Characterization of the DNA Methylome during Human B-Cell Differentiation

Marta Kulis,*,1 Simon Heath,*,2 Giancarlo Castellano,*,1 Renée Beekman,*,1 Angelika Merkel,*,2 Emanuele Raineri,*,2 Anna Esteve,*,2 Ana C Queirós,*,3 Guillem Clot,*,4 Ronald Schuyler,*,2 Simone Ecker,*,5 Vera Pancaldi,*,5 Daniel Rico,*,5 Lidia Agueda,*,2 Julie Blanc,*,2 David Richardson,*,6 Laura Clarke,*,6 Avik Datta,*,7 Nuria Russiñol,*,1 Marien Pascual,*,8 Xavier Aguirre,*,8 Felipe Prosper, MD,9 Diego Alignani,*,10 Bruno Paiva, PhD,11 Gersende Caron,*,12 Thierry Fest, MD PhD,*,13 Marcus O. Muench,*,14 Marina Fomin,*,15 Seung-Tae Lee, MD,*,16 Joseph L. Wiemels, PhD,17 Alfonso Valencia,*,5 Marta Gut,*,2 Paul Flicek,*,6 Hendrik G. Stunnenberg,*,18 Reiner Siebert,*,19 Ralf Küppers, PhD,20 Ivo G. Gut,*,2 Elias Campo, MD,21 José I. Martín-Subero,*,3

1Hospital Clínic, Universitat de Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
2Centro Nacional de Análisis Genómico, Parc Científic de Barcelona, Barcelona, Spain
3Unidad de Hematopatología, Servicio de Anatomía Patológica, Hospital Clínic, Universitat de Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
4Hospital Clínic, IDIBAPS, Barcelona, Spain
5Structural Biology and Biocomputing Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
6European Bioinformatics Institute, European Molecular Biology Laboratory, Cambridge, United Kingdom
7European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Cambridge, United Kingdom
8Area de Oncología, Centro de Investigación Médica Aplicada (CIMA), Universidad de Navarra, Pamplona, Spain
9Clínica Universitaria de Navarra, Pamplona, Spain
10Servicio de Hematología, Clínica Universidad de Navarra, Pamplona, Spain
11Clínica Universidad de Navarra, Pamplona, Spain
12INSERM U917, Rennes, France
13INSERM U917 / University Hospital of Rennes, Rennes, France
14University of California, San Francisco, San Francisco, CA
15Blood Systems Research Institute and Department of Laboratory Medicine, University of California San Francisco, San Francisco,
16Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
17University of California San Francisco, San Francisco, CA
18Nijmegen Centre For Molecular Life Sciences, Nijmegen, Netherlands
Abstract

Introduction: Modulation of the DNA methylation landscape during cell differentiation is a well-established phenomenon. The B-cell lineage represents a paradigmatic cellular model to study the dynamic epigenome during cell development and specification because major B-cell maturation stages are well defined and display differential phenotypic and gene expression features. Furthermore, different B-cell subpopulations show different proliferation abilities, microenvironmental influences and life spans, providing a window of opportunity to study the epigenome in the context of multiple processes.

Methods: We performed whole-genome bisulfite sequencing (WGBS), high-density methylation microarrays and gene expression profiling of ten purified human B-cell subpopulations spanning the entire differentiation program, ranging from uncommitted progenitors to terminally-differentiated plasma cells.

Results: The results of both WGBS and methylation microarrays indicate that B-cell ontogenesis involves an extensive and gradual reconfiguration of the DNA methylome. We uncovered that non-CpG methylation at CpApC trinucleotides is present in progenitor cells and disappears upon B-cell commitment independently of CpG demethylation. CpG methylation, in contrast, changed extensively during the entire B-cell maturation program, with one quarter of all measured CpGs showing dynamic methylation. B-cell enhancers suffered more extensive methylation changes than promoter regions, especially in the early differentiation steps up to the germinal center B-cell (gcBC) stage, and their demethylation seemed to be mediated by binding of lineage-specific transcription factors. Enhancers with dynamic methylation were related to genes involved in a large B-cell network that showed high gene expression variability throughout differentiation. In highly proliferative gcBCs, we observed a shift of dynamic methylation from regulatory towards non-functional elements; gcBCs start to undergo global demethylation of late-replicating heterochromatic regions and methylation of polycomb-repressed regions. This signature becomes particularly extensive in long-lived memory B cells and plasma cells, indicating that these changes start in highly proliferative cells and then accumulate in non-proliferative cells with extended lifespan.
Conclusion: Our epigenomic analysis of the B-cell differentiation program extends our knowledge on how the DNA methylome is modulated during cell specification and maturation and offers a resource for researchers in the field, both at global and single gene levels.

Disclosures
No relevant conflicts of interest to declare.

Author notes
*Asterisk with author names denotes non-ASH members.

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