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The plasmacytoid dendritic cell as the Swiss army knife of the immune system: Molecular regulation of their multifaceted functions

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Abstract

Plasmacytoid dendritic cells (pDC) have been regarded as the "professional type I interferon producing cells" of the immune system following viral recognition that relies on the expression of Toll-like receptor (TLR)7 and TLR9. Furthermore, pDC link the innate and adaptive immune systems via cytokine production and antigen presentation. More recently their ability to induce tolerance and cytotoxicity has been added to their "immune skills". Such broad range of actions, resembling the diverse functional features of a Swiss army knife, requires strong and prompt molecular regulation to prevent detrimental effects, including autoimmune pathogenesis or tumor escape. Over the last decades, we and others have started to unravel some aspects of the signaling pathways that regulate the various functions of human pDC. Here we review aspects of the molecular regulatory mechanisms to control pDC function in light of their multifaceted roles during immunity, autoimmunity, and cancer.

Introduction

Plasmacytoid dendritic cells (pDC), a subset of the dendritic cell family, develop from hematopoietic stem cells in the bone marrow. The intermediate progenitor cell stages of human pDC are to be defined, but mouse pDC differentiate from either common DC progenitors or lymphoid-primed multipotent progenitors(1). Human and mouse pDC development depend on Fms-like kinase 3 ligand (Flt3L)(2, 3), expression of the transcription factor Spi-B, an Ets-family member controlling expression of the anti-apoptotic gene Bcl2A1(4–7), and the basic helix-loop-helix protein E2-2(8, 9). PDC are key mediators of innate immunity mainly against viruses by sensing their nucleic acids via Toll like receptor (TLR)7 and TLR9. Following TLR7/9 triggering, pDC produce large amounts of type I Interferons (IFNα/3B2) that control viral replication(10). PDC produce also the pro-inflammatory cytokines IL6 and TNFα that regulate T, B, NK cell and conventional (c)-DC

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responses together with IFNα/β(10). Further, pDC play a role in T cell activation as TLR ligation induces pDC maturation into so-called pDC-derived DC, that exhibit DC morphology and antigen-presentation capacity(11). Over the past years, the molecular pathways involved in controlling pDC activation and maturation are being unraveled, thereby uncovering new aspects of pDC functions, such as cytotoxic and tolerogenic abilities. Such pleiotropic immune abilities, similar to the features of a Swiss army knife (Figure 1), may have detrimental effects when uncontrolled as seen in autoimmune diseases. We review here the main molecular mechanisms that should keep activated pDC "on physiological track" and highlight some aspects of deregulated pathways as observed in disease with a particular focus on human pDC.

TLR signaling

The first 6 hours following TLR7/9 activation, pDC devote up to 60% of their transcriptome to expression of type I IFN genes (IFNα, β, and ω) and type III genes (IFNλ1–3)(12, 13). Such robust secretion capacity requires specific cellular and molecular mechanisms and as such their "plasmacytoid" secretory morphology resembles antibody-secreting plasma cells. The rapid and substantial IFNα/β production by pDC in response to TLR ligation is mediated by constitutive expression of the master regulator Interferon Response Factor (IRF)7 (reviewed in (14)) (Figure 2). The signaling cascades downstream of TLR7/9 depend on the adaptor protein MyD88, that complexes with IL-1 receptor–associated kinase (IRAK)1 and IRAK4, tumor necrosis factor receptor-associated (TRAF)6 and TRAF3, and IRF7 and IRF5 (reviewed in (14)). Both TLR signaling pathways culminate in activation of nuclear factor κB (NFκB) depending on phosphorylation of inhibitory (I)κB proteins by the kinases IκBα and IκBβ and subsequent degradation(15, 16). Known NFκB members are RelA/p65, RelB, cRel, p52, and p50 that form homo- or heterodimers. The RelA/p50 heterodimer is most frequently activated after TLR signaling(15). RelA/p50 dimers are directly responsible for expression of co-stimulatory molecules (i.e. CD40, CD80, CD86), while IRF5 together with NFκB and mitogen-activated protein kinase (MAPK) activation is crucial for the production of IL6 and TNFα (reviewed in (14)). Phosphorylation of IRF7, likely mediated by PI3K activation, leads to IRF7 nuclear translocation with the help of osteopontin (OPN) leading to IFNα/β gene transcription(17, 18). Auto/paracrine production of IFNα/β promotes pDC survival via induction of anti-apoptotic genes, whereas TNFα supports pDC maturation. Currently it is believed that ligation of TLR in the early endosomal/ lysosome-related compartment will preferentially turn on IFN production, whereas late endosomal/lysosomal engagement regulates pro-inflammatory cytokine production and maturation((19) and reviewed in (14)).

