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Diversification of dendritic cell subsets
Emerging roles for STAT proteins

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The term dendritic cell (DC) refers to a population of hematopoietic cells with critical roles in immunity, including immune activation in response to pathogen-elicited danger signals and immune tolerance. Aberrant DC activity is an important contributing factor in autoimmunity, while severe DC depletion accompanies certain immunodeficiency conditions. By contrast, DCs have become attractive candidates to manipulate in immune therapy. Recent studies show that STAT transcription factors have unique roles in DCs, a feature that might be exploited in future DC-based therapies. Here, we focus on the functions of STAT1, STAT3, and STAT5 in DC generation and DC-mediated immune responses.

Dendritic cells (DCs) are a discrete population of cells with important functions in immune surveillance, maintaining self-tolerance in homeostasis and eliciting immune activation upon exposure to pathogen- or injury-induced "danger" signals. DCs were first discovered by virtue of their distinct morphology in immune cell cultures;[1] subsequently the integrin CD11c was employed as a marker to identify DCs, a method still utilized widely today. Although DCs have been identified relatively recently, significant advances have been made in understanding the mechanisms that control their generation and their contribution to the immune system. This review provides an overview of the DC lineages, their major functions and the mechanisms by which they are regulated, with a specific focus on the role for cytokines and STAT transcription factors in DC development and function.

Introduction to DC Development and Immune Function

DCs derive from hematopoietic stem cells (HSCs) via common myeloid (CMP) or common lymphoid progenitors (CLP) expressing the tyrosine kinase receptor Flt3, with DC development mediated by Flt3-dependent signal transduction.[2-5] CMPs give rise to a common DC progenitor (CDP), which generates both conventional (cDC) and plasmacytoid DCs (pDCs).[6,7] A minor proportion of pDCs show evidence of RAG1 expression and IgH D-J rearrangement.[8] This population appears to develop primarily from CLPs through $CD11c^{-}SiglecH^{+}$ precursors, whereas cDC production from CLPs is relatively inefficient.[9]

Several discrete DC subsets have been classified based on their tissue distribution, immune function, cell surface molecule expression, and dependence upon transcriptional regulators.[10-14] Identification of DC subsets using surface markers can be problematic, however, as many of these molecules are dynamically regulated by cytokines and/or shared with other myeloid lineages (e.g., CD11b and CD103). For example, inflammatory conditions accompanied by elevated cytokine production elicit unique cell populations that resemble DCs in terms of cell surface protein expression; however, these cells appear more closely related to monocyte/macrophages than DCs derived under homeostatic conditions.[15] Recent advances in gene profiling such as the Immunological Genome Project have revealed key genes that are differentially expressed in DCs compared with other immune cell types, including specific transcriptional regulators, or genes that are distinctly expressed among DC subsets (e.g., *Flt3*, *Xcr1*, and *Zbtb46*).[16] Thus, analysis of both cell surface marker and transcriptional regulator expression is likely to provide a more definitive assessment of DC subset identity, relative to surface phenotype alone.

In lymphoid organs and peripheral blood of mice, DCs are divided primarily into pDC, $CD11b^{+}$ DC, and $CD11b^{-}$ DC subsets, with the latter 2 encompassed within the more general "cDC" population. In humans, the major distinctions are pDCs, and the BDCA-1^{+} and BDCA-3^{+} "myeloid DCs" (also known as $CD1c^{+}$ and $CD141^{+}$ DC subsets, respectively).[10,11,13,14] In both species, pDCs are a specialized population that displays a plasma cell-like morphology and expresses the B cell marker B220, yet shows relatively low (mouse) or non-detectable expression (human) of CD11c.[17] Thus, to distinguish pDCs, additional surface markers have been utilized, including PDCA-1 and SiglecH in mice or BDCA-2, BDCA-4, and CD123 (IL-3Rα) in humans. pDCs respond to viral infection or Toll-like receptor (TLR) 7 or 9 agonist stimulation by producing an abundant amount of type I interferon (IFN), suggesting an important role in antiviral responses.[17,18] An interesting exception occurs with the Peyer patch pDC (PP pDC) population, which appears to be

