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A revised scheme for developmental pathways of hematopoietic cells: the myeloid-based model

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Abstract

Blood cells comprise very diverse cell types with a wide range of crucial functions; however, they share a common progenitor cell type—the hematopoietic stem cell (HSC). Clarifying how HSCs differentiate into these diverse cell types is important for understanding how they attain their various functions and offers the potential for therapeutic manipulation. Various theories exist about how HSCs diversify; in particular, one model (the 'classical' model) proposes that lymphocytes and myelo-erythroid lineages branch separately at an early stage of hematopoiesis, whereas another model (the 'myeloid-based' model) proposes that the myeloid potential is retained for much longer among cells that can become lymphocytes. This article describes and compares these models and outlines recent evidence supporting the myeloid-based model.

Keywords: hematopoietic stem cells, lineage commitment, myeloid cells, T-cell progenitors, thymus

Introduction

The blood cell family consists of a variety of cell types, all of which are formed from a hematopoietic stem cell (HSC). Over the last century, the classification of blood cell types was largely based on morphological criteria, leading to the emergence of the classical dichotomy concept, in which the blood cell family was subdivided into two major lineages—a myelo-erythroid lineage and a lymphoid lineage. Therefore, it has been stated in most textbooks that the first branch point from the HSC produces progenitors for these two lineages.

This classical textbook model is, however, unable to explain recent findings on hematopoietic processes. As discussed in this article, on the basis of results starting from murine fetal progenitors, we have previously proposed an alternative 'myeloid-based model', in which myeloid potential is retained in all erythroid, T and B cell branches, even after these lineages have segregated from each other. Our most recent finding that the early progenitors in the adult thymus retain myeloid potential strongly argues that the classical model may not fully explain the process of adult hematopoiesis. We emphasize that an exact map of developmental potential is primarily important for the study of the molecular mechanisms of lineage commitment of hematopoietic cells.

Two different maps of lineage branches in hematopoiesis

All blood cells are generated at the site where HSCs reside, i.e. in the liver during the fetal period and in the bone marrow after birth, except for T cells, which are formed in the thymus from progenitors derived from these hematopoietic sites. The HSCs lose their pluripotency in a stepwise fashion, ultimately giving rise to unipotent progenitor cells. This lineage restriction is also referred to as a 'cell fate decision' or 'lineage commitment'.

The model that has been presented in most textbooks for >30 years is depicted in Fig. 1A, which we now call the classical model. In this long-standing model, the HSC firstly generates a common myeloid–erythroid progenitor (CMEP) and a common lymphoid progenitor (CLP), which produce myeloid or erythroid cells and T or B cells, respectively. In 2001, we proposed an alternative myeloid-based model, which postulates that the HSC first diverges into the CMEP and a common myelo–lymphoid progenitor (CMLP); there is no CLP in this model (Fig. 1B) (1–3). The CMLP then generates T and B cell progenitors through a bipotential myeloid–T progenitor and a myeloid–B progenitor stage, respectively. These two models are critically different in that the progenitors at the branching point toward T and B cells

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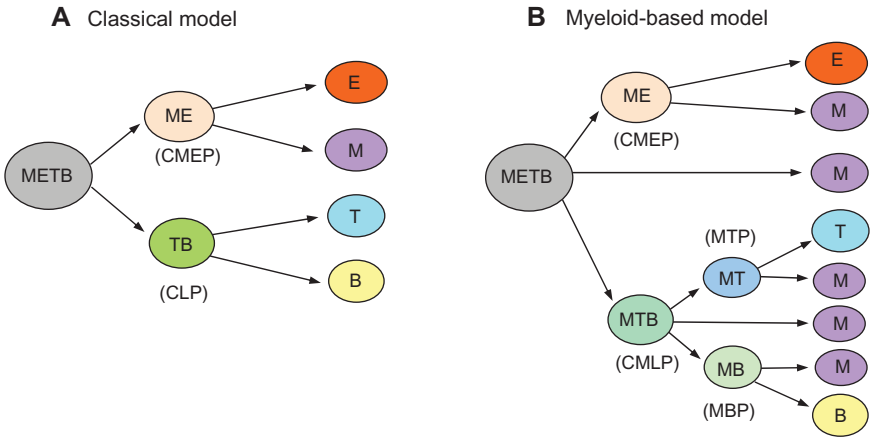