Counter regulation of TLR signaling

TLR7/9 signaling needs to be counter regulated to prevent ongoing cytokine production as this is deleterious for the host. Cell surface receptors on human pDC that dampen TLR-induced responses include the C-type lectin blood dendritic cell antigen 2 (BDCA2), dendritic cell immunoreceptor (DCIR), immunoglobulin-like transcript 7 (ILT7), high-affinity immunoglobulin (Ig)E receptor (FcεRI), natural killer protein 44 (NKp44), adenosine diphosphate P2Y receptors, a nitric oxide-induced cGMP-dependent receptor, and

Prostaglandin E2 receptors(20–22). Viruses can highjack the signaling pathways downstream of such receptors and escape from immune recognition (Figure 2). For example, the hepatitis C virus (HCV) envelope glycoprotein E2 binds to BDCA2 and DCIR, which inhibits IFNα production in pDC when exposed to HCV-infected hepatocytes(23). Moreover, exposure of pDC to HCV-infected hepatoma cells prevents NFκB phosphorylation via an endocytosis-dependent mechanism resulting in a lack of cell surface expression of CD40, CCR7, CD86 and TRAIL, and of TNFα and IL6 secretion(24). Another example is HIV, that induces production of IFNα via TLR7 signaling to elicit antiviral activity in acute infection(25). In addition, HIV gp140 binds to DCIR(26) to recruit phosphatases (e.g. SHP1 and SHP2) and tyrosine kinases (e.g. Src, Fyn, Hck, Syk) to the immunoreceptor tyrosine-based inhibitory motif (ITIM) domain of DCIR(27, 28). Recruitment of this signalosome is important for DCIR activity with regard to HIV binding/entry and enhanced HIV replication(26). It is possible that DCIR activation via gp140 inhibits IFNα production in pDC thereby increasing HIV replication. Following HIV-induced IFNα secretion is expression of interferon stimulated genes (ISG), such as MxA and BST2/Tetherin(29) in surrounding cells. While increased expression of BST2 on leukocytes, including $CD4^+$ T cells, may play a role in decreasing HIV virion release from infected cells in acute HIV infection(30), BST2 binding to its inhibitory receptor ILT7 expressed on pDC may dampen IFN production(31) and increase viral replication at least during the acute phase. During chronic HIV infection sustained levels of IFNα return likely as a result of persistent immune activation leading to HIV pathogenesis. During chronic infection, pDC express increased levels of IRF7(32) and lower levels of ILT7(33) that may contribute to persistent IFNα secretion as well. In addition to IFNα, TNFα may be responsible for persistent immune activation as treatment of SIV infected Rhesus Macaques with an antibody to TNFα reduced expression of pro-inflammatory cytokines and immunopathology in lymphoid tissues(40).

A new layer of regulation involved in fine tuning immune responses are microRNAs (miRNA)(34), which are involved in post-transcriptional regulation of protein expression also in pDC. MiR-155 and miR-155* have an opposite role in controlling TLR-induced IFN production by human pDC(35). MiR-155* augments IFNα/β expression by suppressing the negative TLR7 signaling mediator IRAKM(36). MiR-155 inhibits IFN expression by targeting the adaptor TAK1-binding protein 2 (TAB2)(37). We showed that miR-146a is induced in human pDC by TLR7/9 agonists, but not IL3, thereby interfering with cytokine production, maturation and survival(38). Together with similar data in the mouse(39, 40) miR-146a is recognized as a “brake of the immune response” by downregulating IRAK1 and TRAF6 expression and hence dampening of TLR-induced responses.

