Year of publication 2016

Leïla Perié, Ken R Duffy (2016 Jul 13)

Retracing the in vivo haematopoietic tree using single-cell methods.

FEBS letters : DOI : 10.1002/1873-3468.12299

Summary

The dynamic process by which self-renewing stem cells and their offspring proliferate and differentiate to create the erythroid, myeloid and lymphoid lineages of the blood system has long since been an important topic of study. A range of recent single cell and family tracing methodologies such as massively parallel single-cell RNA-sequencing, mass cytometry, integration site barcoding, cellular barcoding and transposon barcoding are enabling unprecedented analysis, dissection and re-evaluation of the haematopoietic tree. In addition to the substantial experimental advances, these new techniques have required significant theoretical development in order to make biological deductions from their data. Here, we review these approaches from both an experimental and inferential point of view, considering their discoveries to date, their capabilities, limitations and opportunities for further development.

Konstantinos D Kokkaliaris, Daniel Lucas, Isabel Beerman, David G Kent, Leïla Perié (2016 Mar 22)

Understanding hematopoiesis from a single-cell standpoint.

Experimental hematology : 447-50 : DOI : 10.1016/j.exphem.2016.03.003

Summary

The cellular diversity of the hematopoietic system has been extensively studied, and a plethora of cell surface markers have been used to discriminate and prospectively purify different blood cell types. However, even within phenotypically identical fractions of hematopoietic stem and progenitor cells or lineage-restricted progenitors, significant functional heterogeneity is observed when single cells are analyzed. To address these challenges, researchers are now using techniques to follow single cells and their progeny to improve our understanding of the underlying functional heterogeneity. On November 19, 2015, Dr. David Kent and Dr. Leïla Perié, two emerging young group leaders, presented their recent efforts to dissect the functional properties of individual cells with a webinar series organized by the International Society for Experimental Hematology. Here, we provide a summary of the presented methods for cell labeling and clonal tracking and discuss how these different techniques have been employed to study hematopoiesis.

Tom S Weber, Leïla Perié, Ken R Duffy (2016 Jan 7)

Inferring average generation via division-linked labeling.

Journal of mathematical biology

Summary

For proliferating cells subject to both division and death, how can one estimate the average generation number of the living population without continuous observation or a division-diluting dye? In this paper we provide a method for cell systems such that at each division there is an unlikely, heritable one-way label change that has no impact other than to serve as a distinguishing marker. If the probability of label change per cell generation can be determined and the proportion of labeled cells at a given time point can be measured, we establish that the average generation number of living cells can be estimated. Crucially, the estimator does not depend on knowledge of the statistics of cell cycle, death rates or total cell numbers. We explore the estimator's features through comparison with physiologically parameterized stochastic simulations and extrapolations from published data, using it to suggest new experimental designs.

Year of publication 2015

Leïla Perié, Ken R Duffy, Lianne Kok, Rob J de Boer, Ton N Schumacher (2015 Jul 20)
The Branching Point in Erythro-Myeloid Differentiation.
Cell : 1655-62 : DOI : 10.1016/j.cell.2015.11.059

Summary

Development of mature blood cell progenies from hematopoietic stem cells involves the transition through lineage-restricted progenitors. The first branching point along this developmental process is thought to separate the erythro-myeloid and lymphoid lineage fate by yielding two intermediate progenitors, the common myeloid and the common lymphoid progenitors (CMPs and CLPs). Here, we use single-cell lineage tracing to demonstrate that so-called CMPs are highly heterogeneous with respect to cellular output, with most individual CMPs yielding either only erythrocytes or only myeloid cells after transplantation. Furthermore, based on the labeling of earlier progenitors, we show that the divergence between the myeloid and erythroid lineage develops within multipotent progenitors (MPP). These data provide evidence for a model of hematopoietic branching in which multiple distinct lineage commitments occur in parallel within the MPP pool.

