The report by Chen *et al.*[1] also highlights the parallels between sex chromosomes with different origins. Some genes or chromosome regions seem to have a role in sex determination across many species, but even non-homologous sex chromosomes differentiate by analogous processes of rapid degradation of the sex-specific element. This degradation produces gene dosage inequality, which may be mitigated by shaping genes for a sex-specific role and/or regulating their expression[13] by mechanisms chosen from a common epigenetic toolbox.

It is inspiring that such insights have come from a thorough genomic analysis of a distinctly non-model fish species. Other important discoveries about sex determination and sex-chromosome differentiation have come from medaka and stickleback fishes, as well as from reptiles like dragons and geckos. These and other non-model species with interesting sex chromosomes would also repay exhaustive genomic analysis.

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Stem cell fate regulation by dynein motor protein Lis1

Britta Will & Ulrich Steidl

Cell fate regulation is a central component of maintaining tissue homeostasis, yet the mechanisms instructing cell division diversity in tissue-specific stem cells have not been well understood. A new study uncovers a central role for microtubule motor–regulating protein Lis1 in hematopoietic stem cell fate determination and in leukemogenesis.

Cell fate diversification is required for the establishment of the architecture of complex tissues and, thereby, for organ function and also allows for efficient adaptation to environmental changes. Embryonic stem cells and tissue-specific stem cells, as well as a few multipotent progenitor cells, can diversify their fate by generating daughter cells with distinct identities upon division. Such asymmetric division is facilitated by (i) tightly regulated activity of cell polarity factors that polarize the dividing cell, (ii) positioning of the mitotic spindle and, subsequently, (iii) polarized deposition of fate determinants in the daughter cells during division. Whereas asymmetric divisions diversify pools of cells, symmetric divisions drive their expansion by generating identical daughter cells. On page 245 of this issue, Tannishtha Reya and colleagues demonstrate that *Lis1* is required for spindle orientation in polarized hematopoietic stem cells (HSCs); this finding not only shows that HSCs can actively transition between asymmetric and symmetric division modes but also indicates that cytoskeletal motor activity is critical in preserving HSC identity and in leukemic transformation[1].

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Cell fate diversity regulation

Many tissue-specific stem cells, including HSCs, have the ability to perform asymmetric and symmetric cell divisions, depending on cues they receive internally (developmental signals) as well as externally (environmental signals). This flexibility allows these tissue-specific stem cells to precisely balance self-renewal and differentiation commitment, ensuring the production of appropriate numbers of stem cells and differentiated cells during tissue development, homeostasis and repair[2], and can also contribute to malignant transformation in various tissues (reviewed by Knoblich[3]).

Cell-intrinsic mechanisms instructing the adoption of a distinct fate upon cell division drive a multistep process (**Fig. 1**; see also Knoblich[3] for a review). In addition, the microenvironment (or niche) in which tissue-specific stem cells reside can also specify stem cell identity[4,5], allowing for the fine-tuning of fate determination in a dynamic environment. The exact mechanisms and effector molecules driving the different steps of cell polarization, fate specification and switching between different modes of division are incompletely known, especially in mammalian stem cells. Many adult stem cells are mostly quiescent and rarely divide under steady-state conditions, rendering the study of division mode regulation for these cells very challenging. However, recent studies using mouse genetic models and RNA interference (RNAi) screening have identified critical regulators of HSC fate including *Lkb1* (refs. 6,7) and the PPAR-δ pathway[8], regulators of HSC quiescence and proliferation such as *Prox1*, *Pard6a* and *Prkcz*[9], and upstream regulators of the cell fate determinant *Numb* such as *Msi2* (refs. 9,10) and *Satb1* (ref. 11). Several of these fate regulators are linked with aberrant HSC function in leukemia[10,12]. These past studies demonstrated the requirement for balanced asymmetric and symmetric stem cell divisions in the hematopoietic system. Zimdahl *et al.* now show how symmetric cell divisions are executed in HSCs at a subcellular, mechanistic level and demonstrate that this mechanism is not only critical to ensuring the maintenance of stem cells but also is important for the outgrowth of leukemic cell clones[1].

Lis1 in HSC (dys)function

Zimdahl *et al.* have identified a new player in the regulation of HSC fate, the cytoplasmic dynein-binding protein lissencephaly-1 (encoded by *Lis1*, also known as *Pafha1B1*)[1]. The authors ablated *Lis1* within the hematopoietic system during different times in development and demonstrated that *Lis1* deficiency impaired primitive (fetal) HSC expansion and