Fig. 1. Representative models of hematopoiesis. (A) This model proposes that the HSC firstly diverges into a CMEP and a CLP. Note that CMEPs are sometimes referred to as common myeloid progenitors (CMPs). E, M, T and B represent the progenitor potential for erythroid, myeloid, T and B cells, respectively. (B) In this model, the first branch point generates CMEPs and CMLPs, and the myeloid potential persists in the T and B cell branches even after these lineages have diverged.

do not retain any myeloid potential in the classical model, whereas in the myeloid-based model, the potential to generate myeloid cells is retained in all erythroid, T and B lineage branches.

Derivation of the classical myeloid–lymphoid dichotomy model

How was the classical myeloid–lymphoid dichotomy concept originally formed? Microscopic observation has been the basic tool of hematology, and ~100 years ago, many blood cell types were described based on morphological features, e.g. erythrocytes, platelets, granulocytes, macrophages and lymphocytes (4, 5). Morphologists were also aware that erythrocytes, platelets, monocytes and granulocytes differentiate in the bone marrow. Thus, erythrocytes and platelets were placed together with phagocytic cells into the 'myeloid' lineage. On the other hand, lymphocytes were originally found as cells seen in lymph. Subsequent histological studies showed that lymphocytes reside in spleen, thymus and lymph nodes.

Morphologically, lymphocytes have no particular features with little cytoplasm or intracellular organelles, and their function long remained unclear. Studies on the function of lymphocytes began in the second half of the 20th century. In 1968, bone marrow-derived (B) cells and thymus-derived (T) cells were identified as functionally distinct types of cells, i.e. cells that produce antibody and cells that help antibody production, respectively (6). Although T and B cells exert very different functions, researchers at the time paid more attention to their common property—both types of lymphocyte respond in an antigen-specific manner. Thus, the concept of a 'lymphoid lineage' remained unchanged or even strengthened.

In 1977, using radiation-induced chromosomal aberrations as clonal markers, it was demonstrated for the first time that myeloid cells, T cells and B cells are derived from a common HSC (7). After this finding, the classical model of hematopoiesis came to appear in most textbooks and was based on a hypothetical myeloid–lymphoid dichotomy concept. The findings in the 1980s that T and B cells use a common machinery for the somatic rearrangement of the T-cell receptor and Ig genes also strongly supported the idea that T cells and B cells are closely related.

In 1997, Weissman and colleagues (8) reported that they detected CLPs as a lineage marker-negative IL-7R^{+}c-kit^{low} population of murine bone marrow cells, and similar results were subsequently published by several other groups (9, 10). These reports have lead many researchers to think that the existence of CLPs was substantiated.

Proposal of a myeloid-based model

By 1997, we had developed a clonal assay that is able to examine the developmental potential of individual progenitors toward myeloid, T and B lineages (multilineage progenitor assay) (11). Using this assay system, we analyzed hematopoietic progenitor cells in the murine fetal liver. Progenitors generating two types of cells and those generating only one type were detected, in addition to progenitors generating myeloid, T and B cells.

As is always the case with any clonal analysis, a possibility remains that the final readouts do not necessarily reflect the complete developmental potential of the seeded progenitors, except for the case of progenitors generating all detectable lineages. However, the consistent detection of progenitors generating myeloid and T cells and myeloid and B cells in the face of a complete absence of progenitors generating only T and B cells led us to the idea that myeloid potential is retained even after the segregation of the T and B cell lineages (11–13). We subsequently extended our clonal analysis to include the erythroid lineage and identified CMLP and CMEP in murine fetal liver (14). On the basis of these findings, we came to propose the myeloid-based model (Fig. 2B) (1–3).

The classical model proposes to classify blood cells into two major lineages, but finally differentiated cells are placed

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in parallel (Fig. 2A). In contrast, the myeloid-based model proposes the idea that myeloid cells represent a prototype of hematopoietic cells, whereas erythroid, T and B cells represent specialized types (Fig. 2B). According to this concept, hematopoiesis can be understood as follows: specification toward erythroid, T and B cell lineages proceeds on a basis of a prototypical developmental program to construct myeloid cells. Prototypic cells, namely myeloid cells, are equipped with the basic machinery required for host defense cells, e.g. phagocytic activity and mobility. In specialized cells, a new level of machinery is added, while the basic machinery is more or less modified or shutoff. For example, in the case of B cells, phagocytic activity is reduced but still maintained while the antigen-presenting ability is rather strengthened, and finally, an ability to recognize specific antigen is newly acquired.