Year of publication 2014

Leïla Perié, Shalin H Naik (2014 Nov 11)
Toward defining a 'lineage'–The case for dendritic cells.
Seminars in cell & developmental biology : 3-8 : DOI : 10.1016/j.semcdb.2015.02.004

Summary

The immune system consists of a heterogeneous ensemble of cell types that immunologists have tried to classify and order for decades. This classification has relied on varying criteria,

resulting in major debates in the immunology community. Discovered in the late 1970s [1], dendritic cells (DCs) are no exception, and their membership to a distinct immune lineage is still vividly debated [2-6]. Here, we review recent work on the origin of DCs and discuss the possible definition of a separate 'DC lineage'.

Shalin H Naik, Ton N Schumacher, Leïla Perié (2014 Apr 15)
Cellular barcoding: a technical appraisal.
Experimental hematology : 598-608 : DOI : 10.1016/j.exphem.2014.05.003

Summary

Cellular barcoding involves the tagging of individual cells of interest with unique genetic heritable identifiers or barcodes and is emerging as a powerful tool to address individual cell fates on a large scale. However, as with many new technologies, diverse technical and analytical challenges have emerged. Here, we review those challenges and highlight both the power and limitations of cellular barcoding. We then illustrate the contribution of cellular barcoding to the understanding of hematopoiesis and outline the future potential of this technology.

Year of publication 2013

Leïla Perié, Philip D Hodgkin, Shalin H Naik, Ton N Schumacher, Rob J de Boer, Ken R Duffy (2013 Oct 14)
Determining lineage pathways from cellular barcoding experiments.
Cell reports : 617-24 : DOI : 10.1016/j.celrep.2014.01.016

Summary

Cellular barcoding and other single-cell lineage-tracing strategies form experimental methodologies for analysis of in vivo cell fate that have been instrumental in several significant recent discoveries. Due to the highly nonlinear nature of proliferation and differentiation, interrogation of the resulting data for evaluation of potential lineage pathways requires a new quantitative framework complete with appropriate statistical tests. Here, we develop such a framework, illustrating its utility by analyzing data from barcoded multipotent cells of the blood system. This application demonstrates that the data require additional paths beyond those found in the classical model, which leads us to propose that hematopoietic differentiation follows a loss of potential mechanism and to suggest further experiments to test this deduction. Our quantitative framework can evaluate the compatibility of lineage trees with barcoded data from any proliferating and differentiating cell system.

Year of publication 2012

Shalin H Naik, Leïla Perié, Erwin Swart, Carmen Gerlach, Nienke van Rooij, Rob J de Boer, Ton N Schumacher (2012 Apr 2)

Diverse and heritable lineage imprinting of early haematopoietic progenitors.

Nature : 229-32 : DOI : 10.1038/nature12013

Summary

Haematopoietic stem cells (HSCs) and their subsequent progenitors produce blood cells, but the precise nature and kinetics of this production is a contentious issue. In one model, lymphoid and myeloid production branch after the lymphoid-primed multipotent progenitor (LMPP), with both branches subsequently producing dendritic cells. However, this model is based mainly on in vitro clonal assays and population-based tracking in vivo, which could miss in vivo single-cell complexity. Here we avoid these issues by using a new quantitative version of 'cellular barcoding' to trace the in vivo fate of hundreds of LMPPs and HSCs at the single-cell level. These data demonstrate that LMPPs are highly heterogeneous in the cell types that they produce, separating into combinations of lymphoid-, myeloid- and dendritic-cell-biased producers. Conversely, although we observe a known lineage bias of some HSCs, most cellular output is derived from a small number of HSCs that each generates all cell types. Crucially, in vivo analysis of the output of sibling cells derived from single LMPPs shows that they often share a similar fate, suggesting that the fate of these progenitors was imprinted. Furthermore, as this imprinting is also observed for dendritic-cell-biased LMPPs, dendritic cells may be considered a distinct lineage on the basis of separate ancestry. These data suggest a 'graded commitment' model of haematopoiesis, in which heritable and diverse lineage imprinting occurs earlier than previously thought.