Transcriptional and epigenetic networks in the development and maturation of dendritic cells

Dendritic cells (DCs) are professional antigen-presenting cells that provide a critical link between the innate and adaptive immune responses. The genetic program required for differentiation of DCs from their hematopoietic precursors is controlled by both cytokines and transcription factors. The signals transduced from cytokines recruit specific transcription factors, enabling the expression of a distinct transcriptome that is required for specification of different DC lineages. The establishment of a distinct transcriptome also depends on chromatin modifications associated with critical cis elements of lineage-specific genes. In this review, recent advances in the understanding of the transcriptional network governing DC lineage specification are summarized, along with current views of the dynamic DC epigenome.

Phenotypic & functional heterogeneity of DCs

DCs are professional antigen-presenting cells that develop from progressively restricted bone marrow progenitors [4,5]. They are found in most tissues, including lymphoid and nonlymphoid organs, and form an interface between the external environment and the adaptive immune system. After recognizing pathogens through pattern-recognition receptors, they take up and convert them into smaller pieces and display the antigenic fragments on their cell surfaces [6]. The DCs then travel to draining lymph nodes where they present antigens to T lymphocytes to induce the adaptive immune response [7]. In the steady state, DCs are equally responsible for the maintenance of immune tolerance, which is critical for the prevention of adverse autoimmune responses [8].
DCs are heterogeneous populations of cells and consist of distinct subsets with different abilities to process antigens and respond to environmental stimuli [9]. These functional differences in DCs result in different immunological responses by engaging with distinct effector lymphocytes via cell-type-specific surface receptors. Based on the distinct expression patterns of surface receptors, DCs are categorized into three major cell types in mice and humans: conventional DCs (cDCs); plasmacytoid DCs (pDCs); and monocyte-derived DCs (moDCs).

cDCs comprise the predominant DC subset and are specialized for antigen processing and presentation [10,11]. cDCs can be subdivided into two major classes according to their primary locations and migration patterns: lymphoid tissue-resident DCs and migratory DCs. Lymphoid tissue-resident DCs reside in lymphoid organs throughout their lifetime and circulate in the bloodstream at a very low frequency. The expression of the surface markers CD4 and CD8α is used to further classify lymphoid tissue-resident DCs into CD4+ DCs, CD8αα DCs, and CD4 CD8αα DCs. CD8αα cDCs are highly efficient at cross-presenting exogenous antigens and priming cytotoxic CD8+ T-cell responses [12,13]. By contrast, CD4+ and CD4 CD8αα cDCs are generally considered to be poor cross-presenters in vivo but appear to be more efficient at priming CD4+ T cells through major histocompatibility (MHC) class II-restricted presentation [14,15]. In contrast to lymphoid-resident DCs, migratory DCs reside in nonlymphoid tissues and migrate to the draining lymph nodes via afferent lymph, where they can initiate immune responses. Migratory DCs can be broadly subdivided into CD11b+ DCs and CD103+ DCs [16-19].

pDCs are characterized by their ability to secrete large amounts of type I interferons in response to virus and/or virus-derived nucleic acids [20]. Functionally, pDCs are not phagocytic and are inefficient at presenting exogenous antigens to CD4+ T cells [21]. This population of cells expresses several characteristic markers, including B220, Siglec-H and Bst2 in mice, and BDCA2 in humans [22–25].

Circulating blood monocytes, which are normally derived from bone marrow precursors, can be direct precursors of DCs under inflammatory conditions [26]. Granulocyte–macrophage colony-stimulating factor (GM-CSF) treatment in vitro or Toll-like receptor 4 (TLR4) activation in vivo induces DC differentiation from blood monocytes [27–29]. The antigen-presenting function of the fully differentiated DC-SIGN/CD209a+ moDCs is equivalent to that of cDCs, including cross-presentation of proteins and live Gram-negative bacteria on MHC class I in vivo [29].

Developmental and lineage relationships among DC populations in mouse bone marrow are starting to be characterized. Hematopoietic stem cells differentiate into common myeloid progenitors [30], a fraction of which differentiate into more restricted macrophage and DC progenitors (MDPs) [31]. Common dendritic cell progenitors (CDPs) [32,33], which originate from MDPs following the loss of monocyte lineage potential, produce precursor cDCs (pre-cDCs) and pDCs [34,35], pre-cDCs home to tissues and differentiate locally into lymphoid tissue-resident CD8α or CD8α+ cDCs and nonlymphoid tissue-resident cDCs [34–36]. By contrast, pDCs complete their maturation in the bone marrow and travel through the blood to secondary lymphoid organs [32,33].