Does the myeloid-based model explain only fetal hematopoiesis?

Our myeloid-based model was based mainly on findings made with fetal progenitors, whereas the studies supporting the classical model were performed using adult progenitors (8–10). Therefore, to reconcile the classical- and myeloid-based models, an idea was proposed that the myeloid-based model describes fetal hematopoieisis, whereas the classical model describes adult hematopoiesis (15–17). However, it is well known that fetal liver hematopoiesis belongs to the same class as that in adult bone marrow, namely 'definitive' hematopoiesis that is specified to produce adult type blood cells, which is different from 'primitive' hematopoiesis occurring in the yolk sac. It is thus highly probable that the basic events, such as the lineage-restriction processes, are the same in fetal liver and adult bone marrow.

In 2002, using mice expressing green fluorescent protein under the control of the *Rag1* promoter, Kincade and colleagues (18) showed that the early lymphoid progenitors in adult bone marrow retain myeloid potential. Subsequently, Jacobsen and colleagues (19) succeeded in identifying CMLPs in the adult bone marrow, which are the counterpart of those we had identified in fetal liver in 2002 (14). We interpreted these findings in support of the myeloid-based model, making it applicable for adult hematopoiesis as well. However, in the model proposed by Jacobsen and colleagues, the CMLP was placed between the HSC and CLP in their modified classical model (Fig. 3), leaving the CLP concept unchallenged.

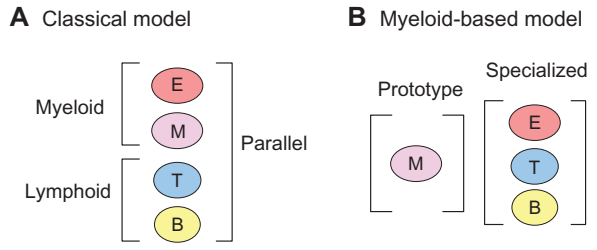

Fig. 2. The concept of the myeloid-based model. (A) In the classical model, erythroid, myeloid, T and B lineage cells are placed in parallel. (B) The myeloid-based model proposes that myeloid cells represent a prototype of blood cells, whereas erythroid, T and B cells represent specialized types.

T-cell progenitors retain myeloid potential: the classical model should be reinterpreted

To examine whether the classical model really represents adult hematopoiesis, we recently investigated which of myeloid or B-cell potential is retained longer along with the process of T-cell development in the adult thymus. We and other groups have already demonstrated that most T-cell progenitors in the earliest population in the adult thymus have already lost B-cell potential (20, 21). Therefore, we analyzed whether these early T-cell progenitors retain myeloid potential or not. We cultured these early thymic progenitors with stromal cells modified to support both T and myeloid cells and found that a substantial proportion of thymic T-cell progenitors produced macrophages (22). We also demonstrated *in vivo* that ~30% of thymic macrophages are derived from T-cell progenitors. A branch point for the T versus myeloid lineage was thus demonstrated to exist after termination of B-cell potential (Fig. 4). A similar finding was reported by Bell and Bhandoola (23) in the same issue of the journal that published our report (22). They also showed that thymic T-cell progenitors produce a significant proportion of granulocytes

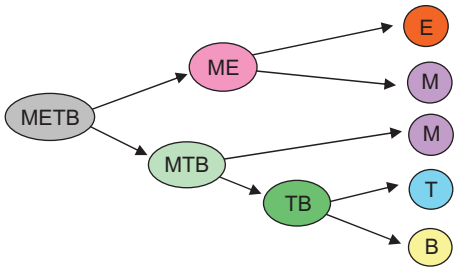

Fig. 3. The modified classical model as proposed by Jacobsen and colleagues (19). Here, the CMLP (MTB-progenitor) is placed between the HSC (METB) and the CLP (TB).

