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Disease Target: Cancer

Hematopoietic Stem Cell-Enriched MicroRNAs in Human Stem Cell Differentiation and Self-Renewal

My laboratory seeks to better understand the pathophysiology of normal blood-forming hematopoietic stem progenitor cells (HSPCs) and leukemias. Propelled first by my lab's discovery that a number of the tiny snippets of RNA of the class called microRNAs are selectively expressed in human HSPCs, we and others have shown that certain microRNAs can be powerful post-transcriptional regulators of HSPC and leukemia biology. The overall goal of this MSCRF project was to further understand the effects of microRNAs in early hematopoiesis. We hoped that this deeper understanding might lead to specific new approaches to expand the quantities of HSPCs for clinical transplantation and of more mature blood cells for transfusion therapies, as well as provide new molecular targets for leukemia treatment. In this MSCRF project, we identified and evaluated multiple microRNAs and related molecules that affect HSPC and LSC functions and identified some of novel target molecules that contribute to the mechanisms of these effects. Both of these sets of discoveries have direct translational implications. In an example of the translational power of one set of our discoveries, we found that several microRNAs are expressed at only low/absent levels in many leukemias, as compared to normal HSPCs or more mature hematopoietic cell types. Since (re)expressing these down regulated microRNAs in leukemias reduced cell proliferation and increased apoptosis, we considered the potential of these and other leukemia suppressive microRNAs for antileukemic therapies. However, while systemic delivery of microRNAs has promise for the future, there are still no clearly effective means to deliver a variety of microRNAs to cancer cells at all sites in the human body. As an alternative, we investigated the idea of discovering small molecule drugs that alter the levels of specific microRNAs in human cells, which would open a novel strategy for treatment of leukemias (and other cancers). Via high-throughput screening of clinical drug libraries, we identified a new set of drugs that selectively upregulate miR-34 and/or other leukemia suppressive micro-RNAs.

Among validated lead candidate drugs from our high-throughput drug screens, the Artemisinin antimalarials are particularly exciting,because of their known broad preclinical antineoplastic efficacy with low clinical toxicity. Our ongoing studies show that Artemisinins have significant potential to be repurposed for treatment of leukemias. A second new translational project started from our discovery in this MSCRF project that RAB GTPase14 is targeted by both members of the miR-144-451 micro RNA cluster, which we showed to be selectively expressed and functionally important during human erythropoiesis. Expression of RAB GTPase14 protein decreases during erythroid differentiation, and lentiviral shRNA-mediated RAB14 GTPase knockdown increased the frequency and total numbers of erythroid cells and decreased expression of the ET02 erythroid transcriptional repressor, which in turn controls expression of several globin genes. Thus, RAB GTPase14 is a novel endogenous physiologic inhibitor of normal human erythropoiesis (17). Since RAB GTPase7b and RAB GTPase27b have been reported to be involved in megakaryocytic differentiation, and since we had found separately in this MSCRF project that RAB GTPase5C overexpression inhibited growth of human leukemia cells (18), we evaluated the erythropoietic effects of RAB GTPase5C and our ongoing results suggest that RAB GTPase5C is a novel positive erythropoietic regulator. Therefore, we have launched a new project to investigate the cellular and molecular mechanisms by which RAB GTPase14 and RAB GTPase5 modulate normal human hematopoiesis. By determining how RAB GTPases regulate hematopoiesis, we hope to identify novel therapeutic targets for ex-vivo manipulation of HSPCs and erythroid progeny to generate the numbers of cells needed for clinical transplantation and/or transfusion products.