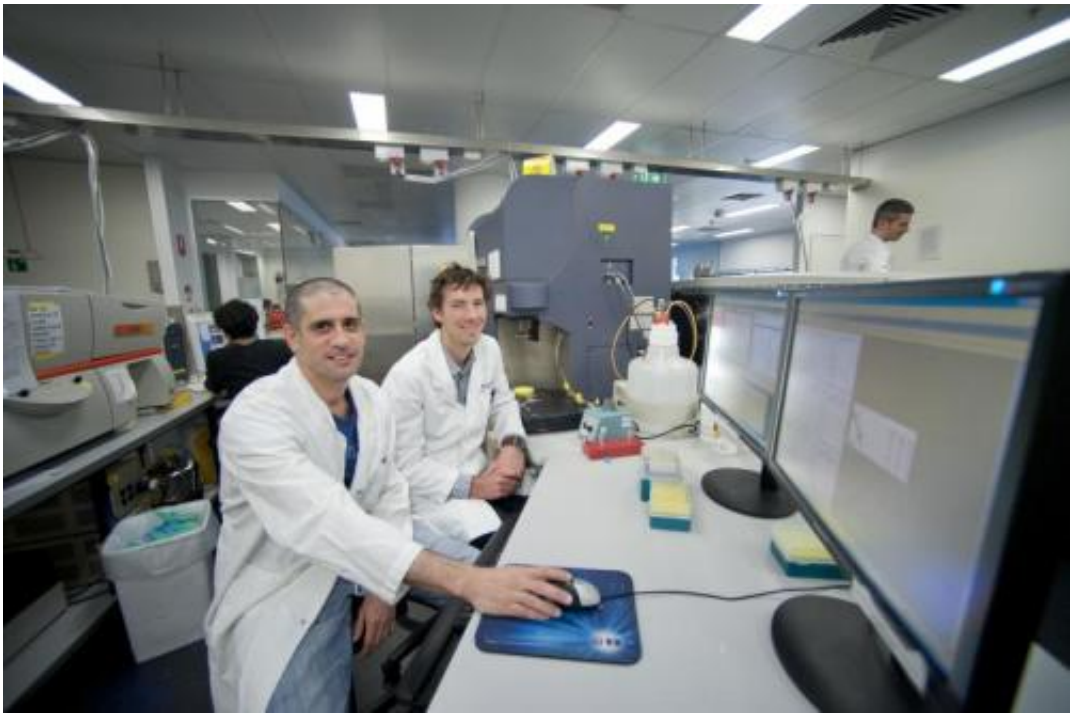
Immune system kill switch could be target for chemotherapy and infection recovery

December 6 2012



Dr. Seth Masters (right) and Dr. Motti Gerlic were part of a research team from the Walter and Eliza Hall Institute in Melbourne, Australia, that discovered an immune system ‘kill switch’ that destroys blood stem cells when the body is under severe stress, such as that induced by chemotherapy and systemic infections. Credit: Walter and Eliza Hall Institute

Researchers have discovered an immune system 'kill switch' that destroys blood stem cells when the body is under severe stress, such as that induced by chemotherapy and systemic infections.

The discovery could have implications for protecting the blood system during chemotherapy or in diseases associated with overwhelming infection, such as sepsis.

The kill switch is triggered when internal immune cell signals that protect the body from infection go haywire. Dr Seth Masters, Dr Motti Gerlic, Dr Benjamin Kile and Dr Ben Croker from the Walter and Eliza Hall Institute led a research project that found blocking these internal signals, in particular a cell receptor called NLRP1, could stop blood stem cells from self-destructing, preventing death after chemotherapy and boosting recovery from infection. The findings were published today in the journal *Immunity*.

NLRP1 is part of a family of immune receptors that acts as a protective mechanism, instructing immune and blood stem cells to die because it has 'sensed' infection or severe stress-related damage. However this protective mechanism can go too far, Dr Masters said.

"One theory is that when stem cells are infected with a bacteria or virus, they can effectively pass the infection on to all their blood cell offspring, helping to spread the pathogen throughout the body," Dr Masters said. "So the body has evolved to activate this pathway to kill the infected stem cell, reducing the risk of infection. However, in the case of sepsis, or in a cancer patient who contracts an infection, the NLRP1 receptor inappropriately instructs blood stem cells to die, and too many are killed, until the patient can't recover their immune cells, leaving them at much higher risk of death."

Dr Croker said it is the first time that immune receptor-mediated killing of blood stem cells has been suggested to be a critical factor in sepsis, a severe inflammatory disease that kills one person every few minutes worldwide. "Sepsis is the leading cause of death in critically ill patients, leading to shock, organ failure and death," Dr Croker said. "People with

sepsis have very low numbers of immune cells in the blood and the ability of the immune system to recover and immune cells to repopulate the body is strongly linked to the patient's chance of survival," he said.

Most research has focused on the 'cytokine storm' theory of sepsis, which says that an excess of inflammatory signals sent out by immune cells cause the severe symptoms in patients. However Dr Croker said all the clinical trials based on this theory have failed. "Our research provides a different view of the disease, one in which the death of blood stem cells leaves the patient unable to repopulate their red and white blood cells, and therefore unable to recover," he said.

Dr Masters said the research could, in the future, lead to treatments for sepsis. "Therapies for sepsis are non-existent at the moment," Dr Masters said "We are really still just treating the infection, in a situation where most people die not from the infection, but from the body's immune response to it."

The research team is involved in testing inhibitors of this pathway to treat severe infections, and have high hopes for its future use. "It is early days, but we are optimistic that this is a pathway that could help to prevent blood cell death and treat severe cases of sepsis, as well as other conditions where blood stem cells are critically depleted, such as during chemotherapy," he said.

Provided by Walter and Eliza Hall Institute