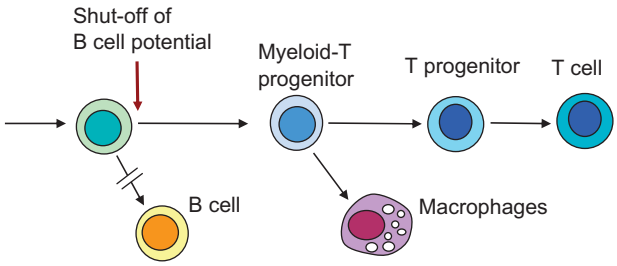

Fig. 4. T-cell progenitors retain myeloid potential after terminating B cell potential. We have recently demonstrated that early T-cell progenitors in the adult thymus that have lost B-cell potential still retain a substantial capacity to generate macrophages. We also revealed that a certain proportion (~30%) of thymic macrophages are produced by myeloid–T progenitors, by firstly making bone marrow chimeric mice carrying bone marrow cells from wild-type mice and from human-CD3ε transgenic mice that lack T lineage cells and subsequently assessing contribution rate of wild-type versus transgenic cells for the production of thymic macrophages (22). Bell and Bhandoola (23) also demonstrated that granulocytes in the thymus are substantially produced from T-cell progenitors, by genetically marking T-cell progenitors using the expression of Rag gene. These findings strongly argues against the existence of CLPs on the physiological pathway from the HSC to T cells in adult hematopoiesis.

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that reside in thymus. Therefore, it is now clear that the classical model should be reassessed.

To conduct studies on the molecular mechanisms of lineage commitment, exact information about developmental potential of progenitors is required. In this context, the CLP concept of the classical model may lead to confusion in the studies of the T-cell and also B-cell lineage commitment processes. For example, in the classical model, the occurrence of T-cell lineage commitment is regarded as the point of termination of B-cell potential. This scenario cannot explain our recent finding that the potentials to produce macrophages, dendritic cells and NK cells are retained in T-cell progenitors up to the midst of the DN2 stage (Fig. 5A and B), while these non-T lineage potentials are terminated after the midst of DN2 stage, just synchronizing with down-regulation of PU.1 (24), a transcription factor essential for myeloid lineage cells (25).

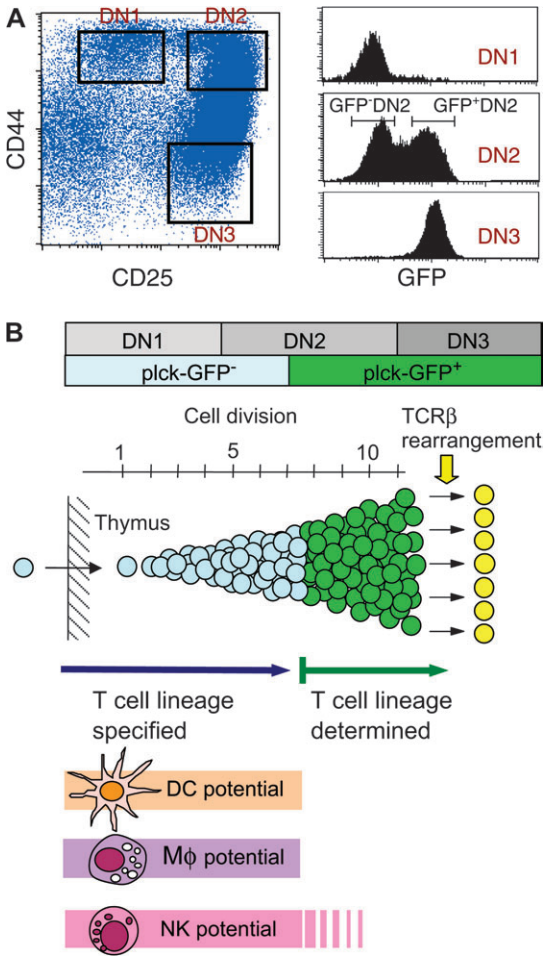

Fig. 5. Thymic progenitors shut off their myeloid potential around the midst of the DN2 stage. (A) The CD44 versus CD25 profile of the $CD3^-$ $CD4^-CD8^-$ [double-negative (DN)] fraction of fetal thymocytes (15-days post-coitum) from transgenic mice in which green fluorescent protein (GFP) is expressed under the control of proximal lck (plck) promoter. The right panels show GFP expression in cells in the gates denoted in the left panel. (B) Schematic illustration of the early differentiation and proliferation of thymic T lineage cells. A single early thymic progenitor undergoes >10 cell divisions during the DN1 and DN2 stages to generate >1000 DN3 cells. The shutoff of myeloid potential occurs during the transition step from the GFP^-DN2 stage to the GFP^+DN2 stage and subsequently the T-cell lineage-determined progenitors undergo several cell divisions before they enter the DN3 stage to initiate TCRβ chain gene rearrangement.