Cytotoxicity

TLR7/9 stimulation of pDC also induces the expression of TNF-related apoptosis inducing ligand (TRAIL/Apo-2L)(41, 42), which is mediates cell death of TRAIL-sensitive infected cells and tumor cells expressing either TRAIL-R1 or TRAIL-R2(43). As TRAIL-expressing pDC accumulate in Basal Cell Carcinoma lesions topically treated with the TLR7 agonist Imiquimod, this suggests that pDC may be involved in Imiquimod-induced regression of tumor lesions(41, 44). In response to HIV, pDC express TRAIL(45) that are present in

peripheral blood and lymph nodes of HIV-infected individuals and may directly kill Death receptor 5 $(DR5)^{+}CD4^{+}$ T cells via the TRAIL/DR5 pathway(46, 47) although this is debated by others (48). We identified NGFI-A-binding protein 2 (NAB2), which is induced by TLR7/9 signaling in pDC, as a regulator of TRAIL expression(49). Autocrine IFNα/β signaling also regulates TRAIL expression in human and mouse pDC(49–52). PDC may kill target cells via the serine protease granzyme B (GrB) as well, which is constitutively expressed in human pDC(53). PDC-derived GrB lyses the erythroleukemic cell line K562 in a perforin-independent, but caspase-dependent manner(54). This could not be recapitulated, however, when using primary T cells as targets(55).

Antigen uptake

The ability of pDC to induce adaptive immunity through direct antigen presentation to T cells remained controversial for a long time. Most research focused on cDC as they are more efficient as antigen presenting cells (APC). Immature mouse pDC are able to take up soluble antigens, but less efficient than cDC possibly due to a lower macropinocytosis activity(56). Human pDC express several receptors to detect and endocytose pathogens that can be processed and presented to T cells. Antigens coupled to antibodies that target the endocytic receptors DEC-205(57), DCIR(58), Fcγ Receptor IIa (FcγRIIa)(59) and BDCA2(60) efficiently induce antigen-specific $CD4^{+}$ T cell activation. While BDCA2(61) and DCIR(58) are downregulated after TLR activation, DEC-205 expression is induced after TLR activation and continues to function as antigen internalization receptor(57).

Human pDC can internalize, process and present antigens via MHC Class I and Class II to $CD8^{+}$ and $CD4^{+}$ T cells, respectively(11, 62–64) at least *in vitro*. Whether pDC act as professional APC in cross-presentation of exogenous antigens has been re-evaluated and data show that pDC have an efficient machinery allowing cross-presentation to $CD8^{+}$ T cells(62, 64–67). Hence, combined with their capacity to produce IFNα/β, pDC are interesting targets for immunotherapy.

Tolerance

In the immature state, pDC have poor ability to support T cell proliferation(68) and even suppress T cell responses indirectly through the induction of regulatory T cells (Treg)(69, 70). PDC contribute to peripheral T cell tolerance in transplantation(71), tumor escape(72), oral-(73) and mucosal tolerance(74). “Tolerogenic” pDC may be present in mouse gut and thymus(75–77). Such pDC may express the chemokine receptor CCR9, that is lost upon TLR triggering correlating with reduced ability to prime tolerance(75). In human, a similar tolerance inducing pDC subset has yet to be identified, but pDC expressing either GrB or indoleamine 2,3-dioxygenase (IDO) impair T cell proliferation(55, 72, 78). GrB is induced in pDC by the cytokines IL21(55), or IL3 plus IL10(78), and inhibition of GrB activity restored pDC-induced T cell activation(55, 78). IL21 may be involved in mediating a negative feed-back loop to terminate adaptive immune responses as human $CD4^{+}$ and NK-T cells are the main producers in viral or bacterial infections(79).

