Medical Xpress

Long non-coding RNA prevents the death of maturing red blood cells

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A long non-coding RNA (lncRNA) regulates programmed cell death during one of the final stages of red blood cell differentiation, according to Whitehead Institute researchers. This is the first time a lncRNA has been found to play a role in red blood cell development and the first time a lncRNA has been shown to affect programmed cell death.

"Programmed cell death, or apoptosis, is very important, particularly in the hematopoietic (blood forming) system, where inhibition of cell death leads to leukemias," says Whitehead Institute Founding Member Harvey Lodish, who is also a professor of biology and a professor of bioengineering at MIT. "We know a lot about the genes and proteins that regulate apoptosis, but this is the first example of a non-coding RNA that plays a role in blood cells. We would not be surprised to find this lncRNA or others like it upregulated in cancers."

And if an upregulated lncRNA is associated with cancer-cell survival, it may represent a new avenue of attack for therapeutics.

Currently, little is known about the specific function of lncRNAs, despite their abundance in cells. Only an estimated 10% of RNAs transcribed in a human cell go on to template proteins, according to a 2007 assessment of the human genome by the Encyclopedia of DNA Elements (ENCODE) Project Consortium, which was funded by the National Human Genome Research Institute. The rest of the RNAs are lumped together under the umbrella term "non-coding RNAs (ncRNAs)." Those longer than 200 base pairs are classified as lncRNAs.

LncRNAs were first identified in the 1980s. Currently about 100 lncRNAs have been studied in multiple types of mammalian tissues. LncRNAs have been shown to regulate gene expression by modifying chromatin, enhancing transcription, and promoting messenger RNA (mRNA) degradation as well as through other methods that have yet to be elucidated.

Despite increasing interest in and study of lncRNAs in a host of biological processes, this is the first research to identify a role for a specific lncRNA in erythropoiesis—red blood cell production. This new lncRNA and its function are described this week in the online edition of the journal *Genes and Development*.

By examining fetal mouse livers, which are rich sources of red blood cells and their progenitors, Wenqian Hu screened the various stages of red blood cell development for the presence of lncRNAs. Hu, the first author of the Genes and Development paper and a postdoctoral researcher in Lodish's lab, found more than 400 lncRNAs expressed in these cells. During the end of the red blood cell maturation process, one lncRNA in particular was found to be highly expressed; the group dubbed this lncRNA "long intergenic non-coding RNA-erythroid-pro-survival" or lincRNA-EPS.

To determine its function, Hu halted expression of lincRNA-EPS in maturing red blood cells; the cells died as they began the differentiation process. Then Hu expressed lincRNA-EPS in maturing red blood cells and grew these cells in the absence of the hormone erythropoietin, which normally prevents the blood cell progenitors from undergoing apoptosis. Instead of dying as expected from the lack of erythropoietin, the cells with lincRNA-EPS continued to live, indicating that lincRNA-EPS by itself can prevent apoptosis.

After further investigation, Hu found that lincRNA-EPS inhibits the

expression of Pycard, a gene that promotes programmed cell death, explaining in part lincRNA-EPS's role in apoptosis prevention.

"These experiments indicate that the normal function of this lncRNA is to protect the red blood cells from death during the last step of differentiation," says Hu. "This is important because the final step of red blood cell maturation is the expulsion of the nucleus from the cell, which in many ways mimics apoptosis. This lncRNA and other factors make sure the cell can get rid of the nucleus and differentiate properly and that it does not go through apoptosis."

Because programmed cell death goes awry in leukemias and other cancers, Hu is currently examining lincRNA-EPS's function in normal and diseased human cells in an effort to determine whether it plays a role in tumor development and growth.

More information: "Long non-coding RNA mediated anti-apoptotic activity in murine erythroid terminal differentiation", *Genes and Development* online, December 8, 2011.

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