Although several surface markers have been used to distinguish these different types of DCs, reliable lineage-specific markers, in particular, heritable epigenetic markers, are not fully available. Only limited evidence has revealed the existence of such putative markers, and further validation is awaited. These markers will be reviewed in the following sections.

Transcriptional network of DCs that mediates responses to pathogens

Several studies have attempted to develop models of transcriptional networks to dissect the molecular pathways underlying DC responses to pathogens. Amit et al. [37] used unbiased global transcriptional profiling combined with systematic application of RNA interference perturbation to elucidate the complex regulatory networks that control the inflammatory and antiviral responses of mouse bone marrow-derived dendritic cells (BMDCs) [37]. On a global scale, they first profiled the dynamic changes in cellular transcripts and identified 125 candidate TFs that could control TLR-induced responses in DCs. They also selected highly informative reporter genes with an expression pattern that accurately classified the state of the DCs. Lentiviral small hairpin RNAs were then used to silence the expression of 144 candidate transcriptional regulators, followed by quantitative evaluation of the resulting changes in gene expression of the reporter genes. From these expression data, they generated a network model that linked candidate regulators to specific target...
genes. They also addressed how each regulator contributes to the control of two major transcriptional programs in DCs: the inflammatory and antiviral responses. This process identified 24 core regulators and 76 fine-tuners, which helped explain how pathogen-sensing pathways achieve specificity.

A complementary approach to the correlation analysis of gene-expression profiles was reported. This approach aimed to distinguish direct from indirect effects of TF binding to DNA sequences, as well as the difference between functional and nonfunctional binding. Garber et al. combined systematic analysis of the in vivo DNA binding data of 25 TFs with the accompanying gene expression and epigenetic profiles [38]. This analysis was intended to establish functional regulator-target links in BMDCs following a pathogen stimulus. By obtaining high-throughput chromatin immunoprecipitation data and combining them with a high-quality computational analysis of over 180,000 TF–DNA interactions, they found that TFs vary substantially in their binding properties including dynamics, number of binding events, preferred genomic locations and interacting TFs. Moreover, comparison of the TF dynamics with the gene-expression patterns showed that many TF–DNA interactions are established prior to a stimulus, predominantly for immediate–early genes. They also identified specific TF ensembles that coordinately regulate gene induction. In particular, to explain how the gene-expression potential of BMDCs is established during lineage commitment, they proposed a model for hierarchically organizing TF networks by dividing TFs into three classes: pioneer factors; primer factors; and dynamic factors. Pioneer factors bind compact chromatin, initiate chromatin remodeling and enable subsequent binding of nonpioneer factors. In their analysis, this top tier consists of two TFs (PU.1 and Cebpb), and the binding of each is relatively static during stimulation and correlates with a low degree of gene induction. The second tier consists of three TFs (Junb, Irf4 and Aft3), and these primer factors bind thousands of genes in an unstimulated state and are highly correlated with future stimulus-dependent gene induction. In the bottom tier, they found TFs that are more dynamic and specialized for the induction of more specific gene sets. These dynamic factors tend to bind a smaller number of regions from specific functional categories, such as inflammatory, antiviral response and the cell cycle.

### Transcriptional networks for lineage commitment of DCs

A specific and dependable means of distinguishing phenotypically diverse DC subsets is essential for determining their lineage and precise functions. The use of surface markers to identify DCs is limited because of ambiguity resulting from shared features with other hematopoietic lineages [39]. For example, although CD11c is the main surrogate marker for DCs, its expression is also detected in other lineages, including macrophages, natural killer cells and natural killer T cells [40–42]. A breakthrough that overcame this problem was reported from systematic analysis of DC-specific molecular signatures. Miller et al. identified comprehensive transcriptional profiles and regulatory networks associated with 26 distinct DC populations isolated from primary and secondary lymphoid tissues, as well as from nonlymphoid tissues [3]. They characterized the expression pattern of regulators along the critical DC-differentiation checkpoints to search for TFs that control the development and specialization of DCs. Several TFs, including Irf8, Bcl11a and Runx2, were identified as specifically induced during the commitment of MDPs to CDPs, whereas decreased expression of Id2, Zbtb46 and Cited2 was associated with the differentiation of CDPs into pDCs. Differentiation of CDPs into cDCs was linked with the downregulation of Irf8, Tcf4 and Runx2, and upregulation of Batf3, Bcl6 and Ciita. The TFs E2-2, Spi-B and IRF8 are abundantly expressed by pDCs, and thus may be factors required for pDC lineage specification [43].

