cells in HIV-infected individuals. *J Immunol* 168, 4796-4801, doi:10.4049/jimmunol.168.9.4796 (2002).
20. Zhang, Z. *et al*. Differential restoration of myeloid and plasmacytoid dendritic cells in HIV-1-infected children after treatment with highly active antiretroviral therapy. *J Immunol* 176, 5644-5651, doi:10.4049/jimmunol.176.9.5644 (2006).
21. Jimenez-Leon, M. R. *et al*. Toll-like receptor agonists enhance HIV-specific T cell response mediated by plasmacytoid dendritic cells in diverse HIV-1 disease progression phenotypes. *EBioMedicine* 91, 104549, doi:10.1016/j.ebiom.2023.104549 (2023).
22. Laffont, S., Seillet, C. & Guery, J. C. Estrogen Receptor-Dependent Regulation of Dendritic Cell Development and Function. *Front Immunol* 8, 108, doi:10.3389/fimmu.2017.00108 (2017).
23. Souyris, M. *et al*. TLR7 escapes X chromosome inactivation in immune cells. *Sci Immunol* 3, doi:10.1126/sciimmunol.aap8855 (2018).
24. Guery, J. C. Sex Differences in Primary HIV Infection: Revisiting the Role of TLR7-Driven Type 1 IFN Production by Plasmacytoid Dendritic Cells in Women. *Front Immunol* 12, 729233, doi:10.3389/fimmu.2021.729233 (2021).

25. Souyris, M., Mejia, J. E., Chaumeil, J. & Guery, J. C. Female predisposition to TLR7-driven autoimmunity: gene dosage and the escape from X chromosome inactivation. *Semin Immunopathol* 41, 153-164, doi:10.1007/s00281-018-0712-y (2019).
26. Smith, C. I. E. *et al*. Do reduced numbers of plasmacytoid dendritic cells contribute to the aggressive clinical course of COVID-19 in chronic lymphocytic leukaemia? *Scand J Immunol* 95, e13153, doi:10.1111/sji.13153 (2022).
27. Orsini, E., Guarini, A., Chiaretti, S., Mauro, F. R. & Foa, R. The circulating dendritic cell compartment in patients with chronic lymphocytic leukemia is severely defective and unable to stimulate an effective T-cell response. *Cancer Res* 63, 4497-4506 (2003).
28. Palma, M. *et al*. Ibrutinib induces rapid down-regulation of inflammatory markers and altered transcription of chronic lymphocytic leukaemia-related genes in blood and lymph nodes. *Br J Haematol* 183, 212-224, doi:10.1111/bjh.15516 (2018).
29. Saulep-Easton, D. *et al*. Cytokine-driven loss of plasmacytoid dendritic cell function in chronic lymphocytic leukemia. *Leukemia* 28, 2005-2015, doi:10.1038/leu.2014.105 (2014).
30. Solman, I. G. *et al*. Impact of long-term ibrutinib treatment on circulating immune cells in previously untreated chronic lymphocytic leukemia. *Leuk Res* 102, 106520, doi:10.1016/j.leukres.2021.106520 (2021).
31. Smith, C. I. E. & Burger, J. A. Resistance Mutations to BTK Inhibitors Originate From the NF-kappaB but Not From the PI3K-RAS-MAPK Arm of the B Cell Receptor Signaling Pathway. *Front Immunol* 12, 689472, doi:10.3389/fimmu.2021.689472 (2021).
32. Moreno, C. *et al*. Immune restoration with ibrutinib plus venetoclax in first-line chronic lymphocytic leukemia: the phase 2 CAPTIVATE study. *Blood Adv*, doi:10.1182/bloodadvances.2023010236 (2023).
33. Blixt, L. *et al*. Covid-19 in patients with chronic lymphocytic leukemia: clinical outcome and B- and T-cell immunity during 13 months in consecutive patients. *Leukemia* 36, 476-481, doi:10.1038/s41375-021-01424-w (2022).
34. Boissel, N. *et al*. Defective blood dendritic cells in chronic myeloid leukemia correlate with high plasmatic VEGF and are not normalized by imatinib mesylate. *Leukemia* 18, 1656-1661, doi:10.1038/sj.leu.2403474 (2004).
35. Wysocka, M. *et al*. Sezary syndrome patients demonstrate a defect in dendritic cell populations: effects of CD40 ligand and treatment with GM-CSF on dendritic cell numbers and the production of cytokines. *Blood* 100, 3287-3294, doi:10.1182/blood-2002-01-0231 (2002).
36. Sala, R. *et al*. Evaluation of marrow and blood haemopoietic progenitors in chronic lymphocytic leukaemia before and after chemotherapy. *Eur J Haematol* 61, 14-20, doi:10.1111/j.1600-0609.1998.tb01055.x (1998).
37. Michalevicz, R. *et al*. Restoration of in vitro hematopoiesis in B-chronic lymphocytic leukemia by antibodies to tumor necrosis factor. *Leuk Res* 15, 111-120, doi:10.1016/0145-2126(91)90091-7 (1991).
38. Kneitz, C. *et al*. Inhibition of T cell/B cell interaction by B-CLL cells. *Leukemia* 13, 98-104, doi:10.1038/sj.leu.2401235 (1999).
39. Fecteau, J. F. & Kipps, T. J. Structure and function of the hematopoietic cancer niche: focus on chronic lymphocytic leukemia. *Front Biosci (Schol Ed)* 4, 61-73, doi:10.2741/s251 (2012).
40. Ten Hacken, E. & Burger, J. A. Microenvironment interactions and B-cell receptor signaling in Chronic Lymphocytic Leukemia: Implications for disease pathogenesis and treatment. *Biochim Biophys Acta* 1863, 401-413, doi:10.1016/j.bbamcr.2015.07.009 (2016).
