ABSTRACT

Hematopoiesis is a vital process in which red blood cells and cells of the immune system are formed. It is initiated during early embryonic development when we find hematopoietic progenitors in separate anatomical sites. Embryonic hematopoiesis comprises three successive and partly overlapping waves of progenitors with a different hematopoietic potential. The primary anatomical place where hematopoiesis takes place shortly before the birth is the bone marrow (BM). Since at this time point of development BM is already populated by hematopoietic stem cell (HSCs) progenitors, it becomes also the site of hematopoiesis in adulthood. However, the bone marrow is not the only place where hematopoietic progenitors emerge and develop. The Yolk sac (YS) and the Aorta-Gonad-Mesonephros (AGM) region are the initial sites of the appearance of the three waves of progenitors in the early embryogenesis. These progenitors and their descendants play an indispensable role during the development of an individual. Because there are no specific markers that would unambiguously characterize progenitors of these individual waves, their physical separation and hence also functional characterization is still incomplete.

Recent studies have shown that Toll-like receptors (TLRs) are expressed on adult HSCs. The stimulation of HSC via TLRs leads to the preferential generation of myeloid lineages. We have shown that TLR2 is expressed on progenitors of the second hematopoietic wave, erythro-myeloid progenitors (EMPs). Since such TLR2 expression allowed the distinction between emerging EMP precursors from the preceding wave of precursors of primitive erythropoiesis, we characterize in detail the emergence, fate, and function of EMPs during early embryogenesis. We were able to show that the progenitors of EMPs emerge much earlier than previously described in the literature. Using various novel transgenic models we have also demonstrated the indispensability of $TLR2^{+}$ EMPs for embryonic development.

Both embryonic and hematopoietic progenitors and cells in the adult traverse through the body via navigation which is based on the interaction between their chemokine receptors and their ligands. One such molecule is the chemokine CXCR4. Using a transgenic mouse model we have shown that CXCR4 hyperactivation has no impact on embryonic hematopoiesis, but affected adult hematopoiesis. The work conducted on medullary thymic epithelial cells also showed that TLR9-regulated expression of chemokines is critical for the process of establishment of central tolerance, specifically, the recruitment of monocyte-derived dendritic cells to the thymic medulla and the generation of regulatory T cells.

This dissertation thesis revolves around three already published articles and one article that has been already submitted and is currently under revision. The first part of this thesis provides a literature overview of embryonic and adult hematopoiesis as well as the structure and function of TLRs. The following chapter defines the main objectives of this work. The three above mentioned papers and one attached manuscript represent the results and specific discussion to each part of my experimental work. The last part of my thesis containing the chapters General discussion and Conclusions summarizes the main output and novelty of presented work. We believe that the presented work will contribute to a better and more comprehensive understanding of both embryonic as well as adult hematopoiesis.