Macrophages and DCs are hematopoietic cells found in all tissues in the steady state. These cells share the ability to sample the environment but have distinct functions in tissue immunity [5]. In an effort to differentiate between classical DCs and macrophages in tissues, Miller et al. defined a ‘core cDC gene signature’, which includes Zbtb46, Flt3 and Ccr7 [3]. Zbtb46 is a TF that restricts responsiveness to non-cDC growth factors. Given that the expression of Zbtb46 is restricted to cDCs and their committed progenitors, this gene may serve as a useful marker for distinguishing cDCs from other mononuclear phagocyte lineages [44,45]. Flt3 encodes a receptor for Flt3L, which is the main regulator of the development of DCs [46,47]. Flt3 expression is maintained throughout DC development and on terminally differentiated DCs, but not on macrophages. The chemokine receptor CCR7 has been shown to control the migration of cDCs to draining lymph nodes [48]. The use of
these cDC gene signatures may help to delineate the heterogeneity of nonlymphoid tissue CD11b+ cDCs, and may provide a new means of distinguishing CD11b+ cDCs from macrophages in nonlymphoid tissues.

Miller et al. also identified the lineage relationship among various tissue DC subsets by defining distinct gene signatures that are unique to each DC cluster [3]. For example, lymphoid tissue CD8+ cDCs and nonlymphoid tissue CD103+ cDCs share a gene signature regardless of the tissue environment in which they reside. The gene signature shared by both CD8+ cDCs and CD103+ cDCs includes Thr3 (that encodes TLR3) and Xcr1 (that encodes the chemokine receptor CCXCR1), which is consistent with published results showing that CD8+ cDCs and CD103+ cDCs share a superior ability to respond to TLR3 ligands [49] and are the only producers of CCXCR1 across the entire hematopoietic cell lineage [50]. Another finding was that regardless of tissue or cellular origin, nonlymphoid tissue CD103+ cDCs and CD11b+ cDCs that migrate to the draining lymph nodes in the steady state upregulate a shared gene signature that encodes components of a transcriptional immunomodulatory program [3].

Some of the genes with the greatest upregulation include Cd274 [51], igfb8 [52], Socs2 [53], Pias3 [54], CD200 [55] and Fas [56]. Those genes have been linked to the production of immunosuppressive cytokines by DCs, dampening of DC activation and diminished DC survival, which leads to the dampening of T-cell activation. These results demonstrated that one of the potential roles of steady-state migratory cDCs is the control of tolerance to self-antigens in vivo by inducing or maintaining regulatory T-cell responses. These extensive analyses of genome-wide expression data associated with DC lineages not only provide an objective definition of the relationships and distinctions among diverse DC subsets, but also indicate the importance of epigenetic regulation in shaping the various profiles of transcriptomes that are suitable for the designated functions of each DC subset in the particular environment.