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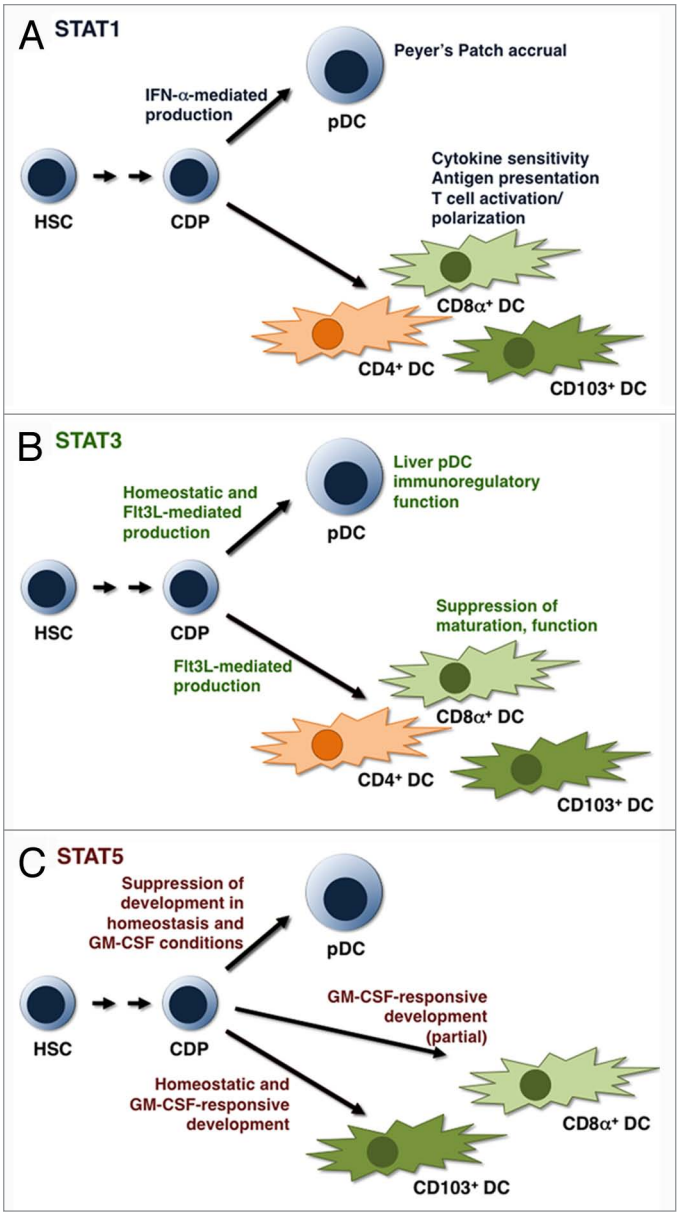

Figure 1. STATs in DC development and function. A schematic diagram illustrating the predominant roles for STAT1 (**A**), STAT3 (**B**), and STAT5 (**C**) in DCs and their progenitors. For simplicity, DC progenitors are indicated by the CDP population. Details of STAT function and appropriate references are located within the text.

conditioned by factors within the microenvironment, dampening the ability of PP pDCs to produce type I IFNs.[19] Following TLR stimulation, pDCs undergo maturation, acquiring the ability to present antigen and activate lymphocyte responses.[20] In addition to their antiviral roles, pDCs regulate oral tolerance.[21] Murine pDCs are uniquely dependent on STAT3 as well as the E protein E2-2;[22-24] human pDCs also require E2-2,[24] while the role for STAT3 remains to be determined. By contrast, GM-CSF, which was used in initial studies to derive DCs and is commonly employed for ex vivo DC generation, has profound suppressive effects on pDC production.[22,25]

