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HAEMATOPOIESIS

Baby tolerance

The human adaptive immune system starts to form at an early stage of fetal development (as early as gestation week 10), which contrasts with mice, in which the adaptive immune system only starts to develop around birth. Therefore, mechanisms must exist in humans to prevent a fetal immune response to maternal alloantigens. Reporting in *Science*, Mold *et al.* show that human T cells arise from different haematopoietic stem and progenitor cell (HSPC) populations during different stages of development and that fetal $CD4^+$ T cells are biased towards immune tolerance.

The authors isolated $CD4^+$ T cells from fetal mesenteric lymph nodes after 18–22 weeks of gestation, and compared them with adult naive $CD4^+$ T cells that were isolated from the blood. Fetal naive $CD4^+$ T cells were more responsive than adult $CD4^+$ T cells to allogeneic stimulation, and a higher proportion of the fetal $CD4^+$ T cells developed into $CD25^+FOXP3^+$ regulatory T (T_{Reg}) cells after stimulation. Furthermore, fetal and adult $CD4^+$ T cells (including fetal and adult T_{Reg} cells) had distinct gene expression profiles, as determined by microarray analysis. These data suggest that fetal and adult $CD4^+$ T cells are distinct populations and that fetal $CD4^+$ T cells are biased towards immune tolerance.

The authors next determined whether fetal and adult $CD4^+$ T cells arise from different HSPC populations. During development, the HSPC pool first resides in the aorta–gonad–mesonephros region, then in the fetal liver and finally in the bone marrow, where most HSPCs are thought to reside throughout adulthood. The authors isolated human HSPCs from fetal liver, fetal bone marrow and adult bone marrow and transferred them to SCID-hu Thy/Liv mice (immunodeficient mice that are engrafted with human fetal thymus and liver tissue and are used to model human haematopoiesis), where they could develop into single positive (SP) thymocytes. A significantly higher number of forkhead box P3 $(FOXP3)^+$ T_{Reg} cells arose from fetal liver- and bone marrow-derived HSPCs than from adult bone marrow-derived HSPCs. Fetal HSPC-derived $CD4^+$ SP thymocytes were highly responsive to allogeneic stimulation *in vitro*, and significantly more developed into T_{Reg} cells compared with adult HSPC-derived $CD4^+$ SP thymocytes. In addition, the gene expression profiles of fetal liver- and fetal bone marrow-derived $CD4^+$ SP thymocytes were indistinguishable, but were distinct from the gene expression profile of adult bone marrow-derived $CD4^+$ SP thymocytes. These observations suggest that haematopoiesis occurs in waves that generate distinct T cell populations at different times of development.

Although it is still not clear whether fetal and adult HSPCs are distinct lineages or whether adult HSPCs arise from fetal HSPCs in the bone marrow, these data show that fetal and adult HSPCs give rise to distinct T cell populations, and that during development the initial waves of $CD4^+$ T cells are biased towards tolerance.

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ORIGINAL RESEARCH PAPER Mold, J. E. *et al.* Fetal and adult hematopoietic stem cells give rise to distinct T cell lineages in humans. *Science* **330**, 1695–1699 (2010)