Bridging the bone marrow–thymus gap

Most T cells are generated in the thymus. Although adult thymi contain highly proliferating progenitor cells, these are not self-renewing and only produce mature T cells over several weeks. Thus, continuous thymic T-cell output is dependent on new thymic immigrants. All T cells are derived from hematopoietic stem cells (HSCs) that reside in the bone marrow and, occasionally, travel through blood. If thymus entry is exclusive, it could be HSCs themselves or defined downstream T-cell progenitors that immigrate. Alternatively, multiple circulating cells enter the thymus and only the ones that can respond to thymic T-cell differentiation signals will proliferate. When and where does T-lineage commitment occur, and what are the characteristics of physiologic thymus-seeding cells? Answering these questions will help improve T-cell generation when urgently needed.

Differentiation of HSCs to mature hematopoietic cells involves loss of self-renewal potential followed by restriction of developmental options (ie, the gradual commitment to different hematopoietic lineages). Using flow cytometry, viable cell populations can be purified according to their expression of biologically relevant markers. It has been shown that bone marrow contains single cells that harbor exclusively lymphoid or myeloid developmental potential (common lymphoid progenitors [CLPs] and common myeloid progenitors [CMPs]). Mouse CLPs and CMPs are capable of protecting animals from lethal infections that are primarily controlled by the lymphoid or myeloid arm of the immune system, respectively. These findings prove a lympho-myeloid dichotomy in bone marrow that results in functionally relevant progenitor cells. Thus, interleukin-7 receptor α-positive (IL-7Rα+) CLPs or their progeny were strong candidates for being thymus-seeding cells. Indeed, pre-T α-expressing CLP progeny in bone marrow, termed CLP-2, were shown to be capable of immigrating to the thymus and producing T cells. However, the concept that CLPs are the major physiologic T-cell progenitors was challenged by experiments where HSCs, CLPs, and thymus-derived progenitors (ETPs) were directly compared. ETPs were capable of generating over a longer time period more thymocyte progeny than CLPs in vivo, and, in contrast to CLPs, had some myeloid potential. This implies that ETPs arise from HSCs without proceeding through a CLP state. Do circulating HSCs themselves then enter the thymus, immediately lose self-renewal potential, and rapidly commit to ETPs upon environmental cues such as Notch ligands? It has been argued that this is not the case because intrathymically injected HSCs that were isolated again from thymus after 3 days maintained at least short-term self-renewing potential, and robust lympho-myeloid repopulation potential in secondary transplantsations, a capacity not found in normal thymi.

In an extension of their previous work, Perry and colleagues (page 2990) now add important information to bridge the bone marrow–thymus gap. They identified candidate immediate precursors of thymus-seeding cells in bone marrow that are functional and phenotypic counterparts of thymic ETPs. As ETPs, they express L-selectin (which might be of importance although not essential in thymic homing), are mostly IL-7Rα+, and produce upon intravenous transfer major waves of thymic T cells, but minor B-cell and very low myeloid engraftment, and do not rescue lethally irradiated recipients. In terms of phenotype and function, L-selectin+ bone marrow progenitors overlap and likely contain the recently defined earliest Rag2- lymphocyte progenitors (ELPs) that are supposed to be upstream of CLPs and ETPs.

Although the existence of common lymphoid- or myeloid-restricted progenitors is not questioned, these new data add to growing evidence that during successive lineage commitment, progenitors are generated that incline to a lineage but maintain alternative options that could become relevant upon changing environmental stimuli. In this view, the migration of progenitor cells will greatly influence their contribution to any given mature cell. This is not reflected well in vitro or in vivo transfer experiments. Most of the irreversible T-cell commitment might occur in the thymus. Moreover, marking of thymus-seeding progenitors that initiate a proliferative T-cell burst and ultimate tracing of the steady-state marrow-blood-thymus sequence still need to be accomplished.

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“Annexing” acute leukemias

A hemorrhagic disorder associated with enhanced thrombin activation and disseminated intravascular coagulation is often observed in acute promyelocytic leukemias
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