assayed by transplant or culture[10,22]. To rule out potential contamination by such cells, we aimed to determine whether megakaryocyte-producing LT-HSC clones *in situ* had properties of classic LT-HSCs in the context of transplantation. For this, we transplanted clonally labelled LT-HSCs isolated from mice four weeks after induction, and at 16 weeks post-transplantation we purified mature lineages from recipients and compared their transposon repertoires with those of cells initially isolated from the donor (Fig. 4f). We observed that six out of eight detected megakaryocyte lineage-restricted LT-HSC clones in the donor were able to generate multilineage progeny in recipients (Fig. 4g, i). We reached similar conclusions when evaluating the culture potential of *in situ* MkP-producing LT-HSC clones (Extended Data Fig. 10d, e). Additionally, our results demonstrate that MkP production is not exclusive to the $CD41^+$ LT-HSC fraction (Extended Data Fig. 10f, g). Thus, we conclude that most megakaryocyte lineage-producing clones residing in the LT-HSC gate are not simply megakaryocyte-restricted progenitors, but clones that can exhibit multipotency upon transplantation.

Our work here uncovers critical features of the native haematopoietic process. In our model, as much as half of the megakaryocyte lineage is produced independently of other lineages by cells at the top of the haematopoietic ladder (Fig. 4j). A heterogeneous hierarchy of lineage-restricted and oligolineage progenitors, historically classified as MPPs, produce other haematopoietic lineages with selective lineage couplings. Although our work still supports a model for progressive restriction of developmental potential, it suggests that these events are clonally heterogeneous and occur much earlier in the haematopoietic hierarchy, in line with recent data[7,8,14,16]. Although our data fail to provide any evidence for CMP or MEP fates *in situ*, many experiments have provided evidence for MEP-like cells at a clonal level[4,12,13,24]. We posit that while megakaryocyte–erythrocyte bipotential exists in transplant or culture settings, this fate is not substantially manifested in unperturbed conditions. Alternatively, such cellular behaviour might be too transient to be captured with our technology.

Our data demonstrate that at least a fraction of LT-HSCs behave as a potent source of MkP, indicating that the megakaryocyte fate is the predominant fate of HSCs *in situ*. However, these same cells exhibit potential for multilineage outcomes following transplantation. Thus, our findings highlight the critical differences between studying native fate versus potential in stem cell biology. Although we are unable to conclude whether a particular subset or all LT-HSCs will eventually display megakaryocyte-producing behaviour, we favour the idea that most LT-HSC clones transition through a megakaryocyte-primed state with age. Our data also suggest that an MPP population (within MPP2) is involved in megakaryocyte production. It remains to be determined whether these represent two different pathways for megakaryocyte production or whether LT-HSCs are upstream of MPP2s. Finally, our results are still consonant with the idea that adult LT-HSCs have a limited lympho-erythromyeloid output during steady state[11,25], although this finding has been debated[26]. Future work with second-generation cell barcoding strategies[27,28] in combination with Cre-based labelling will be needed to elucidate full lineage histories and determine the mechanisms of fate restriction.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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