Distinct from pDCs, the cDC subsets are potently activated by microbial products or cell surface TLRs to produce inflammatory cytokines such as IL-1, IL-6, IL-12, and TNFα. While several unique cDC subsets have been identified on the basis of anatomical location and marker expression, these share the common properties of efficient phagocytosis in the resting state and activation to "professional" antigen-presenting cells upon TLR triggering.[11,14,26] Murine CD11b$^+$ and CD11b$^-$ DCs express relatively high amounts of cell surface CD11c and MHC class II compared with pDCs. Moreover, lymphoid organ CD11b$^-$ DCs also express CD8α (CD8α$^+$ DCs) and the chemokine receptor XCR1 (mice) or BDCA-3 and XCR1 (humans), while a subset of CD11b$^+$ DCs express CD4 (CD4$^+$ DCs, mice).[11,14,27] In peripheral tissues and draining lymph nodes, a migratory DC subset has been identified by expression of CD103 (mouse), or CD141^{hi} or CD1a (human).[28,29] Murine CD103$^+$ DCs were thought to be developmentally related to lymphoid organ CD8α$^+$ DCs, as both subsets express XCR1, demonstrate potent antigen cross-presentation activity, and share dependence on the transcriptional regulators IRF8, Batf3, and Id2.[30,31] However, recent evidence indicates that migratory CD103$^+$ DCs are regulated by distinct mechanisms compared with CD8α$^+$ DCs or other DC populations. For example, GM-CSF and its signal transducer STAT5 are necessary for generation of CD103$^+$ DCs but not other DC subsets in steady-state.[23,32,33] STAT5 also mediates an induction of CD103$^+$ DC numbers in response to elevated circulating GM-CSF.[23] Additional DC populations exist, such as skin Langerhans cells and intestinal DCs. These subsets are included in more comprehensive reviews[11,14] and are beyond the scope of this article.

Function of STATs in DC Lineage Development

DCs arise from hematopoietic progenitors such as CDPs under the control of extrinsic cytokine signals as well as intrinsic transcriptional regulators. The principal cytokines involved in DC development include Flt3L, GM-CSF, and IFN-α, which stimulate STAT3, STAT5, and STAT1, respectively. As discussed herein, each STAT has a distinct role in DC production (**Fig. 1**).

STAT1 regulates DC function and plays a unique role in Peyer patch pDC generation. STAT1 is best known for its ability to mediate signaling responses to type I, type II, and type III IFNs.[34] Engagement of the type I IFN receptor (IFNAR1/IFNAR2 complex) and the type III IFN receptor (IL-28Rα/IFNLR1 coupled with IL10R2) stimulates the phosphorylation of receptor-associated JAK1 and TYK2 kinases, which primarily activate STAT1, STAT2, and the interferon regulatory factor IRF9 (p48) to form the IFN-stimulated gene factor 3 (ISGF3) transcription complex. ISGF3 translocates to the nucleus and interacts with specific IFN-stimulated response elements (ISRE) located upstream of IFN-responsive genes.[34] The type II IFN receptor (IFNGR1/IFNGR2 complex), however, activates JAK1 and JAK2, resulting in STAT1 tyrosine phosphorylation and homodimerization. STAT1 homodimers, which have also been referred to as gamma-activating factor (GAF), regulate genes containing gamma-interferon activation sites (GAS elements).[34]

Type I (IFN-α/β) and type III IFNs (IFN-λ/interleukin 28/29) are produced by pDCs, cDCs, and other leukocytes in response to viral infection, while type II IFN (IFN-γ) is secreted primarily by activated NK and T cells. In turn, IFNs, STAT1, and STAT2 have been shown to regulate DC function (**Fig. 1**). For example, type I IFN signaling and STAT1 activation in DCs are required for induction of MHC molecules, co-stimulatory molecules, and antigen presentation, including cross-presentation to activate $CD8^+$ T cells,[35-37] and thus are important in mediating the rejection of immunogenic tumor cells or regulating exogenously delivered MHC class I-restricted peptide vaccination. STAT1-depleted DCs elicit deficient immune responses to *Listeria monocytogenes* and *Leishmania major*, due to impaired Th1 cell priming or an increase in antigen-specific regulatory T cells.[35,38] Furthermore, STAT1 induces expression of the IL-31 receptor α chain in IFNγ-stimulated human $CD1c^+$ DCs, stimulating responsiveness to IL-31 and subsequent IL-31-dependent production of inflammatory mediators.[39] By contrast, viral infection or IFNβ treatment impairs Flt3L-responsive DC production ex vivo and causes a significant reduction in $CD8\alpha^+$ DCs in vivo, with both effects dependent upon STAT2.[40] Type I IFN signaling in the context of viral infection, which is initiated in part by pDC-mediated type I IFN production, induces pDC apoptosis in spleen.[41] These data suggest IFN-mediated negative feedback loops may operate to control DC abundance and type I IFN production during virus exposure.

