Repetitive elements trigger RIG-I-like receptors to enhance hematopoietic stem cell formation

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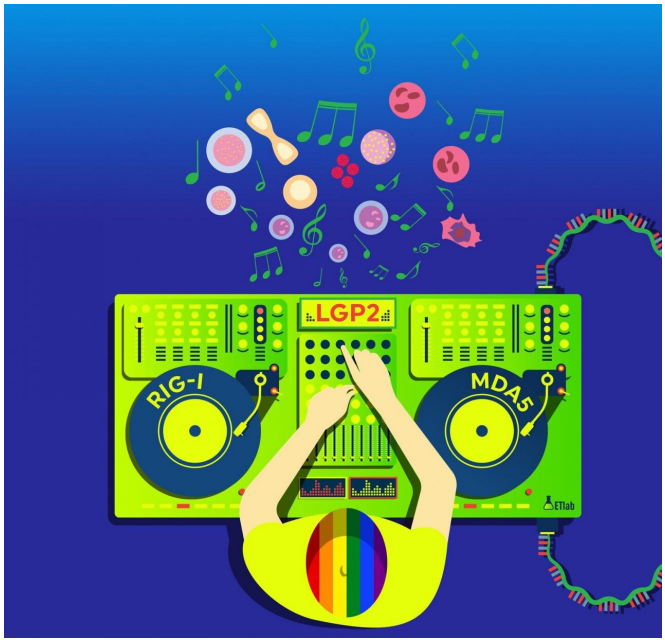

Repetitive elements induce a RIG-I-like receptor-mediated inflammation that regulates the emergence of hematopoietic stem and progenitor cells. Lefkopoulos et al. report that repetitive element (RE) RNA present during developmental hematopoiesis activates the RIG-I-like receptor pathway to provide the inflammatory signals necessary for HSPC formation. The RE RNA is depicted as cables that fuel the 'DJ controller' with electricity. RIG-I and MDA5 function as decks for the controller to play music, which represents the inflammatory signals turning into blood cells, whereas LGP2 functions as a mixer by controlling the levels of inflammation RIG-I and MDA5 provide. Nature is all-inclusive, like a rainbow. Credit: Illustration concept by M. Derecka, Marika ki and ET. Cover art by @kostispavlou.

Hematopoietic stem cells can replenish all the different cell types of our blood system. For this reason, hematopoietic stem cells are the cells used in many blood diseases when patients need transplantations. Thus, our ability to generate, amplify and maintain these cells is important for human health. The lab of Eirini Trompouki at the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, in collaboration with scientists the Albert Einstein College of Medicine, the University of Trento and the Chinese Academy of Sciences, discovered a novel mechanism that enhances hematopoietic stem cell formation during development. They showed that RNA from repetitive elements, remnants of viruses integrated through evolution into the genome of many animals, is produced during hematopoietic development. Repetitive element RNAs activate innate immune receptors to induce inflammation—the good kind—and increase the formation of embryonic hematopoietic stem cells.

Hematopoietic stem cells are the foundation of the blood system from fish to humans and give rise to leukocytes for fighting off pathogens, erythrocytes for transferring oxygen to tissues, and every other cell type that can be found in our blood. Importantly, hematopoietic stem cells born during development are also the foundation of our blood system when we are adults and their improper function can lead to multiple blood diseases. Therefore, hematopoietic stem cells are precious both in sickness and in health and understanding the mechanisms that govern their formation during development can help simply: "make blood."

Repetitive element RNA enhances HSC formation

During the process of embryonic hematopoiesis in zebrafish, the lab of Eirini Trompouki found small bits of RNA expressed from a part of the genome considered as 'junk DNA.' "Contrary to what many people believe, genes only comprise a very small part of our genome. The largest part of it contains

other sequences, among which many are the remnants of viruses accumulated within the vertebrate genome through years of infections and evolution. Such sequences are for example several types of the so-called repetitive elements that usually remain repressed," explains Eirini Trompouki, Max Planck group leader and member of the Centre for Integrative Biological Signalling Studies, Cluster of Excellence at the University of Freiburg.

To investigate the possible role of these RNA molecules in hematopoietic stem cell formation, the team used chemicals that enhance the expression of repetitive elements or injected a repetitive element copy RNA in zebrafish embryos. These experiments resulted in an increase in hematopoietic stem cell numbers generated within injected embryos. The next question of the team was how do repetitive elements exert their function in hematopoietic development? They hypothesized that, since these RNAs are viral remnants, they might be sensed by cell proteins that are normally used to sense everyday viral infections.

One of the key sensors of viral infection is the RIG-I-like receptor (RLR) family, which establishes a host response once activated by such a pathogen. Eirini and her team thought that in order to prove that repetitive elements are sensed by RLRs they needed to show that the increase in HSC numbers, observed upon chemical induction or overexpression of repetitive elements should not happen if RLRs are missing from the cells. Indeed, the team showed that injection of the same repetitive element RNA copy could not enhance hematopoietic stem cell development in RLR-deficient zebrafish embryos, which proved that the influence of these RNAs on hematopoietic stem cell generation depends on the presence and function of RLRs.

Functions of RLRs in hematopoiesis

The researchers then reasoned that if the function of repetitive elements in hematopoiesis depends on RLRs, then ablation of RLRs should have an impact on hematopoietic stem cell biology. The RLR family includes three different members, namely RIG-I, MDA5 and LGP2. In their experiments, the team showed that the absence of either Rig-I or Mda5 severely reduced the numbers of hematopoietic stem cells born in zebrafish embryos.

On the contrary, the absence of the third family member, Lgp2, increased the numbers of hematopoietic stem cells. "In every organism, for every process to be maintained within normal healthy boundaries and especially during development, we always need a switch setting the process on, but also a switch setting the process off or containing it. In this case, it seems that the RLR family can function as an independent system that involves both the positive and negative regulatory mechanisms," says Stelios Lefkopoulos on the dual role of the receptor family in hematopoiesis.

Repetitive RNA activates viral sensors

Knowing the role of RLRs in hematopoiesis, the team next tackled the question how these receptors regulate hematopoietic stem cell generation. They found that when they reduced the levels of either Rig-I or Mda5 in their experiments, inflammatory signals beneficial for hematopoietic stem cells were downregulated, whereas when they reduced the Lgp2 levels these signals were upregulated. These observations explained how Rig-I or Mda5 normally induce, whereas Lgp2 impairs developmental hematopoiesis.

"All these events constitute a novel mechanism modulating hematopoiesis. Hematopoietic stem cells originate in embryos from endothelial cells of the aorta. It therefore seems that during the transition from one cell type to the other, different repetitive elements are expressed. One can speculate that while this transition is happening, newly expressed repetitive elements are sensed by RLRs and thus, actively participate in shaping the developmental fate by orchestrating inflammation signals," says Eirini Trompouki.

A universal mechanism of tissue generation and integrity?

Since repetitive elements and RLRs are also expressed in other non-blood cells, it could be possible that a similar mechanism can be pertinent

in more setups and conditions such as other tissues, stem cells or for adult hematopoiesis. "Nature never maintains through evolution something that is of no use; these repetitive elements have been maintained within vertebrate genomes for a reason, and we now know that activating RLRs and regulating developmental hematopoiesis is one of them," says Stelios Lefkopoulos.

More information: Stylianos Lefkopoulos et al, Repetitive Elements Trigger RIG-I-like Receptor Signaling that Regulates the Emergence of Hematopoietic Stem and Progenitor Cells, *Immunity* (2020). DOI: 10.1016/j.immuni.2020.10.007