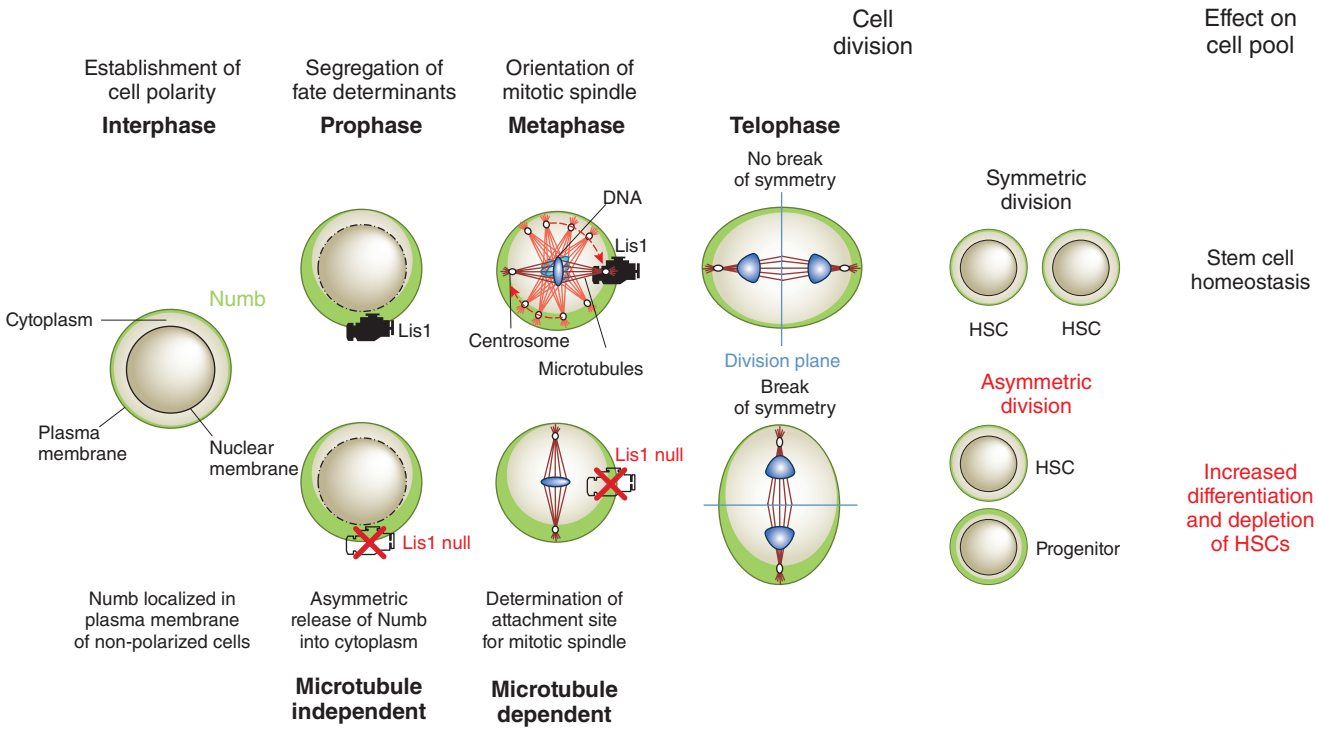

Figure 1 Lis1 in symmetric division of HSCs. Establishment of a polarity axis followed by asymmetric cytoplasmic localization of Numb is unaffected in Lis1-null cells. Spindle orientation determines the division plane and, thus, symmetric or asymmetric deposition of Numb upon division. Spindle rotation is impaired in Lis1-null cells, resulting in exclusively asymmetric divisions.

caused rapid depletion of definitive (adult) HSCs. Hematopoiesis originating from *Lis1*-deficient HSCs showed cellular and molecular hallmarks of accelerated differentiation, and HSCs derived from *Lis1*-null mice were consequently incapable of reconstituting the hematopoietic system of lethally irradiated recipient mice. Loss of functional stem cells can be triggered by alterations in the regulation of cell fate, such as an increase in apoptosis or cell proliferation, or by changes in self-renewal and differentiation commitment. Interestingly, *Lis1*-deficient HSCs showed neither higher rates of apoptosis nor increased proliferation.

As Lis1 regulates dynein motility[13] and is critically involved in nuclear migration, mitosis and cargo transport, the authors tested whether the cell division mode was altered in the absence of *Lis1*. They undertook a series of elegant live-cell imaging experiments in combination with experiments monitoring inheritance of the cell fate determinant Numb upon division of immature hematopoietic cells and discovered that, whereas cell polarization through Numb occurred normally upon *Lis1* deletion, mitotic spindles failed to orient perpendicular to the polarization axis in polarized cells, preventing equal segregation of the fate determinant and, thus, symmetric cell division (**Fig. 1**). This change in the cell division mode increased HSC differentiation rates and was consistent with the rapid exhaustion of the stem cell pool in *Lis1*-null mice. These findings show the necessity for active mitotic spindle positioning in polarized HSCs. Previous studies in *Drosophila melanogaster* demonstrated that polarization by Numb is not necessarily a prerequisite for its asymmetric segregation[14]. Thus, it remains to be determined whether *Lis1* deficiency causes defects in spindle positioning and cell fate determination in cells not polarized by Numb before division. *Lis1* deficiency could also affect fate determination in non-polarized, symmetrically dividing (either self-renewing or differentiating) stem cells, in addition to its reported effect in polarized cells.

The authors also found that transformed hematopoietic cells in acute myeloid leukemia appeared to rely on Lis1-mediated regulation of cell division mode during a critical phase of leukemogenesis, the clonal outgrowth of differentiation-impaired cells, in two mouse leukemia models. Notably, knockdown of *LIS1* in primary, human-derived $CD34^+$ cells also led to significantly impaired leukemic growth.

These observations show that the ability to undergo symmetric divisions is an actively regulated process in Numb-polarized HSCs, executed through the positioning of the mitotic spindle, and demonstrate a role for *Lis1* in instructing the transition from asymmetric to symmetric cell divisions in healthy HSCs as well as in acute myeloid leukemia, reminiscent of its role in neuronal differentiation during cortical development[15]. The report by Zimdahl *et al.* inspires further dissection of the role of other dynein-dependent molecular mechanisms in stem cell fate regulation, as well as evaluation of modulating cell fate diversification and specifically spindle positioning as a potential novel therapeutic strategy in leukemia and other cancers.

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