IFN-α and IFN-γ also promote the proliferation of quiescent hematopoietic stem cells (HSCs) through STAT1-dependent signals, indicating involvement of IFNs and STAT1 in hematopoiesis.[42,43] Consistent with this, IFN-α treatment stimulates an approximate 2-fold increase in bone marrow lin^- $Flt3^+$ DC progenitors[44] (**Fig. 1**). The abundance of the bone marrow and splenic DC populations are normal in *Stat1*$^{-/-}$ and *Stat2*$^{-/-}$ mice in steady-state conditions,[40,44] suggesting IFN-STAT signaling is not necessary for homeostatic DC generation in these organs. However, elevated circulating amounts of IFN-α, similar to those observed during acute viral infection, stimulate pDC amounts in bone marrow and spleen.[44] While at first glance this appears to contradict the pro-apoptotic role for type I IFNs found for splenic pDCs, it is important to point out that pDC apoptosis was induced during ongoing viral infection;[41] bone marrow pDCs and their progenitors remain to be analyzed in these conditions. IFN-α, therefore, may exert differential effects depending on developmental stage and/or other cues within the environment. This could be particularly relevant for understanding pDC responses during infection or autoimmunity, which would evoke distinct background conditions.

STAT1 and IFNAR are vital for accrual of pDCs within Peyer patches (PP),[44] secondary lymphoid organs present in the gut (**Fig. 1**). The PP pDC population can be derived from CDPs and is responsive to Flt3L treatment (i.e., induced by Flt3L),[44] similar to pDCs in bone marrow and spleen. In addition, PP pDCs resemble other pDC populations by expressing the cell surface markers B220, SiglecH, and PDCA-1 as well as the transcriptional regulators IRF7 and IRF8.[19,44] These results imply a common developmental pathway for PP, bone marrow, and splenic pDCs, with IFNAR-STAT1 signaling operating at later developmental stages to regulate accumulation of pDCs within PPs. PP pDCs show reduced expression of the transcription factor E2-2 and are inefficient at producing type I IFNs upon TLR activation, effects that may result from conditioning via IFNAR-STAT1 signals in the intestinal microenvironment.[44] Thus, the collective evidence suggests that IFNs, STAT1, and STAT2 have discrete roles during DC development and in mature cells, an idea that requires further validation by targeted genetic approaches.

STAT3 regulates Flt3L-responsive DC progenitor proliferation, pDC homeostasis and cDC function. DC development is highly dependent upon Flt3L-Flt3 signaling as evidenced by the significant depletion of pDCs and cDCs in *Flt3l*$^{-/-}$ or *Flt3*$^{-/-}$ mice.[4,5] Moreover, Flt3L induction via injection of recombinant cytokine, Flt3L-encoding plasmid (utilizing hydrodynamic gene transfer), or enforced transgene expression results in a striking expansion of CDPs and their progeny, including pDCs, $CD8\alpha^+$, $CD4^+$, and $CD103^+$ DCs.[2,23,45,46] Addition of recombinant Flt3L to human or mouse bone marrow, or murine fetal liver cell cultures results in the generation of pDCs and $CD11b^{hi/+}$, $CD11b^{lo/-}$, and $CD103^+$ DCs that appear to be counterparts of DC subsets found in vivo.[22,25,47,48]