41. Li, Y. *et al*. Risk factors for poor outcomes in hospitalised COVID-19 patients: A systematic review and meta-analysis. *J Glob Health* 11, 10001, doi:10.7189/jogh.11.10001 (2021).
42. Spiering, A. E. & de Vries, T. J. Why Females Do Better: The X Chromosomal TLR7 Gene-Dose Effect in COVID-19. *Front Immunol* 12, 756262, doi:10.3389/fimmu.2021.756262 (2021).
43. Zhang, S. Y., Zhang, Q., Casanova, J. L., Su, H. C. & Team, C. Severe COVID-19 in the young and healthy: monogenic inborn errors of immunity? *Nat Rev Immunol* 20, 455-456, doi:10.1038/s41577-020-0373-7 (2020).
44. Zhang, Q., Bastard, P., Effort, C. H. G., Cobat, A. & Casanova, J. L. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 603, 587-598, doi:10.1038/s41586-022-04447-0 (2022).
45. Severa, M. *et al*. Differential plasmacytoid dendritic cell phenotype and type I Interferon response in asymptomatic and severe COVID-19 infection. *PLoS Pathog* 17, e1009878, doi:10.1371/journal.ppat.1009878 (2021).
46. Asano, T. *et al*. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Sci Immunol* 6, doi:10.1126/sciimmunol.abl4348 (2021).
47. Campbell, T. M. *et al*. Respiratory viral infections in otherwise healthy humans with inherited IRF7 deficiency. *J Exp Med* 219, doi:10.1084/jem.20220202 (2022).

48. 48 Casanova, J. L. & Anderson, M. S. Unlocking life-threatening COVID-19 through two types of inborn errors of type I IFNs. *J Clin Invest* 133, doi:10.1172/JCI166283 (2023).
49. Reizis, B. Plasmacytoid Dendritic Cells: Development, Regulation, and Function. *Immunity* 50, 37-50, doi:10.1016/j.immuni.2018.12.027 (2019).
50. Li, X. D. *et al*. Pivotal roles of cGAS-cGAMP signaling in antiviral defense and immune adjuvant effects. *Science* 341, 1390-1394, doi:10.1126/science.1244040 (2013).
51. Vinuesa, C. G., Grenov, A. & Kassiotis, G. Innate virus-sensing pathways in B cell systemic autoimmunity. *Science* 380, 478-484, doi:10.1126/science.adg6427 (2023).
52. Mackensen, A. *et al*. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med* 28, 2124-2132, doi:10.1038/s41591-022-02017-5 (2022).
53. Ah Kioon, M. D. *et al*. Plasmacytoid dendritic cells promote systemic sclerosis with a key role for TLR8. *Sci Transl Med* 10, doi:10.1126/scitranslmed.aam8458 (2018).
54. Baechler, E. C. *et al*. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci U S A* 100, 2610-2615, doi:10.1073/pnas.0337679100 (2003).
55. Davison, L. M. & Jorgensen, T. N. New Treatments for Systemic Lupus Erythematosus on the Horizon: Targeting Plasmacytoid Dendritic Cells to Inhibit Cytokine Production. *J Clin Cell Immunol* 8, doi:10.4172/2155-9899.1000534 (2017).
56. Jorgensen, T. N., Roper, E., Thurman, J. M., Marrack, P. & Kotzin, B. L. Type I interferon signaling is involved in the spontaneous development of lupus-like disease in B6.Nba2 and (B6.Nba2 x NZW)F(1) mice. *Genes Immun* 8, 653-662, doi:10.1038/sj.gene.6364430 (2007).
57. Mathian, A., Weinberg, A., Gallegos, M., Banchereau, J. & Koutouzov, S. IFN-alpha induces early lethal lupus in preautoimmune (New Zealand Black x New Zealand White) F1 but not in BALB/c mice. *J Immunol* 174, 2499-2506, doi:10.4049/jimmunol.174.5.2499 (2005).
58. Furie, R. *et al*. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol* 69, 376-386, doi:10.1002/art.39962 (2017).
59. Rowland, S. L. *et al*. Early, transient depletion of plasmacytoid dendritic cells ameliorates autoimmunity in a lupus model. *J Exp Med* 211, 1977-1991, doi:10.1084/jem.20132620 (2014).
60. Pellerin, A. *et al*. Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. *EMBO Mol Med* 7, 464-476, doi:10.15252/emmm.201404719 (2015).
61. Furie, R. A. *et al*. Trial of Anti-BDCA2 Antibody Litifilimab for Systemic Lupus Erythematosus. *N Engl J Med* 387, 894-904, doi:10.1056/NEJMoa2118025 (2022).
62. Werth, V. P. *et al*. Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus. *N Engl J Med* 387, 321-331, doi:10.1056/NEJMoa2118024 (2022).
63. Karnell, J. L. *et al*. Depleting plasmacytoid dendritic cells reduces local type I interferon responses and disease activity in patients with cutaneous lupus. *Sci Transl Med* 13, doi:10.1126/scitranslmed.abf8442 (2021).
64. Lu, P. *et al*. Safety and pharmacodynamics of venetoclax (ABT-199) in a randomized single and multiple ascending dose study in women with systemic lupus erythematosus. *Lupus* 27, 290-302, doi:10.1177/0961203317719334 (2018).
65. Lorenzi, L. *et al*. E-Cadherin Expression and Blunted Interferon Response in Blastic Plasmacytoid Dendritic Cell Neoplasm. *Am J Surg Pathol* 45, 1428-1438, doi:10.1097/PAS.0000000000001747 (2021).