Unraveling the Layers of Embryonic Myelopoiesis

Tissue resident macrophages can originate from primitive macrophage (unipotent) progenitors and (multi/bi-potent) erythromyeloid progenitors (EMPs) that are both produced within the yolk sac during a developmentally restricted time window. In contrast to primitive progenitors, EMPs migrate to the fetal liver where they undergo a massive expansion followed by cohabitation with hematopoietic stem cells (HSCs) within the same niche. As such, developmental hematopoiesis constitutes a layered system with contributions coming from primitive progenitors, EMPs and HSCs, although the dynamics of this are not well understood. Yolk sac-derived tissue resident macrophages persist throughout adulthood and represent a unique subset of the immune system that are capable of self-renewing without relying on input from hematopoietic stem cells (HSCs), thus perpetuating this layered system in adults. Little is known about how the differentiation pathways of EMPs are regulated and whether this may impart unique functional characteristics to their descendants later in life. For this reason, we are studying the dynamics of yolk sac EMPs and their progeny on the cellular and molecular level.

To do this, we use genetic pulse chase labeling to trace yolk sac EMPs independently of HSCs, and then measure the contribution of EMPs to intermediate progenitor pools in the fetal liver and how this relates to lineage output. Single cell sequencing is allowing us to uncover the heterogeneity of EMP-derived progenitor pools and explore differentiation trajectories.

Our results support the notion that yolk sac-derived EMPs are the predominant source of hematopoietic lineages from early- to mid-gestation, despite their overlapping residence with HSCs in the fetal liver. EMPs are rapidly diversified with differential niche- and/or time-dependent outputs. We find that the immunophenotype typically used to define EMPs encompasses a largely heterogeneous pool of progenitors that already have biased expression of lineage-specific markers. We are in the process of comparing the differentiation trajectories of EMP-derived progeny with HSC-derived counterparts to determine whether EMP-derived myeloid cells utilize distinct differentiation pathways and/or hierarchies.

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Authors :
References : , , ,

Authors

Laina Freyer 1, Lorea Iturri 1, Rebecca Gentek 2, Marc Bajénoff 2, Elisa Gomez Perdiguero 1,

1. Developmental and Stem Cell Biology, Institut Pasteur, Paris, FRANCE
2. CIML, Marseille, FRANCE