Diminished Microrna Plays Big Role in Myeloid Leukemias

November 18, 2013

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Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) are cancers of the type of white blood cells known as myeloid cells. Both AML and the advanced stage of CML, blast crisis (BC), are characterized by the overgrowth of abnormal immature hematopoietic cells that accumulate in the bone marrow and interfere with normal blood cell development. One subtype of AML, acute promyelocytic leukemia (APL), can be treated with drugs that drive the differentiation of leukemic cells to mature myeloid cells that eventually die. However, other subtypes of AML are resistant to the effects of these drugs. Understanding why other subtypes of AML have a block in cell differentiation may lead to novel therapeutic strategies. A new study led by postdoctoral fellow Dr. Valerie Morris in the laboratory of Dr. Vivian Oehler (Clinical Research Division) describes a role for microRNA-150 in controlling differentiation and cell growth in myeloid leukemias.

MicroRNAs (miRNAs) are short non-protein coding RNAs that control protein levels in cells. These miRNAs have many biological roles, including regulation of normal blood cell development, and their levels are altered in leukemias. Morris *et al*. determined that miRNA-150 levels were significantly lower in both BC CML and AML patient cells than in healthy bone marrow cells, and a subset of adult AML patient samples had 100 to 1000-fold lower miRNA-150 levels. The decrease in miRNA-150 levels was observed across multiple molecular subtypes of AML. In pediatric AML patient samples, miR-150 expression was lowest in patients stratified to have poor-risk status by molecular changes.

To determine if decreased miRNA-150 expression plays a functional role in leukemia cells, the researchers overexpressed miRNA-150 in four human AML cell lines with low levels of miRNA-150 expression. During myeloid differentiation, cells undergo a characteristic change in their morphology and acquire the expression of specific cell surface markers. In all cell lines examined by the researchers, miRNA-150 decreased cell growth and increased myeloid differentiation as determined by morphology under the microscope and cell surface marker expression by flow cytometry (see figure). This effect was augmented with drugs, such as all-trans retinoic acid (ATRA), which differentiate these cell lines. Furthermore, cells overexpressing miRNA-150 demonstrated increased expression of genes associated with myeloid differentiation by gene expression analysis.

Morris *et al*. then examined the effect of miRNA-150 on normal human hematopoietic progenitor cells. Again, the researchers observed that miRNA-150 expression promoted myeloid differentiation as evidenced by changes in morphology, cell surface markers, and gene expression, as well as the ability to form myeloid colonies in methylcellulose. Notably, the authors saw similar effects by reintroducing miRNA-150 expression in six different human AML patient cells and two BC CML patient samples.

Previous published work had defined a role for miRNA-150 in development of other blood cells, specifically T and B cells, natural killer cells, and megakaryocytes. miRNA-150 exerts its effects in these cells by targeting the transcription factor MYB. MYB is expressed in progenitor cells to maintain self-renewal of cells and MYB expression is decreased in fully mature myeloid cells. In the AML cell lines, miRNA-150 decreased MYB protein expression. Overexpression of MYB could partially abrogate the effect of miRNA-150 on myeloid differentiation, suggesting that miRNA-150 functioned, at least in part, by decreasing MYB protein levels.

These results support a previously uncharacterized role for miRNA-150 in promoting myeloid differentiation, and demonstrate that low miRNA-150 expression contributes to the leukemic phenotype in various AML subtypes and BC CML. Confirming these results, a published study using a murine model of AML showed that miRNA-150 expression decreased the proliferation of leukemic cells and increased the survival of mice (Jiang *et al*., 2012). "The discovery of non-coding RNAs has dramatically altered our thinking regarding how normal cells and cancer cells are regulated and identified a completely novel way that cancer cells may be targeted in the future. We are now using high-throughput miRNA library screening approaches to identify other miRNAs with currently unknown roles in cell differentiation, growth or death and examining how a subset of these miRNAs are regulated," according to Dr. Oehler. "Lastly, although, still technically difficult, one ultimate goal is to establish if miRNAs can be therapeutics in their own right and if so which are the best candidates."

Morris VA, Zhang A, Yang T, Stirewalt DL, Ramamurthy R, Meshinchi S, Oehler VG. 2013. MicroRNA-150 Expression Induces Myeloid Differentiation of Human Acute Leukemia Cells and Normal Hematopoietic Progenitors. *PLoS One* 8:e75815.

See also: Jiang X, Huang H, Li Z, Li Y, Wang X, Gurbuxani S, Chen P, He C, You D, Zhang S, Wang J, Arnovitz S, Elkahloun A, Price C, Hong GM, Ren H, Kunjamma RB,Neilly MB, Matthews JM, Xu M, Larson RA, Le Beau MM, Slany RK, Liu PP, Lu J, Zhang J, He C, Chen J. 2012. Blockade of miR-150 maturation by MLL-fusion/MYC/LIN-28 is required for MLL-associated leukemia.*Cancer Cell* 22(4):524-535.

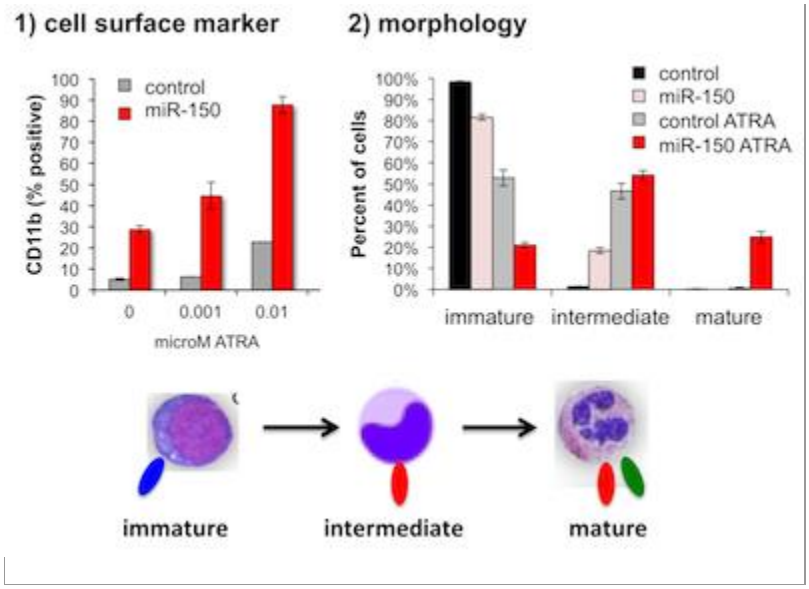

Image provided by Dr. Valerie Morris

Expression of miRNA-150 promotes differentiation of human AML cells as determined by cell surface markers of differentiation (CD11b) and morphology compared to control cells. HL-60 cells were assayed in the absence and presence of differentiation agent all-trans retinoic acid (ATRA).