Melanoma progression in humans may be associated with tumor-infiltrating pDC promoting pro-inflammatory Th2 and Treg through OX40L and ICOSL, respectively(80), although this

contradicts with the observation that patients with metastatic melanoma receiving intranodal injections of pDC mount anti-tumor responses(81). In addition, a subset of pDC expressing lymphocyte activation gene 3 (LAG3) negatively regulates T cell activation and positively regulates Treg function by production of IL6(82, 83). Furthermore, ILT7 on pDC engages BST2(31), which is endogenously expressed in tumors(reviewed in (84)), thereby suppressing infiltrating pDC to produce IFN in response to TLR ligands and hence an anti-tumor response.

Autoimmune diseases

Despite the low frequency of pDC in blood and lymphoid tissues, their high potential to produce IFNα also in response to self-nucleic acids raised questions about their putative role in autoimmunity. Unwanted IFNα production by pDC is involved in autoimmune pathogenesis including systemic lupus erythematosus (SLE)(85, 86), Sjögren's syndrome(87), and psoriasis(88). Blood and tissue cells of these patients have an IFN-signature indicating that Interferon-inducible upregulation of ISG can be used as disease biomarker(89). In addition to deleterious effects of IFN, pDC differentiate into mature pDC with antigen presenting capacity able to steer T cell responses adding to the pathogenesis of autoimmune diseases.

In SLE, auto-antibodies directed to nuclear antigens are aberrantly produced and deposited in tissues causing inflammation. Nucleic acid-containing immune complexes (IC) trigger IFNα release from pDC upon FcγRIIa-mediated uptake into endosomes and local engagement of TLR7/9(90, 91). PDC numbers in blood of SLE patients are reduced, but pDC infiltration is found in skin and renal lesions(92). The IFN-signature correlates with disease activity and severity(85, 93), but is independent of the relative TLR7 gene copy number(94). SLE pathogenesis can be linked to increased IL6 production by activated pDC, which together with IFNα promotes survival and differentiation of auto-reactive B cells into auto-antibody-secreting plasma cells(10). IFNα production by SLE-IC can be inhibited by blocking FcRγ-mediated uptake of IgG(95), by hydroxychloroquine, which increases the intracytoplasmic pH and prevents acidification and maturation of endosomes(96), or by C-reactive protein, which binds apoptotic cells and nucleoprotein auto-antigens(97). Reduced miR-146a expression is found in PBMC of SLE patients and may add to elevated IFNα and IL6 levels(98). Accordingly, SLE is associated with miR-146a polymorphisms(99–101). Lower expression of miR-146a may be linked to a miR-146a promoter variant binding less efficiently to Ets1(100). Not all studies support an association of SLE and miR-146 polymorphisms(102). Other negative regulators of TLR-induced IFNα production in pDC inhibiting SLE pathogenesis are BDCA2 and ILT7, which complex both with FcεRIγ(103, 104). This involves a B cell receptor-like signaling mechanism relying on activation of adaptors such as Syk, B cell linker (BLNK), and B lymphoid tyrosine kinase (BLK). Reducing BLK levels in mouse pDC increased TLR9-induced IFNα production(105). Given that genetic variants in the BLK locus are identified in SLE patients by genome-wide association studies, it is notable that certain polymorphisms correlate with reduced BLK levels(106). Consequently, this may elevate IFNα secretion and hence contribute to SLE predisposition. SLE patients are generally treated with glucocorticoids (GC) that exert an anti-inflammatory effect likely by inhibition of NFκB activation. However, these drugs do

not convey maintenance of disease control in the majority of patients due to inefficient NFκB inhibition in pDC(107), thereby preventing GC-induced pDC death and consequently ongoing IFNα production. Improved therapeutic advantage may be gained by treating SLE patients with inhibitors of Syk (108), BTK (109) or TLR(110). Future intervention may aim at altering expression of miR-29b/c, involved in TLR-inhibited GC-induced pDC apoptosis by directly targeting Mcl-1 and Bcl-2(111).

