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Control switches found for immune cells that fight cancer, viral infection

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Medical science may be a significant step closer to climbing into the driver's seat of an important class of immune cells, researchers at Washington University School of Medicine in St. Louis report in *Nature Immunology*.

The researchers showed that a single protein, HS1, enables key functions of natural killer (NK) cells, which kill early cancers and fight off viral infections. The protein allows the NK cells to pursue their targets, latch on to them and configure the cellular machinery it uses to kill them.

"Further study of how HS1 controls these processes may open up new possibilities for revving up the NK cells to fight infection and cancer," says senior author John Cooper, M.D., Ph.D., professor of cell biology and physiology. "We also may be able to use this same protein to inhibit the activities of other immune cells and prevent them from contributing to autoimmune conditions such as diabetes."

Cooper, who is a member of the Siteman Cancer Center at Washington University and Barnes-Jewish Hospital, studies how different types of cells use a primary component of their skeletal system known as an actin network. Earlier, his laboratory had probed the role of a protein called cortactin in specialized cells that break down bones. They showed that cortactin's effects on the actin network made it possible for the cells to form a tightly sealed bond with bones.

"This bond is analogous to a plunger," says first author Boyd Butler,

Ph.D., a postdoctoral fellow in Cooper's laboratory. "The cell sits down on the bone, seals tightly, and then starts secreting the acid and other compounds that break down the bone."

NK cells have to form a similar plunger-like bond, known as a lytic synapse, with the targets they attack. They do not make cortactin but produce HS1, which is a very similar protein. Butler decided to see what would happen to NK cells in human blood samples if he turned down their ability to make HS1. The resulting cells were severely disabled: They couldn't effectively pursue target cells, bind to them or prepare to kill them.

Prior research by other scientists had revealed that when NK cells are in motion or attacking a target, HS1 has chemical modifications attached to it at specific points. Giving the NK cells normal HS1 restored their lost functions, but when researchers gave the NK cells HS1 where these attachment points had been altered, the cells were selectively disabled. Changing one attachment point prevented them from pursuing target cells, while changing the other impaired their ability to bind to targets and kill them.

"Tight regulation is very important to prevent NK cells from harming the body's own tissues," Boyd says. "This ability to switch where the control signal goes makes HS1 a powerful regulator of NK cell activity—it allows the cells to provide just the right services at the right time."

Cooper and Boyd plan follow-up studies that will start at the attachment points on HS1 and trace connections with and influences on other proteins.

"NK cells are very good at nipping early cancers in the bud," says Cooper. "If we can better understand how they're activated, this could lead us to ways to make them better killers of cancers and cells infected

by viruses and other invaders."

Source: Washington University in St. Louis