A new technique to study how myeloids become white blood cells

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University of Illinois cell and developmental Biology professor Fei Wang and colleagues have created a new technique to study how myeloids, a type of blood stem cell, become the white blood cells important for immune system defense against infections and tissue damage. This approach offers new insights into the molecular mechanisms at work during myeloid differentiation, and may improve our ability to treat myeloid diseases like leukemia, the researchers report. Their findings appear in the journal *Blood*.

Myeloids are blood stem cells from bone marrow or the spinal cord that differentiate into common types of white blood cells like neutrophils and macrophages. Deficiencies in this differentiation process can cause leukemia.

Researchers in the field had previously studied myeloid differentiation by using cells taken directly from animals, or they transformed leukemia tumor cells to their previous myeloid stem cell-like states. Primary cells are hard to grow and manipulate genetically, however, and tumor cells still contain the genetic mutations that caused them to divide uncontrollably in the first place. The drawbacks of these systems prompted Wang to develop a better method for studying the mechanisms of myeloid differentiation.

Wang and his team began by turning mouse embryonic stem cells into myeloid progenitor cells. They then added a protein called Hoxb8 to these cells that had been shown previously to immortalize myeloid

progenitor cells.

"This really simplified the whole system, so, number one, we didn't have to deal with animals or human bodies, and, number two, we immortalized these cells so that they can be easily handled in culture and maintain normal myeloid progenitor cell genetic information," Wang said.

The researchers wanted to prove that their model is effective in helping them determine the molecular mechanisms important to myeloid differentiation, so they turned to a class of enzymes, called protein kinases, that are known to mediate processes like cell development, immune response, and cell differentiation. The researchers screened a variety of protein kinase inhibitors to find potential key regulators of myeloid differentiation.

A protein kinase inhibitor of a molecule called mTor, a master regulator of cell behavior, was found to interfere with myeloid differentiation, signifying that mTor is a key regulator of this process. Further experiments showed that this molecule is necessary for myeloid differentiation.

"This is the first evidence showing that this molecule plays a significant role in myeloid differentiation," Wang said.

This finding serves as a proof of principle that the new approach provides a powerful tool for future studies of normal and abnormal myeloid differentiation, Wang said.

"Using this system, we can introduce genetic manipulations that tell us something very important about how normal myeloid differentiation works, and what kind of molecular events in this process can go wrong, leading to diseases like leukemia," Wang said.

"People can use this as a platform for large-scale screening analysis for drugs that potentially can promote myeloid differentiation and can slow down or stop myeloid disease processes."

More information: *Blood* blood journal.hematology library … 2-03-414979.abstract

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