In psoriasis, a disease of chronic skin inflammation, lesions contain activated pDC secreting IFNα/β(88, 112) due to the presence of cathelicidin peptides, including LL-37, produced by activated keratinocytes(113). LL-37 complexes with self-DNA/RNA released by dying cells and engages TLR7/9 leading to chronic IFNα production(113, 114). Psoriatic lesions are effectively treated with Vitamin D (VitD) analogs, which have anti-inflammatory properties(115). PDC may contribute to the tolerance induction, since VitD impairs the ability of pDC to induce T-cell proliferation and secretion of the Th1 cytokine IFNγ(116). It remains unresolved how VitD programs the tolerogenic properties in pDC, but this is not due to altered expression of co-stimulatory molecules, MHC Class II, or production of IFNα. Despite the pathological role of pDC in autoimmune skin diseases, the physiological importance of pDC in initiating skin wound healing is also reported. Following skin injury, pDC are rapidly recruited to the site of tissue damage to sense self-nucleic acids released by dying cells in combination with cathelicidins, and to initiate tissue repair via TLR-induced IFNα production(117).

Conclusions

PDC are major actors of immune responses against viruses and bacteria through TLR7/9 activation. PDC are not only capable of linking the innate and adaptive immune system via rapid and sustained production of cytokines, including type I IFN, IL6 and TNFα, but can also activate T cells through direct antigen presentation *in vitro* and likely *in vivo*. In addition, pDC are able to directly kill bystander tumor cells, thereby participating in cancer-induced immune responses. Although the beneficial role of pDC in immunity is undisputable, their recently discovered “tolerogenic” face in different tumors suggests their involvement in tumor escape mechanisms. Such a broad range of action requires tight regulation, both at the transcriptional and post-transcriptional level, to control development, differentiation, function, and survival of pDC. System failures do exist, however, given the existence of type I IFN-mediated autoimmune diseases. More extensive research on pDC is required to unravel the pathways leading to uncontrolled cytokine production and differentiation to enable therapeutic intervention for curing or stabilizing diseases.

