B cell development is a multilayered process that involves the re-structuring of the transcriptional landscape of progenitor cells. As B cells progress through differentiation, they pass through discrete stages, during which alternative lineage potential is lost, and a mature phenotype is acquired. The sequential orchestration of shifting cellular transcriptomes during this process is delicately controlled. Whereas the presence of transcriptional activators and repressors are important players in genetic programming during development, their functions are intertwined with and dependent on the chromatin configuration of the genes that they control. Transcriptome analysis has enabled many groups to determine important gene sets present in developing and mature subsets, including those of the T and B cell lineages [1]. However, to fully elucidate the gene regulatory networks of cells of a specific lineage at a defined developmental stage, the status of DNA occupancy must be assessed, in addition to the levels of mRNA for each regulator-target gene pair. Furthermore, the histone signatures that mark “open,” “closed”, and “poised” chromatin configurations are important for understanding how genes change over developmental time, even before mRNA expression commences. Thus, assessing the epigenetic regulation of gene expression during B cell development will be critical for a full picture of how these processes are regulated.

Here, Kikuchi et al. [2] show that the HAT, GCN5, is directly linked to transcriptional control of IRF-4, an important regulator of B cell development. The widespread expression and functions of HATs in development have made it challenging to study these genes in a loss-of-function approach in specific cell types. Kikuchi et al. [2] have therefore taken the clever approach of creating a somatic GCN5 germline deletion (GCN5−/−) in the chicken immature B cell line, DT40. First, they used a quantitative RT-PCR approach to survey these cells for expression of known regulators of B cell development and showed that cells lacking GCN5 showed a significant reduction in the expression of IRF-4 and Blimp-1. Next, they were also able to show by reconstitution studies that forced IRF-4 expression could rescue Blimp-1 expression in GCN5−/− cells, consistent with the known role for IRF-4 in direct up-regulation of Blimp-1 in developing B cells [3]. Blimp-1 reconstitution of GCN5−/− DT40 cells, however, failed to restore IRF-4 expression, suggesting that Blimp-1 does not regulate IRF-4 or that regulation of IRF-4 by Blimp-1 is GCN5-dependent. Importantly, ChIP analysis showed that GCN5 binds to and acetylates the histones within the 5′ region of IRF-4, indicating a direct mode of regulation. GCN5 was incapable, however, of binding to the upstream promoter region of Blimp-1, indicating that the loss of Blimp-1 was mediated primarily by the disruption in IRF-4 expression. These results elegantly show that epigenetic regulation of IRF-4 is critical for the maintenance of a genomic landscape compatible with B cell differentiation.

Numerous studies have begun to unravel the epigenetic regulation of genes during different stages of B cell development, but the way in which chromatin remodeling factors are targeted to specific genes in distinct cell types is still largely unknown. It has been shown recently that the accessibility of transcription factor genes important for the pro-B cell stage, such as EBF-1, can be regulated based on their presence in specific genome “domains”, which specify transcriptionally permisive or repressive states [4]. EBF-1 itself has the ability to interact with chromatin at its target genes to open up the locus, thus acting as a “pioneer” factor [5]. On the other hand, Blimp-1 has been shown to interact with H3 methyltransferase G9a [6] and histone deacetylase 1 and 2 [7], both of which aid in transcriptional silencing. The results of Kikuchi et al. [2] therefore suggest a cascade of events that begins with the GCN5-dependent upregulation of IRF-4, followed by GCN5-independent induction and activity of Blimp-1, which then silences a suite of genes that restrain plasma cell development, including Bcl6 and Bach2 (Fig. 1). How GCN5 is targeted to IRF-4 in the DT40 cells and whether that targeting is also found in primary B cells, however, remain to be determined.

One gene that was decreased in expression in GCN5−/− DT40 cells and not restored by IRF-4 or Blimp-1 was Ikaros, which associates with nucleosome remodeling deacetylase complexes and participates in chromatin remodeling but is also instrumental in the up-regulation of genes critical for lymphoid lineages [9]. However, the results reported here suggest that expression of Ikaros itself may be GCN5-dependent (Fig. 1). Other studies have shown that Ikaros expression is HAT-dependent under some conditions [10], consistent with this hypothesis. Interestingly, GCN5 can also acetylate transcription factors themselves and influence their activity directly. For instance, GCN5 has been shown to interact directly with and acetylate the E2A-Pbx oncogenic fusion protein, resulting in increased protein stability [11]. This raises the possibility of developing GCN5-specific inhibitors to destabilize E2A-Pbx in B cell leukemias and emphasizes the importance of understanding the impact of disruption in GCN5 activity on immature B cells on a wider scale. If GCN5 interacts with the WT form of E2A in a similar manner, then the loss of GCN5 in DT40 cells might be expected to result in a decrease in E2A protein levels or activity that would not be detectable at the mRNA level. Thus, there are many layers of regulation that are impinged on when removing GCN5 that should be considered.

Although these results provide important information about the regulation of IRF-4 and Blimp-1 in the context of an
transcriptional landscape of effector B cells in a way that would be very difficult to achieve in primary cells. However, although global investigations provide vast and comprehensive data sets, it is imperative to confirm individual protein interactions and mechanisms of gene regulation, which Kikuchi et al. [2] have reported here with GCN5, IRF-4, and Blimp-1.

REFERENCES


KEY WORDS: 
gene expression - transcription factor networks - chromatin structure - Blimp-1 - histone acetyltransferase - DT40 cells
Editorial: GCN5 opens the door for the IRF-4-mediated cascade of B cell differentiation

Amanda J. Moore and Michele Kay Anderson

J Leukoc Biol 2014 95: 386-387
Access the most recent version at doi:10.1189/jlb.0913479

References
This article cites 11 articles, 3 of which can be accessed free at:
http://www.jleukbio.org/content/95/3/386.full.html#ref-list-1

Subscriptions
Information about subscribing to Journal of Leukocyte Biology is online at
http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Permissions
Submit copyright permission requests at:
http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Email Alerts
Receive free email alerts when new an article cites this article - sign up at
http://www.jleukbio.org/cgi/alerts

© 2014 Society for Leukocyte Biology