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Fruit Fly Will Aid Blood Studies

Researchers have discovered a gene in the fruit fly that aids survival of developing blood cells. Because the gene shows striking conservation with a corresponding gene family in mammals, including humans, the scientists speculate that the fruit fly may provide a far simpler model in which to study blood-cell formation. Among other things, this will enable researchers to investigate how aberrant genes trigger the prolongation of blood cell survival that results in certain leukemias.

The researchers, led by Howard Hughes Medical Institute investigator Norbert Perrimon at Harvard Medical School, published their findings in the July 13, 2004, issue of the journal *Developmental Cell*. Other co-authors are from the European Molecular Biology Laboratory in Germany.

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The researchers studied a gene in the fruit fly *Drosophila* that codes for a receptor molecule called PDGF/VEGF receptor (PVR). PDGF (platelet-derived growth factor) and VEGF (vascular endothelial growth factor) are signaling molecules that, when bound to their receptor, promote cell growth.

Like other receptors, the PVR protein nestles in the membranes of cells and translates external signals into changes in the cellular machinery. It is present on the surface of blood cells called macrophages, which remove dead cells and pathogens by engulfing and digesting them in a process called phagocytosis. According to the researchers, studies of the PVR gene by others had implicated it as a key gene in the fly's blood-forming, or hematopoietic, system.

In their studies, the researchers isolated mutant flies and studied the effect of turning off PVR in a fly blood cell line. Said the paper's first author, Katja Brückner in Perrimon's laboratory, "Previous studies of PVR had focused on

its role in governing migration of embryonic blood cells to the appropriate place in the embryo. But our studies of flies with loss-of-function PVR mutations showed that the effects are only partly due to defects in migration. In fact, the majority of the effects are due to a problem in cell survival."

The scientists found that flies lacking PVR had large aggregates of blood cells, which resulted from the cannibalistic phagocytosis of dying blood cells by remaining cells. The unusually large number of dying cells led them to conclude that PVR must play a role in protecting blood cells against the "cell suicide" process called apoptosis, which normally rids organisms of cells that have become defective or are no longer needed in embryonic development.

The researchers also switched on cell signaling pathways that they theorized PVR might normally trigger, and found that this restored normal blood cell function, even in the absence of functioning PVR. Further, they demonstrated that eliminating PVR function increased cell death in a *Drosophila* blood cell line, independently confirming their findings in the flies.

According to Brückner, the researchers' findings offer a promising new model for studying hematopoiesis. "We found a striking conservation of *Drosophila* with the vertebrate system," she said. "In the vertebrate system, it's known that members of the large PDGF/VEGF receptor family are important for hematopoietic stem cells and various lineages during hematopoietic differentiation. We now find that in *Drosophila* the same is true for the only PDGF/VEGF receptor present in the genome of *Drosophila*. This makes *Drosophila* a simple genetic system to study the same questions in hematopoiesis."

A major problem with studying development in mammals, said Brückner, is that they possess multiple receptors for similar functions. Thus, knocking out a gene for just one receptor in the family often does not produce clear-cut effects. In other cases, mammalian receptors have multiple functions that cannot be uncovered easily. In *Drosophila*, blood cell proliferation precedes other events in hematopoiesis, which is a big advantage of the system. The vast range of *Drosophila* mutants and the ease of gene silencing by RNA interference (RNAi) in *Drosophila* cell culture will further aid such studies.

According to Brückner, the cell culture system will be invaluable for genome-wide RNAi screens to study mechanisms of blood cell survival, offering insights that can then be applied to studies in whole flies and mammals.

The parallels in fly and vertebrate hematopoiesis offer the potential for a highly useful system for studying certain leukemias, said Brückner. "For example, it is known that more than one-third of acute myeloid leukemias and some cases of chronic myeloid leukemia show an over-activation of PDGF/VEGF receptors," she said. "And these mutations are necessary to produce the full malignant phenotype of the leukemia, including proliferation and/or survival advantage of the cells. So, for such leukemias, it is important to understand the mechanism of action of these receptors and other disease-associated genes."

The simplified *Drosophila* system will also make it possible to study cell survival independent of proliferation, to tease apart the roles of these two processes in leukemias, said Brückner. For example, she said, researchers can introduce other disease-related genes into PVR-disabled *Drosophila* mutants, to determine whether they restore blood cell survival. Such studies could reveal new targets for therapies, she said.

"Now that many molecularly targeted therapies are being developed, it will become more and more important to distinguish targets of disease-related genes and whether they play a role in proliferation or survival of cells," she said.