The interaction of Flt3L with Flt3 activates the intrinsic tyrosine kinase activity of the receptor, which subsequently phosphorylates and stimulates multiple signal transduction cascades, including STAT3 as well as the MAPK and PI3K pathways.[22,49] While the precise mechanism by which STAT3 is activated remains unclear, Flt3L-Flt3 engagement induces rapid phosphorylation of STAT3 on Y705 (within 15 min),[22] suggesting STAT3 is directly or indirectly coupled to Flt3 to undergo tyrosine phosphorylation. Analysis of mice with conditional STAT3 deletion in hematopoietic cells (Tie2/*Tek* cre-mediated) or $CD11c^+$ DCs (CD11c cre-mediated) revealed a major role for STAT3 in pDC but not cDC homeostasis.[22,23,44,50] By contrast, an earlier study found significant depletion of $CD11c^+$ cells in lymphoid organs of hematopoietic *Stat3*-deficient mice.[51] The reason for the discrepancy in these data remains unclear and could relate to the genetic background of hematopoietic *Stat3*-deficient mice or their general health status (e.g., hematopoietic *Stat3*-deficient mice develop a lethal inflammatory syndrome[52]). Nevertheless, all studies to date agree that STAT3 is essential for pDC homeostasis as well as Flt3L-mediated expansion of pDCs and cDCs in bone marrow and spleen (**Fig. 1**). Interestingly, however, non-lymphoid organ $CD103^+$ DCs are induced by Flt3L independent of STAT3 signaling.[23] STAT3 may regulate pDC and lymphoid organ cDC amounts by controlling Flt3L-mediated proliferation of the lineage-negative (lin^-) $Flt3^+$ DC progenitor population.[22] Furthermore, as discussed below, STAT3 also influences the expression of E2-2, a transcription factor that drives pDC generation.[23] Thus, major roles for STAT3 include the regulation of Flt3L-dependent DC progenitor growth and pDC lineage development.

In differentiated cDCs, STAT3 serves a negative regulatory function (**Fig. 1**), which parallels its inhibitory role in other mature myeloid populations. This activity may be particularly significant in specific microenvironments such as tumors or

inflammatory lesions. For example, STAT3 suppresses TLR-triggered inflammatory cytokine production from DCs, macrophages and neutrophils, a response that is likely to contribute to the progressive inflammation observed in animals with hematopoietic-, myeloid-, or DC-restricted STAT3 deletion.[50,52,53] STAT3-activating cytokines also inhibit DC maturation from monocytes and DC maturation in response to TLR signaling.[54-56] IL-6-mediated STAT3 activation in DCs suppresses induction of MHC class II and the co-stimulatory molecules CD80/CD86, and has been implicated in restraining DC-mediated antigen presentation to $CD4^+$ and $CD8^+$ T cells.[54] Furthermore, IL-6 and IL-10, either added exogenously or via autocrine signaling, induce the generation of tolerogenic DCs from monocytes, which facilitate activation of regulatory T cells.[55-58] By contrast, STAT3 is not involved in controlling TLR-inducible type I IFN production from pDCs, yet it appears to mediate IL-27 signaling in liver pDCs to enhance their immunoregulatory function (e.g., via IL-27-induced upregulation of B7-H1 and induction of $FoxP3^+$ T regulatory cells).[22,59] The effects of STAT3 signaling in DCs have profound consequences in the context of cancer, in which excessive STAT3 activation is observed in tumor cells as well as tumor-infiltrating immune subsets.[60] STAT3-mediated inhibition of DC differentiation suppresses inflammatory mediator production and sensing, promoting tumor tolerance.[61,62] Thus, approaches to inhibit STAT3 are under active investigation for potential therapeutic use.[63,64]

STAT5 controls the generation of nonlymphoid organ $CD103^+$ DCs. GM-CSF was among the original cytokines used in ex vivo DC culture systems and continues to be employed widely in applications to generate cDCs from mouse and human bone marrow progenitors, embryonic precursors, or monocytes for experimental or clinical use. Strategies to induce systemic GM-CSF amounts remarkably enhance the production of $CD11b^+$ and $CD103^+$ DCs.[44,65-67] However, mice lacking GM-CSF or the GM-CSF receptor β chain demonstrate only a small decrease in $CD11b^+$ and $CD11b^-$ DCs in spleen and thymus, which led to the suggestion that GM-CSF is dispensable for DC generation in vivo. This idea has been overturned by recent work that reveals a crucial role for GM-CSF in controlling the abundance of nonlymphoid organ $CD103^+$ DCs, including lamina propria $CD103^+$ DCs.[32,33,68] Reciprocal bone marrow transfer experiments suggest that GM-CSF regulates these populations at least in part through effects on cell survival.[33]

