Normal hemopoetic cells and their malignant counterparts
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This thesis contains a collection of papers pertaining to hemopoiesis (the generation of blood cells) and hematological malignancies in children.

A general review of normal hemopoiesis is given in the introductory chapter 1. The body’s continuous demand for erythrocytes, platelets, and leukocytes requires a balanced hemopoietic system. Such hemopoietic system comprises 1. pluripotent stem cells and their progeny 2. a hemopoietic organ, that is a microenvironment, permissive and directive to these stem cells and their progeny, and 3. a regulatory system (humoral and cellular) to control the hemopoietic hierarchy. This thesis deals with the items mentioned under 1. and 2. More in particular the distribution of hemopoietic cells is studied in the principal hemopoietic organ before birth, that is the fetal liver.

In chapter 2 data of our first study on the development and distribution of lymphoid and myeloid cells in bone marrow, thymus, and liver of human fetuses are presented. Our results confirm the predominance of pre-B (CD5−, sIg−) over surface IgM* B cells in liver and bone marrow. Myelomonocytic cells (Leu-M1;CD15+) were more frequent in bone marrow than in liver. Cells expressing mature T cell markers were not seen in fetal liver and bone marrow until several weeks after onset of thymocyte differentiation, suggesting that thymic passage of T cell precursors is required for expression these antigens.

The chapters 3 to 5 concern immunohistological studies. The early studies focussed on B cell development and were performed with immunofluorescent techniques on frozen tissue sections from human and mouse fetuses. Cells of B lineage were only evident in hemopoietic fetal liver and bone marrow, but not in other tissues. B lineage cells were interspersed among other hemopoietic cells in the extrasinusoidal areas. Around day 17 of murine intrauterine life a loose clustering ("starburst") distribution pattern of pre-B cells became evident. The initial wave of these pre-B cells had begun around day 12. In human fetal liver these B cell precursors were seen in the same areas as in the mouse, but no clustering was apparent. These data suggest a model for the in situ generation of B lineage cells in the hemopoietic fetal liver.

The more recent studies (chapters 4 and 5) were then limited to human fetal liver. Mainly immunoenzymatic methods were used to examine the anatomical distribution of cells belonging to the various hemopoietic cell lineages. A large panel of monoclonal antibodies was applied to frozen tissue sections; in some cases also B5 fixed paraffin-embedded tissue was available. The fetal age
range that could be studied was much wider than in our previous studies; also two embryonal livers could be studied. We found evidence for an early hemopoietic progenitor cell, staining with an anti-vimentin and anti-common leucocyte antigen (MT1) monoclonal antibody; however, no reactivity with anti HLA-DR was noted in these cells. Erythroid cell clusters were evident extra-sinusoidal and myelopoiesis concentrated around portal triad vessels. Many proliferating cells were present. The earlier noted lack of mature T cells was confirmed and cells expressing a very early T cell marker (WT1; CD 7) were scattered among the hepatocytes. Even in older cases we did not see the clusters and discrete foci of B lineage cells as noted by by us and others in earlier studies in mice. Rather the scattered distribution pattern was maintained. Cells that expressed early B cell lineage markers (CD 19, CD 10) were present in low numbers and showed the same scattered distribution pattern. No close relation of hemopoietic cells were observed except for the erythroid cell clusters that often had a central macrophage.

The fetal tissue studies have shown the value of examining fetal liver to trace early developmental stages of hemopoietic cells. It should not present major problems to detect the normal counterparts of the leukemic blast cells if they exist. What lacks is a well-defined monoclonal antibody panel that detects early myeloid cells. If such antibodies would become available they should first be tested for non-reactivity with several tissues before use on fetal tissue. Now that antibodies are available for use in paraffin-embedded tissue (1), immunohistological studies on fetal bone marrow should be done to unravel the mysteries of hemopoiesis in the third trimester. Techniques to detect three antigens expressed on the same cell are now available and may be useful for more definite dissection of human hemopoiesis (2). Quantitative studies on hemopoietic cells are reported in mice and should be added for human hemopoiesis (3,4). If well-preserved fetal tissue is obtained, in situ hybridisation studies on tissue sections might offer an opportunity to study the earliest gene rearrangements occurring in B cell lineage and other cells (5,6).

Our studies on hemopoiesis continued by investigating the bone marrow of children, who had been treated with cytotoxic drugs for acute lymphoblastic leukemia (chapter 6). The relative amounts of lymphocyte subsets in this regenerating bone marrow are presented. Such regenerating bone marrow is analogue to fetal tissue in that hemopoiesis has to begin from about the stem cell level. Only for pre-B cells we found a proliferation in excess of
normal values during the first 3 months after cessation of therapy. In contrast to peripheral blood cell counts and clinical status of impaired immune response the T cell subsets and the NK (natural killer) cells did not change during and after therapy. Other studies have shown a major rise in bone marrow lymphocytes in these circumstances. Studies like the present one could elucidate the nature of these cells by using a large array of monoclonal antibodies. In chapter 6 we also deal with the methodologic problems one can encounter in immunocytoLOGY studies of bone marrow.

The second part of this thesis concerns hematological malignancies in children, that is: acute lymphoblastic leukemia (ALL), acute non-lymphocytic leukemia (ANLL) and non-Hodgkin lymphoma (NHL). The introductory chapter 1 provides a summary of these 3 malignancies to get the reader acquainted with terminology. It also puts the combination in this thesis of normal and malignant hematopoietic cells into proper perspective.

In chapter 7 and 8 the current literature on the extensive diversity of the leukemic cell mass (i.e. heterogeneity) in both ALL and ANLL is reviewed. Both reviews focus on the immunophenotypic heterogeneity. From these reviews it is clear that we are moving away from a morphologic definition of acute leukemia and toward a molecular definition. Currently unclassifiable leukemias will then be properly categorized. Also the true nature of so-called hybrid leukemias could be revealed by the joined effort of scientists, involved in the multiple marker analysis of leukemia. What clearly lacks is a panel of monoclonal antibodies recognizing antigens on discrete stages of myeloid hematopoietic cells. At present treatment strategies, hence prognosis, are being based on the well-known differences but the future potential is even greater. Only multi-institutional trials will be able to solve the many questions left.

Chapter 9 presents data on acute leukemia in infants. In this age group unique patterns of ALL as well as ANLL occur, which may be valuable in disclosing the probably many etiological factors in acute leukemia. We emphasize the apparent association of high proliferative activity of monocytic cells in this age group and the high incidence of acute monocytic leukemia. Studies using the recent advances in molecular and cellular biology will be needed to demonstrate cytogenetic anomalies in the leukemic blasts associated with important gene rearrangements.

Finally, in chapter 10, we provide data augmenting the need for studies on the homing preferences of normal and malignantly transformed hematopoietic cells. Studies have been reported emphasizing the prognostic impact of cell
markers associated with sessile or motile properties of such a cell, e.g. PNA (peanut agglutinin lectin) receptor presence on T cell ALL (7) and the occurrence of hand mirror cells in ALL (8). In mice lymphocytes reacting with the MEL-14 monoclonal antibody are able to cross the high endothelial venule of the lymph nodes (9). Also monoclonal antibodies that are useful for the study of human lymphocyte traffic, have been reported (10). Presently it remains to be solved why primarily local hemopoietic tumors (e.g. NHL) have an immunophenotype that is very uncommon in primarily systemic malignancies (e.g. ALL) and vice versa. Here again the need for accumulation of patient data is apparent and multiple markers studies should be encouraged. Also monoclonal antibodies recognizing cells at particular functional stages are required.

REFERENCES

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