also their capacity to selectively transduce widely distributed human CD8+ T cells in vivo.

Immunologically retargeted lentiviral vectors capable of efficiently and selectively transducing specific functional classes of differentiated human lymphocytes could have important therapeutic applications. Two potential extensions of the current work can be immediately envisioned. For the immuno-compromised cancer patient or transplant recipient with a drug-resistant or otherwise untreatable life-threatening viral infection, in vitro or, particularly, in vivo transduction of CD8+ T cells to express TCRs specific for epitopes of critical viral proteins known to be presented by 1 or more HLA alleles of the patient, could induce rapid development of meaningful resistance. Similarly, CD8-targeted lentiviral vectors encoding high-affinity TCRs or chimeric antigen receptors specific for uniquely or differentially expressed tumor antigens could greatly expedite selective expansion of cytolytic effector T-cell populations in vitro for adoptive therapy. Alternatively, injection of such vectors into draining lymph nodes could foster selective expansions of CD8+ effector T cells expressing the tumor-specific TCRs or chimeric antigen receptors (CARs) both locally and systemically.

Over the past decade, progress in the development of safe vectors for efficient transduction and durable modification of human T cells to express vector-encoded TCRs or CARs specific for tumors or exogenous pathogens as well as genes augmenting, sustaining, or modulating their activity has been extraordinary. Many of these advances are now being tested in clinical trials evaluating immune cells modified with such vectors in vitro. The development of vectors such as described by Zhou et al that can selectively target and efficiently transduce functional subsets of immune cells, in vitro, should facilitate analyses of their respective contributions to short- and long-term immunity, after adoptive transfer. In addition, such vectors may open a therapeutic window to direct modification of the specificity and function of immune cells in vivo.

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REFERENCES


Stem cells need their T

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In this issue of Blood, Li and colleagues demonstrate the requirement for T cells in mediating the action of parathyroid hormone (PTH) treatment to expand primitive hematopoietic stem/progenitor cells (HSPCs), highlighting a complex interaction among cells of the immune system, bone, and the HSPCs.1

Since the development of the niche hypothesis for the hematopoietic stem cell (HSC) by Schofield,2 numerous studies have been performed to improve our understanding of the extrinsic regulators of stem cell number and function. Based on the early observations that CFU-S are present in higher numbers near the endosteal bone surface, Taichman and colleagues hypothesized that bone-forming osteoblasts may be the critical cellular component that supports HSCs in vivo.3 To further support the localization of primitive HSCs in the endostearth, Nilsson and colleagues demonstrated that a primitive


REFERENCES


**LYMPHOID NEOPLASIA**

**Clone wars: IgH subclones in preB-ALL**

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In this issue of Blood, Gawad et al provide an unprecedented look at the clonal diversity of pediatric B-precursor acute lymphoblastic leukemia (ALL).1 Although the presence of coexisting subclones in B-precursor ALL at diagnosis has been previously well reported, using deep sequencing of the IgH locus Gawad and colleagues demonstrate that individual patient samples had up to 4000 unique IgH sequences, suggesting an unexpected degree of clonal heterogeneity (see figure). Interestingly, clonal evolution often showed evidence of allelic exclusion, retained stable JH3 sequences with divergent VDJ, and adjacent NDN regions, consistent with prolific aberrant rearrangement during early leukemogenesis. The critical contribution of this study is the revelation that B-precursor ALL is commonly composed of low frequency subclones, in some cases numbering in the thousands. Relevant to this finding, a report by Mullighan et al revealed that 52% of relapsed ALL clones were derived from minor “ancestral” subclones present at diagnosis, using genomic copy number abnormalities (CNAs) and lesion-specific (PCR) at diagnosis and relapse.2 The findings of Gawad et al provide strong evidence that clonal heterogeneity at diagnosis is the rule, rather than the exception,

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