The GM-CSF receptor β subunit is constitutively associated with JAK2, which undergoes transphosphorylation and activation in response to GM-CSF stimulation, leading to JAK-dependent tyrosine phosphorylation of STAT5A, STAT5B, STAT3, and STAT1. STAT5A and STAT5B are highly related proteins encoded by separate genes, and are considered to be major GM-CSF-responsive signaling proteins based on their predominant activation patterns.[69] *Stat5a*$^{-/-}$ *Stat5b*$^{-/-}$ mice die perinatally, precluding studies on DC development in these animals.[70] However, bone marrow chimeric mice reconstituted with *Stat5a*$^{-/-}$ *Stat5b*$^{-/-}$ fetal liver progenitors suggested roles for STAT5A and STAT5B (referred to herein as STAT5) in GM-CSF-mediated suppression of pDC generation.[22] This result was confirmed in mice with conditional *Stat5* deletion in the hematopoietic compartment (generated by breeding Tie2/*Tek* cre and *Stat5a/b*$^{flox/flox}$ mice).[23] Moreover, hematopoietic *Stat5*-deficient mice have significantly reduced amounts of $CD103^+$ DCs in liver and lymph nodes in steady-state, suggesting STAT5 regulates homeostatic generation of nonlymphoid organ $CD103^+$ DCs.[23] Hematopoietic *Stat5*-deficient mice also fail to upregulate liver $CD103^+$ DCs in response to GM-CSF; by contrast, other cDC subsets are induced by GM-CSF in a STAT5-independent or only partially dependent (i.e., $CD8\alpha^+$ DCs) manner[23] (**Fig. 1**). The specific requirement for STAT5 in nonlymphoid organ $CD103^+$ DCs may precede expression of CD11c, however, as mice with conditional depletion of STAT5 in $CD11c^+$ cells do not demonstrate changes in splenic DC homeostasis.[71] Thus, collectively, the results to date indicate a unique role for STAT5 in suppressing pDCs and in regulating steady-state and GM-CSF-responsive nonlymphoid organ $CD103^+$ development.

Recent work shows STAT5 also has a role in regulating the ability of differentiated DCs to react to thymic stromal lymphopoietin (TSLP) and induce T helper 2 (Th2) allergic responses.[71] DCs lacking STAT5 were unable to upregulate costimulatory molecules upon stimulation with TSLP, which plays a critical role in inducing a Th2-polarized phenotype. As a result, mice with DC-restricted STAT5 deletion (CD11c cre-mediated deletion) fail to mount effective Th2 responses against skin and airway allergens. If STAT5 function is conserved in human DCs, this could lead to new avenues for therapeutic intervention in allergic disease.

Mechanisms of STAT Action in DC Development

Numerous transcriptional regulators have key roles in hematopoietic lineage specification and commitment, including dendritic cells.[12,27,72,73] In many cases, the expression level of a particular transcriptional regulator is a critical component guiding developmental decisions. Expression of specific factors is also restricted to certain lineages and/or developmental stages. Nonetheless, we lack an in-depth understanding of the mechanisms that regulate the developmental timing of expression and the abundance of critical DC transcription factors. Recent data demonstrates important roles for STAT proteins in regulating DC transcription factor expression during cytokine exposure, suggesting mechanisms by which STATs participate in driving DC lineage diversification.

STAT1 and regulation of IRF8. IRF8 is a member of the interferon response factor (IRF) family, with expression limited to hematopoietic progenitors, T and B cells, DCs, and specialized macrophage populations. *Irf8* deficiency in mice leads to severe reduction in pDCs, cDCs, and marginal zone macrophages,[30,31,74,75] suggesting IRF8 is required during early developmental stages of hematopoiesis, such as the macrophage-DC progenitor (MDP), to regulate DC/macrophage production. In support of this idea, *Irf8*$^{-/-}$ mice exhibit a reduced number of CDPs,[76] which are developmentally downstream of MDPs. These animals also show significant expansion of

granulocyte-macrophage progenitors (GMPs) and granulocytes, a phenotype with similarities to pre-leukemic myeloproliferative disorders.[76] Mutations in human IRF8 that interfere with DNA binding or transactivation functions (K108E, T80A) result in a significant loss of pDCs, BDCA-3$^+$ DCs, BDCA-1$^+$ DCs, and monocytes.[77] Thus, evidence from humans and mice indicate the importance of IRF8 in DC and macrophage development.

