# A fateful pause: Genetic mechanism once thought rare may allow rapid cell production

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We take our blood for granted, but its creation requires a complicated series of steps, starting with the formation of blood stem cells during early embryonic development, followed by progressive differentiation into the progenitors of red cells, white cells and platelets, and ultimately the full set of blood cells. Now, in the July 9 issue of *Cell*, researchers at Children's Hospital Boston report a surprising twist in how mature red blood cells form - which may explain the body's ability to rapidly replenish them in response to injury.

Previously, working with zebrafish - whose transparent bodies make it easy to watch blood formation -- the laboratory of Leonard Zon, MD, director of the Stem Cell Program at Children's, found a gene which, when mutated, left the embryonic fish bereft of red blood cells (this profoundly anemic strain was dubbed moonshine). Though the fish did form progenitors for red blood cells (called erythroid progenitors), these cells failed to become mature red blood cells, and instead died.

But why? The new research, led by Xiaoying Bai, PhD, in Zon's lab, showed that when the gene, TIF1 gamma, is mutated, the machinery that allows red blood cells to form from their progenitors is left in suspended animation.

In order for an erythroid progenitor to make a red blood cell, certain genes must be activated, or transcribed, to create templates for building the necessary proteins. Transcription involves an orchestrated series of events: tightly coiled DNA is unwrapped, unwound and its strands

separated, then a portion of one strand is "read" down its length and used to make the template, cued by signals from the cell. But this reading process has been recently discovered to have built-in pauses, requiring another signal to tell transcription to resume.

TIF1 gamma, Bai and colleagues show, regulates this process of resuming transcription, known as transcriptional elongation. When TIF1 gamma is mutated in zebrafish, Bai and colleagues found, transcriptional elongation never happens. As a result, the erythroid progenitors get stuck in "pause" and never make mature red blood cells.

Further tests showed the same to be true in human cells - when erythroid progenitors were taken from patient blood samples and TIF1 gamma was blocked, red cells did not develop from them.

The pausing/stalling of transcription was once thought rare. But Bai, Zon and colleagues think it may provide a way for the body to quickly switch on production of red cells, and perhaps - since TIF1 gamma is found all over the body -- other kinds of cells the body needs to make quickly. Rather than have to laboriously set up all transcription each time red cells are needed, the machinery can simply be left on pause.

"We think this is the fastest way to respond to stimulation," says Bai. "The transcription machinery is already in place, but it's arrested until the right signal tells it to go. When you need massive production that needs to be synchronized to respond to the environment, this is the best way to regulate it."

Several recent genome-wide studies found a similar pausing/stalling to be common in the genome, suggesting it's a critical step in regulating gene activity. But this is one of the first studies to demonstrate a real-life application of stalling, in a live animal. "We think this is the first time anyone has shown genetically, and in vivo, that transcriptional elongation

is involved in cell fate," says Bai.

The findings may have implications for treating severe anemia, as well as leukemia. In a form of leukemia known as MLL, there is evidence that transcription elongation factors are involved in oncogene formation, presumably overriding the "pause" mechanism and causing transcription to be stuck on - so white blood cells (leukocytes) are made over and over.

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