A map of the developmental potentials of progenitors is essential for further investigation

With any type of model, in this case for the lineage branching map, concerns exist to what extent such a process occurs *in vivo*. One cannot claim that the potential detected *in vitro* for a certain lineage represents a physiological pathway to produce that lineage cells *in vivo*. In the case of myeloid potential in T-cell progenitors, we have demonstrated that such a potential is really expressed *in vivo*, as mentioned above (Fig. 4).

Even in the case where a potential detected *in vitro* is not expressed *in vivo*, it nevertheless remains important to describe the potential detected *in vitro*. Rather, the information about the retention of such a potential *per se* is more essential than that of *in vivo* cell fate in the study of lineage commitment process. For example, erythrocytes and B cells are scarcely produced in the thymus in the physiological situation, but it is obvious that the information about whether or not the earliest thymic progenitors retain erythrocyte potential or B-cell potential is a pre-requisite to study early intrathymic lineage commitment processes. It should be further emphasized here that a simple cell-fate map ignoring information of potential pathways that are not expressed in the normal *in vivo* environment could be misleading in investigating the molecular mechanisms of cell differentiation (Fig. 6).

Validity of the myeloid-based model

The myeloid-based model describes both the developmental potential of cells and their physiological cell fate. Although this model was originally proposed almost 8 years ago, so far there is no necessity for major revisions concerning the developmental potential.

A possible minor change would be that IL-$7R^+$ cells, which were originally named as CLPs, have been shown to prominently retain myeloid potential (26, 27). These cells have been reported to serve mainly as B-cell progenitors (28, 29). Therefore, after the bifurcation point when myelo–lymphoid progenitors split toward the T and B cell lineages, it is likely that a myeloid–T–B (MTB) progenitor stage is formed on the way toward the B-cell lineage. Which of the potential lineages (T or myeloid) in these MTB progenitors is shutoff first remains controversial (26, 27). If myeloid potential shuts off first, it would leave the TB stage; however, the presence of progenitors that lack T-cell potential but can produce macrophages and B1-type B cells in adult bone marrow (30) suggests that the MB stage exists next to the MTB stage.

Whether the physiological cell fate is correctly described or not remains to be discussed. Previously, Nakauchi and colleagues (31) showed that HSCs can directly produce myeloid progenitors *in vitro*, but the possibility that these myeloid progenitors retain T and/or B potential was not determined nor was whether such a segregation occurs *in vivo*. It also remains to be quantitatively assessed to what extent

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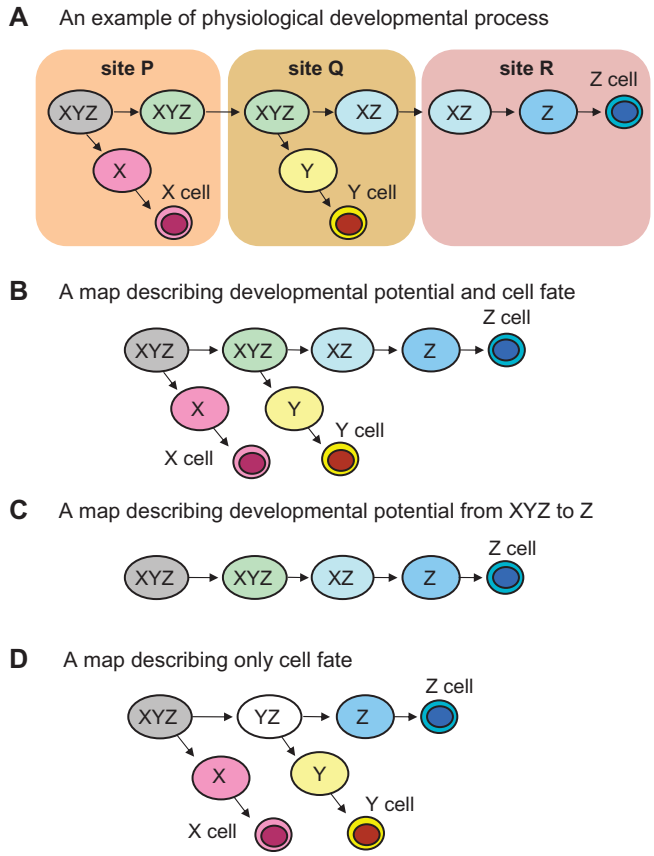