Irf8 expression is relatively high in murine CDPs, cDC precursors and pDCs, compared with differentiated cDC subsets.[31,76,78] This expression pattern could imply roles for *Irf8* in DC progenitors upstream of the divergence of the pDC and cDC subsets, as well as functions within fully developed pDCs, consistent with known requirements for *Irf8* in pDC and cDC generation;[30,31,74,75] however, these ideas remain to be tested rigorously by targeted *Irf8* deletion and/or overexpression at discrete developmental stages. Furthermore, while the factors that regulate developmental expression of *Irf8* remain largely unknown, *Irf8* mRNA is induced in Flt3$^+$ DC progenitors by IFN-α stimulation.[44] Molecular studies revealed this is directed by IFN-α-responsive STAT1 association with consensus STAT elements within the *Irf8* proximal promoter.[44] These data are consistent with previous work that indicates *Irf8* promoter activity is stimulated by IFNγ via STAT1.[79] It remains to be determined whether human *IRF8* is regulated by STAT1, and if *Irf8* induction by IFN-α-STAT1 signaling contributes to IFN-α-mediated expansion of DC progenitors and pDCs.[44]

STAT3 and E2-2. In humans and mice, the E box protein E2-2 is highly enriched in pDCs relative to other DC subsets.[24] Accordingly, E2-2 is crucial for pDC development, with both copies of its gene *Tcf4* necessary for terminal differentiation and TLR-triggered type I IFN production.[24] Inducible deletion of *Tcf4* converts peripheral pDCs into a population resembling cDCs with low SiglecH and upregulated CD11c and MHC class II expression, indicating E2-2 also has an essential function in maintaining pDC lineage identity, consistent with its role in controlling pDC-specific genes.[80]

While the mechanisms that regulate *Tcf4* expression during DC development are largely unknown, recent studies point to an important role for STAT3 in controlling *Tcf4* in response to Flt3L stimulation[23] (**Fig. 2**). For example, *Tcf4* expression is upregulated within CDPs upon Flt3L treatment in vivo. This response requires functional STAT3, as judged by the failure of *Stat3*-deficient CDPs to induce *Tcf4* mRNA.[23] Chromatin immunoprecipitation (ChIP) and electrophoretic mobility shift assays demonstrated Flt3L-activated STAT3 interacts with a STAT consensus site in the *Tcf4* proximal promoter. Furthermore, Flt3L-responsive *Tcf4* expression depends upon STAT3 DNA binding and transactivation domains.[23] These results collectively suggest direct STAT3 binding and potential recruitment of transcriptional co-activators to the *Tcf4* promoter during Flt3L treatment. The *Tcf4* proximal promoter displays an increased amount of activating chromatin marks at the transcriptional start site, and a reduced abundance of the transcriptionally repressive histone 3 lysine 27 trimethylation (H3K27me3) mark across the upstream 2 kb region, in pDCs relative to nonlymphoid organ CD103$^+$ DCs.[23] These results are consistent with the unique expression

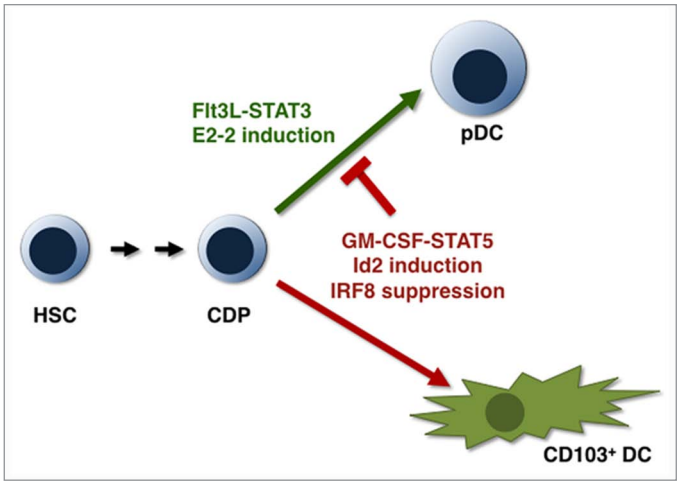

Figure 2. Control of DC transcriptional regulators by cytokine-STAT signals. A schematic diagram that shows the influence of cytokine-STAT signaling on DC transcriptional regulator expression and consequent DC developmental responses. A description of the supporting data and corresponding references are located within the text.

of *Tcf4* in pDCs.[24] However, STAT3 does not appear to have a major role in establishing *Tcf4* promoter H3 modifications or *Tcf4* mRNA expression in homeostatic conditions.[23] These data imply additional factors are involved in *Tcf4* regulation and suggest STAT3 has a principal role in activating *Tcf4* upon Flt3L signaling.