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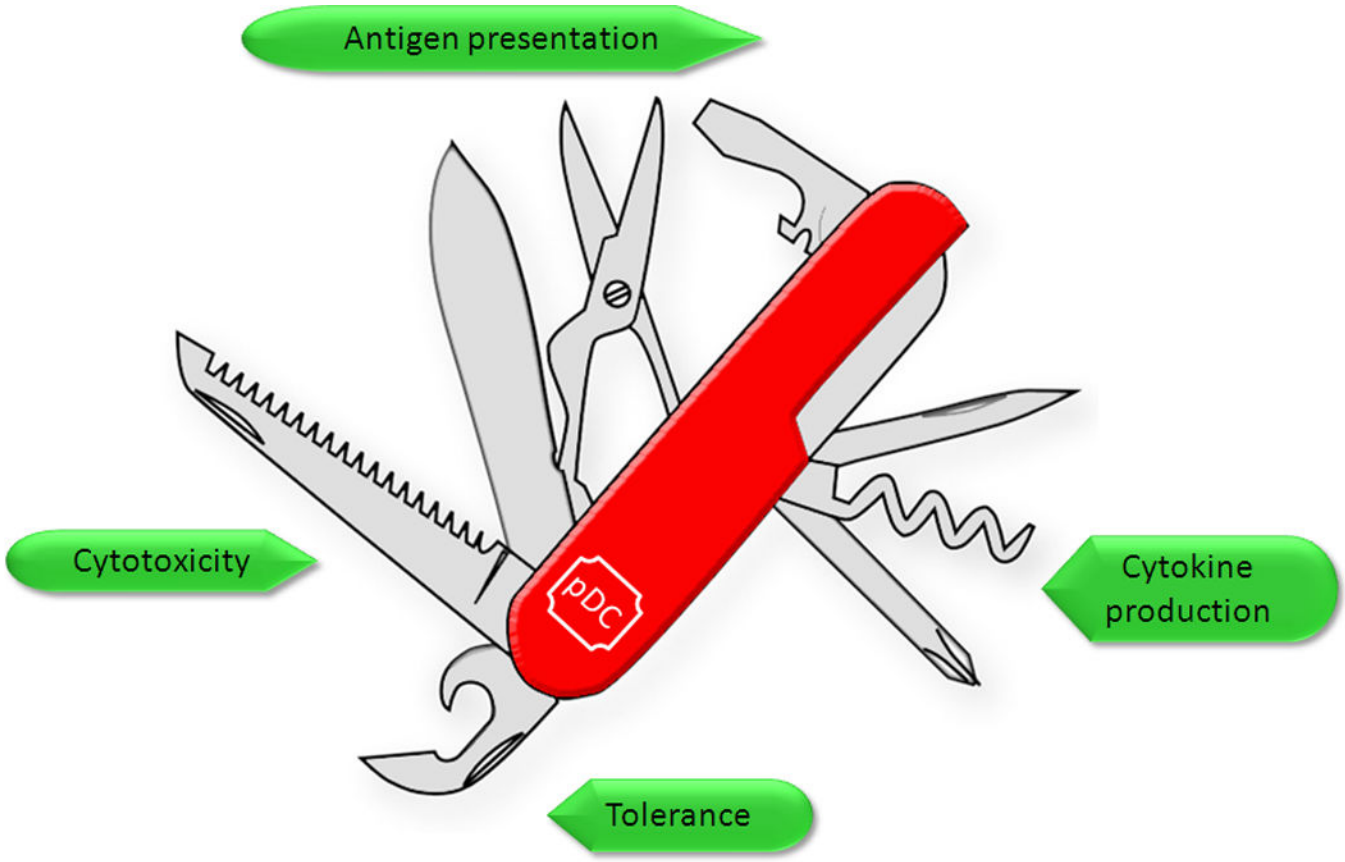

Figure 1. The plasmacytoid dendritic cells as the Swiss army knife of the innate immune system

Illustrated are the multifaceted functions of pDC to produce cytokines, present antigen, induce cytotoxicity and tolerance. Taken together, pDC resemble a Swiss army knife (adapted from clipartist.net) that is equipped with multiple features.