**Chromatin modification in the development & function of DCs**

Although epigenomic studies on DC differentiation are limited, a number of studies have reported potent anti-inflammatory and immunoregulatory effects of histone deacetylase inhibitors (HDACIs) on DCs, hinting at the importance of epigenetic regulation during DC maturation. Trichostatin A treatment of epidermal cell suspensions from mouse skin dramatically reduce the Langerhans cell population without affecting the proliferation of γδ T cells, indicating that HDAC is required for proliferation of skin-resident DCs [57]. The involvement of epigenetic regulation was also shown in the expression of costimulatory DC receptors. DCs express the costimulatory molecules CD40, CD80 and CD86 upon activation to drive the effector function of T cells. A number of studies have shown that diverse HDACIs reduce the expression of costimulators (CD40, CD80 and CD86) on both immature and mature DCs in human and mouse [58–62]. In addition to the reduction in costimulators, HDACIs inhibit the expression of cytokines from DCs. Several studies using different HDACIs (butyrate, MS-275 and LBH589) have shown that HDACI treatment reduces the expression of both inflammatory (TNF-α, IL-6 and IL-12) and anti-inflammatory (IL-10) cytokines from TLR3- or TLR4-activated human DCs [58,63,64]. Similar to the results observed in human DCs, treatment of murine DCs with diverse HDACIs suppresses the expression of the inflammatory cytokines TNF-α, IL-1b, IL-6 and IL-12 [62], and alleviates the pathological symptoms associated with inflammatory diseases and transplantation [65,66]. In addition to regulating the stimulatory signals of DCs, HDACIs appear to boost the expression of the immunomodulatory enzyme, indoleamine 2,3-dioxygenase (IDO), in murine DCs. IDO catalyzes tryptophan, thus limiting the activation of T cells. Suberoylanilide hydroxamic acid treatment induces hyperacetylation of histone 4 in the promoter regions of IDO, resulting in higher IDO expression by DCs [61]. Considering that the levels of costimulators, inflammatory cytokines and immunomodulatory molecules expressed by DC determines their cellular fates, the epigenetic disruptions mediated by HDACIs probably change the function of DCs from immunostimulatory to immunomodulatory. Therefore, the concerted epigenetic regulation of DC function appears to be essential for the maturation of DCs.

The involvement of histone methylation and phosphorylation in the regulation of the gene expression of dendritic cells was also reported. The authors observed a decreased ratio between H3K4me3 and H3K27me2 at the IL-12 promoter in splenic DCs in a mouse model of sepsis, which correlated with downregulation of IL-12 gene expression [67]. DCs generated in the presence of oxidized phospholipids had a substantially diminished T-cell-stimulating capacity after
stimulation with TLR ligands, and the inhibition of histone H3 phosphorylation of the IL-12p40 promoter was identified as a possible mechanism of how oxidized phospholipids can regulate DC function [68]. Despite several lines of evidence indicating the involvement of epigenetic regulation in the development and maturation of DCs, whether these epigenetic modifications are heritable features that determine the lineage-specific functions of DCs is not known. To understand the molecular basis of the epigenetic regulation required for the development and maturation of DCs, genome-wide profiling of epigenetic markers is needed for each developmental stage of DCs. However, due to the lack of proper surface markers that define each DC type and their low abundance, it has been difficult to examine cell-type-specific epigenetic modifications at the genomic level for most tissue-resident DCs. Recently, several studies have examined histone H3 trimethylation on lysine 4 (H3K4me3) and 27 (H3K27me3), as well as acetylation of H3 lysines (H3Ac) in human moDCs [69,70]. These studies showed that both H3K4me3 and H3Ac markers correlate with transcriptionally active genes, whereas H3K27me3 labels inactive promoters in each cell type. This result confirmed that most of the key genes associated with moDC differentiation are transcriptionally regulated and accompanied by histone modifications. However, whether these changes are heritable and define the identity of the cells has not been demonstrated. Different environmental factors can further drive DCs into active or tolerogenic states with a distinct gene-expression pattern. Huang et al. examined the histone markers associated with the different states of lipopolysaccharide-conditioned (activated) or transforming growth factor-β-conditioned (tolerized) moDCs at the genome-wide level [71]. Although many differentially regulated genes showed expression patterns independent of histone modification markers, condition-dependent gene regulation of certain costimulatory molecules, cytokines and their receptors correlates with the histone modification markers in general, indicating the involvement of epigenetic control during the maturation process of moDCs. Although these studies showed the epigenetic changes that are associated with different functional states of DCs, the histone modification markers (H3K4me3, H3Ac and H3K27me3) examined may reflect the transcriptional status of the promoters rather than stable and heritable epigenetic changes defining the specific DC cell lineages. Therefore, identification of H3 lysine 9 dimethylation (H3K9me2) and trimethylation (H3K9me3) as cell-type-specific epigenetic markers is intriguing. Fang et al. identified H3K9me2 as a suppressor of interferon (IFN) and IFN-inducible antiviral gene expression [72]. They found differential H3K9me2 levels at IFN-inducible genes in fibroblasts and DCs and demonstrated that this difference is responsible for the cell-type-specific difference in IFN-stimulated gene expression in response to viral infections (Figure 1). In a similar study, Zhu et al. showed that H3K9me3 levels in the flanking regions of enhancers, rather than sequence-specific cis elements of cell-type-specific genes, direct cell-type-specific expression [73]. In both studies, cell-type-specific expression of histone methyltransferase (G9a) and demethylase (Jmjd2d) caused cell-type-specific modification of H3K9 methylation of genes associated with innate immune functions. Therefore, regulation of di- and tri-methylation of H3K9 by cell-type-specific histone methyltransferases or demethylases plays an essential role in the development and maturation of DCs.