STAT5, IRF8, and Id2. GM-CSF-responsive STAT5 signaling in DC progenitors results in disparate outcomes for the pDC and cDC lineages, with pDC production suppressed and CD103$^+$ DC generation dependent upon this pathway.[22,23,25] In studies to explore pDC inhibition, GM-CSF-activated STAT5 was found to block expression of *Irf8*,[22] which is crucial for pDC development as well as robust type I IFN production (**Fig. 2**). STAT5-dependent *Irf8* blockade was observed in GM-CSF-stimulated lin$^-$ Flt3$^+$ DC progenitors as well as a mature DC cell line, suggesting it may occur at different stages of DC development. *Irf8* is inhibited directly by STAT5, as judged by ChIP experiments that demonstrate GM-CSF-responsive STAT5 interacts with the *Irf8* promoter in vivo.[22] While IRF8 is also required for the CD8α$^+$ and CD103$^+$ DC lineages, STAT5 appears to have little inhibitory effect on CD8α$^+$ DCs in bone marrow reconstitution studies (CD103$^+$ DCs were not evaluated).[22] By contrast, STAT5 is necessary for expansion of both lineages in response to high amounts of circulating GM-CSF.[23] These results suggest differential responses to GM-CSF and/or requirements for IRF8 expression may exist in pDC, CD8α$^+$, and CD103$^+$ DC precursors.

Members of the inhibitor of differentiation (Id) family are potent suppressors of E protein transcriptional functions, acting through reciprocal helix-loop-helix domain interactions to block E protein binding at target gene sequences.[81] Id2 has an essential role in CD8α$^+$ DC, CD103$^+$ DC, and Langerhans cell development, while also restraining pDC production and TLR-triggered type I IFN secretion.[30,82] These roles are reminiscent of the effects of GM-CSF in DC development, suggesting Id2 as an

intermediate in GM-CSF-dependent signaling. Consistent with this, *Id2* expression is induced in CDPs upon GM-CSF stimulation in vivo.[23] Upregulation of Id2 by GM-CSF depends upon STAT5 as well as other factors such as C/EBPβ, and appears to be mediated at least in part by direct STAT5 interaction at the *Id2* promoter.[23] Moreover, Id2 is required for efficient production of CD103$^+$ DCs, as well as suppression of pDC generation, in response to GM-CSF ex vivo.[23] These results collectively suggest that the GM-CSF-STAT5 signaling cascade regulates Id2 expression in DC progenitors, resulting in opposing effects on the commitment and/or terminal differentiation of the CD103$^+$ DC and pDC lineages (**Fig. 2**).

Future Directions: STATs and Human DCs

A variety of STAT mutations have been reported in humans exhibiting compound immunodeficiency.[83] These conditions afford an excellent opportunity to understand whether and how STATs regulate human DC production and function. In fact, this approach has been used to delineate roles for the IFR8 and GATA-2 transcription factors in human DC biology.[77,84] Based on our knowledge of conserved STAT responses in humans and mice, and the critical role of DCs in human immunity, it is reasonable to expect that human STAT mutations will have a major effect on human DCs and DC-mediated immune responses. To date, we have only limited insight centered on STAT3, as DCs in humans with Hyper-Immunoglobulin E (IgE) syndrome (HIES), accompanied by mutations in STAT3, are inhibited in their ability to undergo development into tolerogenic DCs in response to IL-10.[58] Understanding STAT function in human DCs is important not only for revealing basic mechanisms of DC development and function, but also for anticipating potential effects of targeted STAT therapeutics, or pursuing selective DC manipulation in clinical applications. We anticipate exciting results to emerge from these avenues of investigation, which will help guide future treatment options for a variety of diseases including immune disorders and cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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