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Maintenance of CD34$^+$ AML progenitor cells utilizing RepSox and tumor microenvironment cues

Laura F. Gibson
Mary Babb Randolph Cancer Center of West Virginia University, USA

Relapse of leukemia remains a clinical challenge characterized, in part, by the treatment refractory nature of the tumor cells that contribute to disease recurrence. The cells that survive therapy and are capable of reconstituting disease share many characteristics with stem cells, although the contribution of "leukemia stem cells" to disease remains context specific. Regardless of nomenclature, therapies that target the disease initiating cell, increase leukemic-cell immunogenicity, or activate immune cells may best achieve sustained positive outcomes. In recent work we sought to advance targeted therapy-development by exploring non-genetic approaches to maintain acute myeloid leukemia (AML) immature progenitors that exist to varying degrees in primary leukapheresis samples. Cells from AML/MDS leukapheresis specimens were exposed to RepSox, a small molecule inhibitor of TGF-β receptor 1 that facilitates iPSC reprogramming by replacing Sox2 and C-myc in non-hematological models. When combined with human bone marrow stromal cell co-culture and hypoxia RepSox consistently slowed the decline of CD34$^+$ cells that occurs *in vitro*. CD34$^+$ cells that remained viable under these conditions were confirmed to be of tumor cell origin by FISH analysis. In addition, RepSox-treated CD34$^+$ cells expressed less T-cell immunoglobulin mucin-3 (Tim-3), a receptor that restrains anti-tumor immunity. Colony-forming progenitors were concentrated in the CD34$^+$ fraction of the specimens studied, suggesting these primitive CD34$^+$ cells may serve as suitable targets when designing therapies targeting cells with re-population potential. Because RepSox maintains CD34$^+$ AML progenitors and may alter expression of immunomodulatory receptors it may prove a valuable bioengineering tool for developing leukemia immunotherapies *in vitro*.

Biography

Laura F. Gibson, Ph.D., is Deputy Director of the Mary Babb Randolph Cancer Center (MBRCC) and the Alexander B. Osborn Distinguished Professor of Hematological Malignancies in the West Virginia University School of Medicine. Her research focused on leukemia and tumor microenvironment is supported through the National Cancer and the National Heart, Lung, and Blood Institutes. She is a Co-Director of WVU's Clinical and Translational (CTR)-IDeA grant, PI of the MBRCC's Phase III CoBRE for Signal Transduction and Cancer and has participated in diverse NIH study sections, currently serving as a regular member of Basic Mechanisms of Cancer Therapeutics panel.

lgibson@hsc.wvu.edu