DNA methylation in the development & function of DCs

Another important piece of evidence regarding the epigenetic regulatory mechanism of DC development has focused on DNA methylation. Deaton et al. investigated the role of DNA methylation in cell differentiation by analyzing changes in cell-type-specific DNA methylation in hematopoietic stem cells and their progenitors in mice [74]. They combined the biochemical isolation of methylated CpG-rich DNA with deep sequencing [75], and compared the results between CD4+ T cells, B cells and DCs. Surprisingly, few DNA methylation changes were found in CpG islands (CGIs) and non-CGI regions despite large differences in gene expression. For example, fewer than 100 CGIs showing differential methylation were detected when CD4+ T cells were compared with DCs and B cells, whereas over 2000 CGIs showed DNA methylation differences between CD4+ cells and brain cells. Although the number of DNA methylation changes was small among different immune system cells, the changes were mainly associated with genes involved in immunity and defense, cytokine/chemokine-mediated immunity and developmental processes. Interestingly, altered DNA methylation in immune system cells occurred mainly at CGIs within gene bodies, which
have cell-type-restricted promoters. Moreover, a negative correlation was observed between cell-type-specific intragenic CGI methylation and expression of the associated genes in the immune system. However, differently methylated intragenic CGIs often lacked the active histone modification H3K4me3, suggesting that these intragenic CGIs are likely to be sites of transcriptional initiation in non-immune cell types. All these data suggest that the vast majority of DNA methylation changes arise early during lineage commitment, and only a few are acquired during the late stage of terminal differentiation. The DCs they used in this study were a relatively heterogeneous population of CD11c+ cDCs isolated with magnetic beads; therefore, genome-wide analysis of DNA methylation profiles from more purified subsets of DCs should be performed and will help provide another molecular signature marker distinguishing each diverse lineage of DCs.

Although little is known about the genome-wide DNA methylation changes associated with DC development, and DNA methylation may not be the major regulatory mechanism used to induce diverse DC populations, several reports indicate the involvement of DNA methylation in DC-specific gene expression. Frikeche et al. investigated the effects of 5-azacytidine (5-aza), a well-known inhibitor of DNA methylation, on human DCs generated from peripheral blood monocytes [76]. They found that 5-aza does not block GM-CSF/IL-4-driven differentiation of monocytes into DCs and induces few modifications of membrane phenotypes. However, expression of IL-10 and IL-27 was significantly decreased on mature DCs exposed to 5-aza compared with control untreated DCs. Although the underlying mechanisms are not known, DNA methylation may regulate genes and pathways that are involved in cytokine secretion by DCs or may be involved in regulating T-helper cell differentiation. The functional role of DNA methylation in DC programming was investigated by Fedulov and Kobzik [77]. Using genomic, epigenomic and phenotypic analysis of splenic DCs purified from asthma-susceptible neonatal mice, they found that epigenetic changes may program DCs for an altered functional phenotype during an immune response. DCs from allergen-naïve 14-day-old neonates born to asthmatic mothers versus control mothers showed remarkable differences in methylation levels throughout the genome. An overall higher level of methylation was found in the DCs of asthma-susceptible neonates compared with controls. Allergen-naïve offspring of asthmatic mothers contain splenic CD11C+ DCs, which have altered DNA methylation profiles that from birth are capable of polarizing immunity toward a Th2 ‘allergic’ phenotype. This finding provides new evidence for prenatal epigenetic programming in neonatal
DCs as a factor in the maternal transmission of disease risk. This study suggests that epigenetic changes, including changes in DNA methylation levels, may program DCs to an altered functional phenotype during an immune response. Further studies to identify a correlation between DNA methylation changes and DC development, especially comprehensive epigenetic profiling studies combined with transcriptome analysis, will clarify the functional role of DNA methylation and the underlying molecular mechanism in the immune system.

