Transcriptional diversity during lineage commitment of human blood progenitors

Author(s): Lu Chen, Myrto Kostadima, Joost H. A. Martens, Giovanni Canu, Sara P. Garcia, Ernest Turro, Kate Downes, Iain C. Macaulay, Ewa Bielczyk-Maczynska, Sophia Coe, Samantha Farrow, Pawan Poudel, Frances Burden, Sjoert B. G. Jansen, William J. Astle, Antony Attwood, Tadbir Bariana, Bernard de Bono, Alessandra Breschi, John C. Chambers, BRIDGE Consortium, Fizzah A. Choudry, Laura Clarke, Paul Coupland, Martijn van der Ent, Wendy ...

Source: *Science*, Vol. 345, No. 6204 (26 SEPTEMBER 2014), p. 1580

Published by: American Association for the Advancement of Science

Stable URL: https://www.jstor.org/stable/10.2307/24917692

RESEARCH ARTICLE SUMMARY

IMMUNOGENETICS

Transcriptional diversity during lineage commitment of human blood progenitors

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INTRODUCTION: Blood production in humans culminates in the daily release of around 10^{11} cells into the circulation, mainly platelets and red blood cells. All blood cells originate from a minute population of hematopoietic stem cells (HSCs) that expands and differentiates into progenitor cells with increasingly restricted lineage choice. Characterizing alternative splicing events involved in hematopoiesis is critical for interpreting the effects of mutations leading to inherited disorders and blood cancers and for the rational design of strategies to advance transplantation and regenerative medicine.

RATIONALE: To address this, we explored the transcriptional diversity of human blood progenitors by sequencing RNA from six progenitor and two precursor populations representing the classical myeloid commitment stages of hematopoiesis and the main lymphoid stage. Data were aligned to the human reference transcriptome and genome to quantify known transcript isoforms and to identify novel splicing events, respectively. We used Bayesian polytomous model selection to classify transcripts into distinct expression patterns across the three cell types that comprise each differentiation step.

RESULTS: We identified extensive transcriptional changes involving 6711 genes and 10,724 transcripts and validated a number of these. Many of the changes at the transcript isoform level did not result in significant changes at the gene expression level. Moreover, we identified transcripts unique to each of the progenitor populations, observing enrichment in non–protein-coding elements at the early stages of differentiation. We discovered 7881 novel splice junctions and 2301 differentially used alternative splicing events, enriched in genes involved in regulatory processes and often resulting in the gain or loss of functional domains. Of the alternative splice sites displaying differential usage, 73% resulted in exon-skipping events involving at least one protein domain (38.5%) or introducing a premature stop codon (26%). Enrichment analysis of RNA-binding motifs provided insights into the regulation of cell type–specific splicing events.

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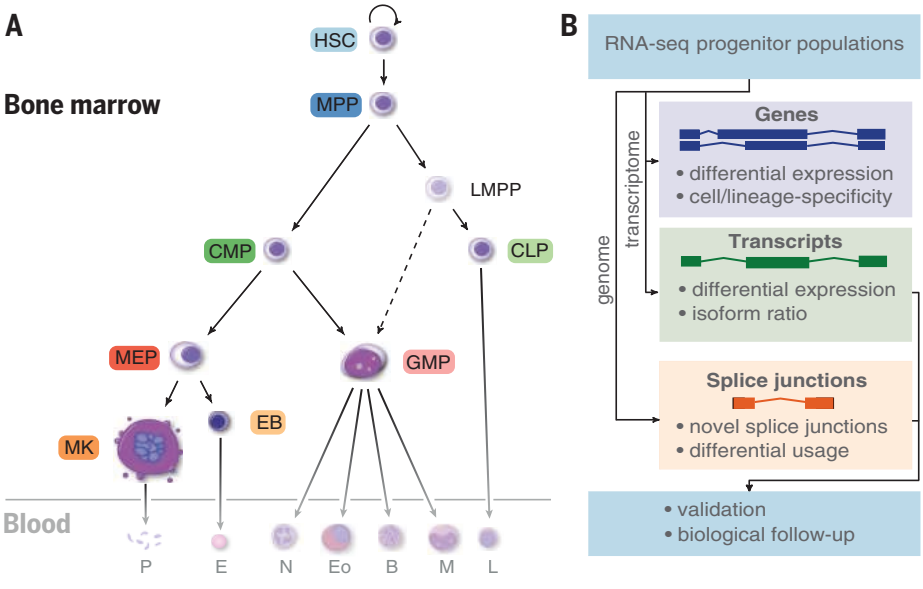
To demonstrate the importance of specific isoforms in driving lineage fating events, we investigated the role of a transcription factor highlighted by our analyses. Our data show that nuclear factor I/B (NFIB) is highly expressed in megakaryocytes and that it is transcribed from an unannotated transcription start site preceding a novel exon. The novel NFIB isoform lacks the DNA binding/dimerization domain and therefore is unable to interact with its binding partner, NFIC. We further show that NFIB and NFIC are important in megakaryocyte differentiation.

CONCLUSION: We produced a quantitative catalog of transcriptional changes and splicing events representing the early progenitors of human blood. Our analyses unveil a previously undetected layer of regulation affecting cell fating, which involves transcriptional isoforms switching without noticeable changes at the gene level and resulting in the gain or loss of protein functions. ■



Overview of methodology. RNA-sequencing reads from human blood progenitors [opaque cells in (**A**)] were mapped to the transcriptome to quantify gene and transcript expression. Reads were also mapped to the genome to identify novel splice junctions and characterize alternative splicing events (**B**).

The list of author affiliations is available in the full article online.
*Corresponding author. E-mail: ar506@cam.ac.uk (A.R.); mf471@cam.ac.uk (M.F.)
Cite this article as L. Chen *et al.*, *Science* **345**, 1251033 (2014). DOI: 10.1126/science.1251033