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Trisomy of chromosome 21 (Down's syndrome) has a number of effects, including perturbations in haematopoiesis, such that 10% of newborns with trisomy 21 have transient myeloproliferative disease (TMD; a preleukaemic condition) that can develop into acute megakaryoblastic leukaemia (AMKL). As TMD is evident at birth, this indicates that alterations in haematopoiesis occur *in utero*. However, these early changes have been difficult to model in mice and cannot be studied *in vivo* in humans. Therefore, three groups have used human trisomy 21 fetal liver cells or human trisomy 21 induced pluripotent stem cells (iPSCs) to examine the early stages of haematopoiesis.

Interestingly, all three papers published in *Proceedings of the National Academy of Sciences USA* studied haematopoiesis at different developmental stages, and it seems that, whereas trisomy 21 has a small effect on primitive haematopoiesis, by the time that haematopoiesis is established in the fetal liver, trisomy 21 is substantially skewing the developing lineages.

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Stella Chou and colleagues, and Glenn MacLean and colleagues, studied the initial stages of haematopoiesis by generating embryoid bodies from trisomy 21 iPSCs. They used similar culture conditions to promote mesoderm formation in the embryoid bodies and subsequent haematopoiesis. Chou and colleagues analysed the early blood cell progenitors produced by their trisomy 21 and euploid embryoid bodies after 7–9 days of differentiation and found that there was no significant difference in the total number of colonies produced by trisomy 21 and euploid blood cell progenitors. However, trisomy 21 blood progenitors produced more erythroid colonies than euploid progenitors and had a reduced frequency of myeloid progenitors. The erythroid colonies produced by these blood progenitors expressed mainly ζ-globin and ε-globin genes, indicating that they were representative of embryonic (yolk sac) blood cell progenitors. These findings indicate that trisomy 21 does not expand the number of blood cell progenitors at this early developmental stage, but does increase the frequency of erythroid colony formation. MacLean *et al.* also saw an increase in the number of erythroid progenitors generated by trisomy 21 embryonic stem cells (ESCs), iPSCs and in a trisomic versus disomic isogenic pair of iPSC lines, which were used to control for the variability of the frequency of early blood cell progenitors produced by iPSCs. However, these authors also observed an increase in the colony-forming potential across all blood cell lineages of the trisomic iPSC line compared with its isogenic disomic control, including megakaryocytic colony-forming potential. These findings were mirrored by independently generated trisomic and disomic iPSCs, and trisomic and disomic ESCs. Interestingly, the erythroid colonies generated by blood cell progenitors in the isogenic iPSC embryoid bodies were more representative of those generated in the fetal liver, as they expressed more γ-globin than ε-globin. MacLean and colleagues suggest that this developmental difference might underlie the increased effect of trisomy 21 on colony-forming potential.

Anindita Roy, Gillian Cowan and colleagues used haematopoietic progenitors isolated from second trimester human fetal livers confirmed as either trisomic or disomic for chromosome 21. These authors have previously shown that the myeloid progenitor compartment is abnormal in trisomic livers. To examine whether this effect is restricted to the myeloid progenitor population or has wider effects on haematopoietic stem cells (HSCs), the authors looked at HSCs, multipotent progenitors (MPPs) and lymphoid-primed multipotent progenitors (LMPPs). The number of HSCs (as determined by immunophenotypic markers) was increased in trisomic samples compared with disomic samples, but the frequency of MPPs and LMPPs was unchanged. Moreover, the clonogenic potential of HSCs, common myeloid progenitors and megakaryocytic–erythroid progenitors was increased, with a marked skewing towards megakaryocytic and megakaryocytic–erythroid colonies. Trisomic fetal liver HSCs also produced fewer progenitor B cells than disomic HSCs, and impairment of B lymphocyte generation was evident in HSCs, LMPPs and early lymphoid progenitors. How this relates to the increased risk of developing B-lymphoblastic leukaemia in Down's syndrome is not yet clear.

Together these papers show that trisomy 21 has specific effects on haematopoiesis, but that these effects are likely to differ depending on the developmental stage of haematopoiesis. They also show that iPSCs generated from cells trisomic for chromosome 21 can be used to study early developmental haematopoiesis when fetal material is not available.

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ORIGINAL RESEARCH PAPERS Chou, S. T. *et al.* Trisomy 21-associated defects in human primative hematopoiesis revealed through induced pluripotent stem cells. *Proc. Natl Acad. Sci. USA* 12 Oct 2012 (doi:10.1073/pnas.1211175109) | MacLean, G. A. *et al.* Altered hematopoiesis in trisomy 21 as revealed through *in vitro* differentiation of isogenic human pluripotent cells. *Proc. Natl Acad. Sci. USA* 12 Oct 2012 (doi:10.1073/pnas.1215468109) | Roy, A. *et al.* Perturbation of fetal liver hematopoietic stem and progenitor cell development by trisomy 21. *Proc. Natl. Acad. Sci. USA* 12 Oct 2012 (doi:10.1073/pnas.1211405109)