Fig. 6. An illustration of why cell-fate maps should not be over-simplified (using hypothetical cell lineages X, Y, and Z). (A) An example of the developmental process to produce X cells, Y cells or Z cells. Suppose that a progenitor having potential for X, Y and Z lineages (XYZ-progenitor) first migrates to a particular site (site P); there, it will make X-progenitors and self-renewing XYZ-progenitors, followed by production of X cells from the X-progenitors. Then, the XYZ-progenitor migrates to the next site (site Q), where they lose their potential to become Y cells to become XZ-progenitors on one hand and on the other hand segregation to Y-progenitors also occurs that become Y cells. Note that the XZ progenitors do not produce X cells in site Q but can produce X cells in other place. The XZ-progenitor then migrates to site R and produces Z-progenitors and finally Z cells there. (B) A simplified model for the process shown in (A), which contains information about developmental potential and cell fate. A map like this is useful not only to understand reality but also for further investigations into differentiation mechanisms. (C) A map of lineage restriction focusing on the way from the XYZ-progenitor to a Z cell. Particularly in studying the molecular mechanisms in lineage commitment for the production of Z cells, the information for the order of lineage restriction [XYZ → XZ → Z] is essential. (D) A map that describes only the physiological cell fate. This map might be misleading because the information about the lineage restriction process shown in (C) is absent.

the myeloid potential in MTB and MB progenitors contributes to the production of myeloid cells. One indication comes from a study by Georgopoulos and colleagues (32) that suggested that myeloid cells including granulocytes are mainly derived from CMLP, rather than from CMEP.

As to the production of other non-B lineage cells from MTB or MB cells along the B cell branch, it has been suggested that plasmacytoid dendritic cells are derived from some early B-cell progenitors (33). Furthermore, it has also been shown that early B-cell progenitors serve as progenitors for conventional dendritic cells in case of viral infection (34). It is probable that the contribution rate of B-cell lineage progenitors for non-B-cell lineage cells is different between the steady state and infection cases, along with aging, and even among species. Although direct production of macrophages from progenitors along the B cell branch has not yet been demonstrated, these findings strongly suggest that myeloid potential in B-cell branch progenitors is active *in vivo*. As for dendritic cell and NK cell potential retained in T-cell progenitors, compelling evidence exists that these cells are produced in thymus (35, 36).

In the myeloid-based model, T-cell, B-cell and erythroid lineages are expressed as single pathways. So far, there seems to be no firm evidence to show alternative pathways for these lineages. For example, Serwolt *et al.* (37) recently showed that IL-7R$^+$ cells can efficiently migrate to the thymus when transferred intravenously into sublethally irradiated mice and argue that IL-7R$^+$ cells produce T cells *in vivo*, but it remains unclear whether such events occur during the steady state.

It may be possible that lineage commitment is a gradual event and thus retention of potential is not an all-or-nothing issue (38). In that sense, over-simplified models may not necessarily represent reality. Nevertheless, we argue that there should be a certain basic rule in the lineage-restriction program during hematopoiesis, and attempts to simplify the model are an important step to figure out the basic rule.

Conclusions

In this paper, we have discussed, contrary to the classical dichotomy concept, a revised concept of the myeloid-based model, in which blood cells are relocated into prototype (myeloid) versus specialized types (erythroid, T and B). The idea of the myeloid-based model might bring about a paradigm shift in the concept of blood cell lineages. We also argued that a proper map of developmental potential is primarily important for studies of molecular mechanisms of lineage commitment.

Acknowledgements

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