Clues to calming a cytokine storm

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By analyzing complex interactions of the immune system in an animal study, pediatric researchers have found potential tools for controlling a life-threatening condition called a cytokine storm that may strike children who have juvenile arthritis and other autoimmune diseases.

In a cytokine storm, the body's immune system rages out of control, resulting in overwhelming inflammation, rapid organ failure and death if not quickly diagnosed and treated. In addition to children with juvenile arthritis, patients with lupus or Epstein-Barr virus infection may also suffer this complication, called macrophage activation syndrome (MAS).

"Our study is a first step toward developing new treatments for MAS," said study leader Edward M. Behrens, M.D., a pediatric rheumatologist at The Children's Hospital of Philadelphia. The researchers published their study online today in the Journal of Clinical Investigation.

Because MAS occurs rarely in children, it is difficult to investigate in patients. Therefore, animal studies are important, said Behrens, whose team was able to develop a variety of mice into the first animal model of MAS. Their study also demonstrated the mechanism of MAS differs importantly from another disease that manifests similar symptoms.

That other disease, called HLH (for hemophagocytic lymphohistiocytosis), also causes a life-threatening cytokine storm in children. Because of the similar manifestations, he added, physicians may use similar treatments for both HLH and MAS—but this is not always appropriate.

HLH is caused by a genetic mutation, but MAS is not. Instead, Behrens and colleagues were able to explain how inflammation from rheumatological diseases like systemic juvenile arthritis causes MAS by acting through immunological pathways. In particular, Behrens showed that overactive immune system proteins called Toll-like receptors interact with the immune system to drive MAS in the absence of gene mutations or infectious triggers.

"We identified two important molecules in the immune system that control the severity of MAS," said Behrens. One molecule is interferon-gamma, which makes MAS more severe. The other molecule is interleukin-10 (IL-10), which has a protective effect. "This research strongly suggests that the relative contribution of these molecules can dial up or dial down the severity of a cytokine storm in MAS," said Behrens.

"Our next studies will be to investigate whether we can reduce the action of interferon-gamma, or enhance the beneficial effects of IL-10, as possible treatments for children who experience this syndrome," Behrens added.

More information: "Repeated Toll-like receptor 9 stimulation results in macrophage activation syndrome-like disease in mice," Journal of Clinical Investigation, published online May 16, 2011, to appear in June 2011 print edition.

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