**Conclusion & future perspective**

As we learn more about the sophisticated immune responses designed to induce pathogen-specific defense, the importance of balanced maintenance of diverse DC populations becomes more obvious. However, under certain disease conditions, balanced DC development is compromised and results in dysregulation of epigenetic networks of DCs. Therefore, elucidation of the epigenetic landscape defining each DC cell type and its associated function will be essential for developing tools to regulate the proper development of DCs. Although current technologies do not allow genome-wide analysis of a small number of cells for each DC cell type, identification of cell-type-specific markers for each DC type, along with development of a sequencing technology sensitive enough for small cell numbers will enable the molecular typing of DCs using heritable epigenetic patterns in the near future. The cell-type-specific epigenetic signature will provide a helpful guide for developing diagnostic and therapeutic DCs, which are anticipated for use in treating infections, cancers and autoimmune diseases.

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**Executive summary**

**Phenotypic & functional heterogeneity of dendritic cells**

- Dendritic cells (DCs) are professional antigen-presenting cells that develop from progressively restricted bone marrow progenitors.
- DCs are heterogeneous populations of cells and consist of distinct subsets with different abilities to process antigens and respond to environmental stimuli.

**Transcriptional network of DCs that mediates responses to pathogens**

- A transcriptional network model was generated using global transcriptional profiling combined with systematic application of RNA-interference perturbation to elucidate a complex regulatory network that controls the inflammatory and antiviral responses of mouse bone marrow-derived dendritic cells (BMDCs).
- By combining systematic analysis of the in vivo DNA binding data for 25 transcription factors with the accompanying gene expression and epigenetic profiles, a model for hierarchically organized transcription factor networks was proposed to establish functional regulator–target links in BMDCs following a pathogen stimulus.

**Transcriptional networks control lineage commitment of DCs**

- Extensive analyses of genome-wide expression data associated with 26 distinct DC populations provide an objective definition of the relationships and distinctions among diverse DC subsets.

**Histone modification in the development & function of DCs**

- The epigenetic disruption mediated by histone deacetylase inhibitors probably changes the function of DCs from immunostimulatory to immunomodulatory.
- Regulation of di- and tri-methylation of H3K9 by cell-type-specific histone methyltransferases or demethylases plays an essential role in the development and maturation of DCs.

**DNA methylation in the development & function of DCs**

- The vast majority of DNA methylation changes arise early in hematopoietic cell lineage commitment, and only a few methylation changes are acquired during the late stage of terminal differentiation.

**Conclusion & future perspective**

- Elucidation of the epigenetic landscape defining each DC type and its associated function is essential for developing tools to regulate the proper development of DCs.
- The cell type-specific epigenetic signature will provide a helpful guide in the development of diagnostic and therapeutic DCs.
References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


** Comprehensive comparative analysis of dendritic cell (DC) subsets across the entire immune system using an extensive gene-expression database created by the ImmGen project, and defines transcriptional network of the dendritic cell lineage.


Transcriptional & epigenetic networks in the development & maturation of dendritic cells

- Used global transcriptional profiling combined with systematic knockdowns to examine the complex regulatory networks that control the inflammatory and antiviral responses of mouse bone marrow-derived dendritic cells (BMDCs).


- The authors systematically investigated in vivo binding dynamics of 25 key transcription factors and associated four chromatin marks following pathogen stimulus of mouse BMDC, and explored hierarchically organized transcription factor networks.


- Kim, Lee, Park & Kim


- Fang TC, Schaefer U, Mecklenbrauker I et al. Histone H3 lysine 9 di-methylation as an

** Provides valuable insight into how epigenetic modification of H3K9 determines the interferon-driven transcription network and innate immune response.


** By comparing the epigenome of BMDCs and fibroblasts, the authors reported that intergenic H3K9me3 plays an important role in regulating enhancer activity to control cell type specificity of gene expression.


** Analyzed changes in cell type-specific DNA methylation in cells of the mouse hematopoietic lineages by combining the biochemical isolation of methylated CpG-rich DNA with deep sequencing.

