How red blood cells nuke their nuclei

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Unlike the rest of the cells in your body, your red blood cells lack nuclei. That quirk dates back to the time when mammals began to evolve. Other vertebrates such as fish, reptiles, and birds, have red cells that contain nuclei that are inactive. Losing the nucleus enables the red blood cell to contain more oxygen-carrying hemoglobin, thus enabling more oxygen to be transported in the blood and boosting our metabolism.

Scientists have struggled to understand the mechanism by which maturing red blood cells eject their nuclei. Now, researchers in the lab of Whitehead Member Harvey Lodish have modeled the complete process in vitro in mice, reporting their findings in *Nature Cell Biology* online on February 10, 2008. The first mechanistic study of how a red blood cell loses its nucleus, the research sheds light on one of the most essential steps in mammalian evolution.

It was known that as a mammalian red blood cell nears maturity, a ring of actin filaments contracts and pinches off a segment of the cell that contains the nucleus, a type of “cell division.” The nucleus is then swallowed by macrophages (one of the immune system’s quick-response troops). The genes and signaling pathways that drive the pinching-off process, however, were a mystery.

“Using a cell-culture system we were actually able to watch the cells divide, go through hemoglobin synthesis and then lose their nuclei,” says Lodish, who is also a professor of biology at Massachusetts Institute of Technology. “We discovered that the proteins Rac 1, Rac 2 and mDia2 are involved in building the ring of actin filaments.”

“We were very interested in that Rac 1 and Rac 2 were involved in disposing the nuclei of red blood cells,” says Peng Ji, lead author and postdoctoral researcher in the Lodish lab. “These proteins are known for their role in creating actin fibers in many body cells, and a necessary component of many important cellular functions including cell division that support cell growth.”

His cell-culture system began with red blood cell precursors drawn from an embryonic mouse liver (in mammalian embryos, the liver is the main producer of such cells, rather than bone marrow as in adults). The cultured cells, synchronized to develop together, divided four or five times before losing their nuclei and becoming immature red blood cells. The researchers used simple fluorescence-based assays that enabled them to probe the changes in the red blood cells through the different stages leading up to the loss of the nucleus.

The researchers plan to further investigate the entire process of red blood cell formation, which may lead to insights about genetic alterations that underlie certain red blood cell disorders.

“During normal cell division, each daughter cell receives half the DNA,” comments Lodish. “In this case, when the red blood cell divides, one daughter cell gets all the DNA. What’s fascinating is that in this case, that daughter cell gets eaten by macrophages. Until now, scientists were unable to study these cells because they were unable to see them.”

Source: Whitehead Institute for Biomedical Research