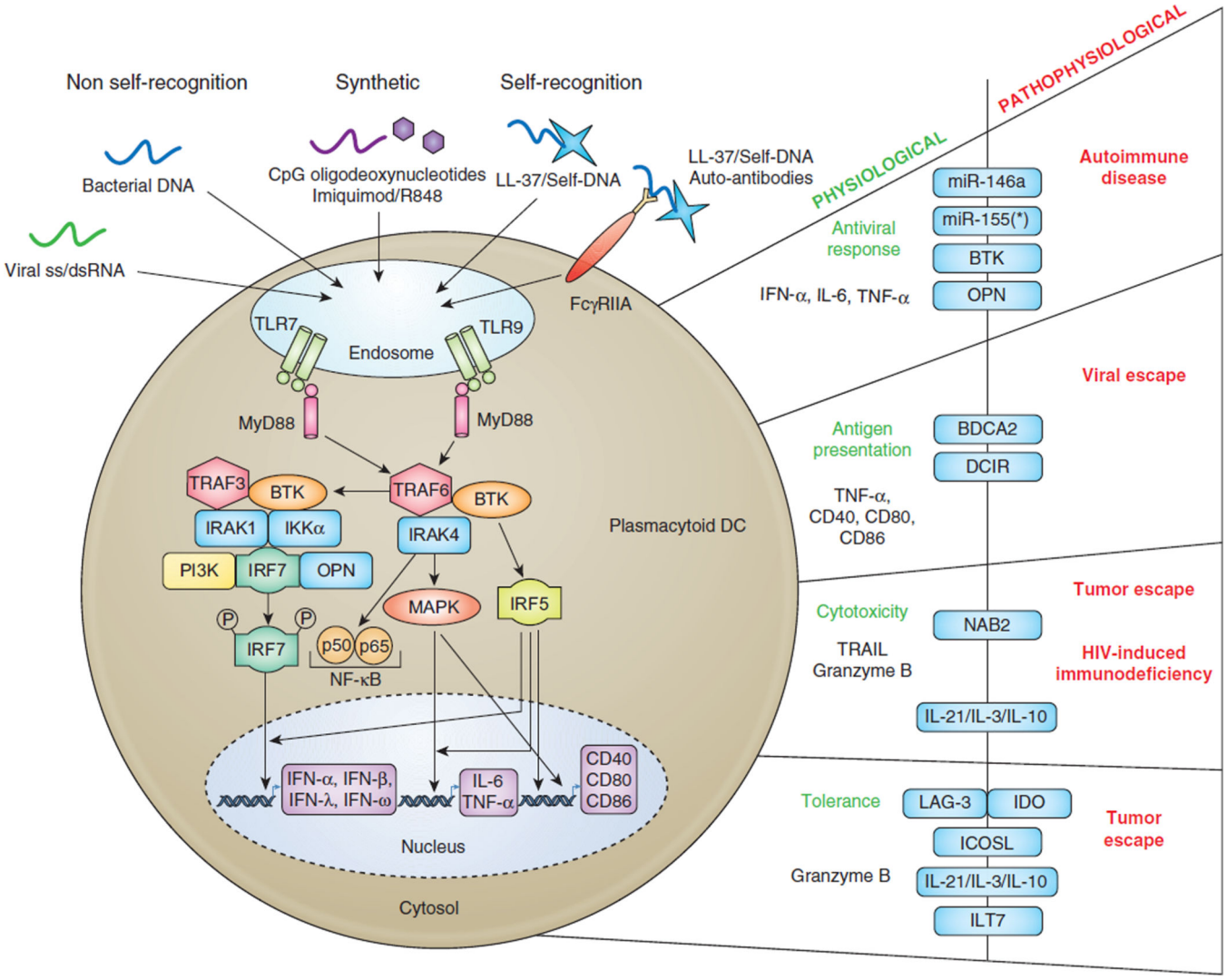

Figure 2. TLR activation pathway in plasmacytoid dendritic cells and its regulation in health and disease

PDC selectively express TLR7 and TLR9, which are expressed in the endosomal compartment. TLR activation is mediated by engagement of viral single strand RNA and bacterial DNA, respectively (non self-recognition). Self-nucleic acids, in complex with the small cationic antimicrobial peptide LL-37 are able to trigger TLR7/9 in pDC. Entry of self-DNA/LL-37 complexes can also be facilitated by plasma cell-derived autoantibodies that engage FcγRIIA. In addition, TLR7 can be activated by synthetic compounds such as Imiquimod or R848, while TLR9 recognizes synthetic CpG oligodeoxynucleotides, including CpG-A and CpG-B. TLR7/9 triggering leads to activation of the myeloid primary-response gene 88 (MyD88) and downstream signaling cascade via NFκB pathway, IRF5/7, and MAPK. This ultimately lead to expression of type I/III IFN, pro-inflammatory cytokines IL6 and TNFα, and costimulatory molecules, such as CD40, CD80, and CD86, that are the key components of pDC-derived antiviral response and antigen presentation. In addition pDC can exert cytotoxic properties via expression of TRAIL, and Granzyme B, which is also involved in the tolerogenic properties of pDC within tumor environment. On the right

are listed the different functions of pDC and the different regulators that separate the physiological aspects from the dysfunctional pDC-derived pathophysiology. Antiviral response is mainly controlled via miRNA regulations (miR-146a, miR-155/miR-155*) and failure to do so can lead to autoimmune diseases such as SLE, Sjögren's syndrome, and psoriasis.