Gene chip technology shows potential for identifying life-threatening blood infection

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Right now there's no rapid way to diagnose sepsis, a fast-moving blood infection that is a leading cause of death in hospital intensive care units. The illness unleashes a powerful inflammatory response that can quickly overwhelm the body, causing organ failure and death, often within days.

With a narrow window of opportunity for halting its lethal spread, doctors who suspect sepsis typically rush to prescribe powerful antibiotics, even before laboratory tests can confirm the diagnosis. But this practice invariably leads to the inappropriate treatment of many patients who have life-threatening, uncontrollable inflammation without an underlying infection, a condition also common among ICU patients.

New research now suggests that doctors one day could quickly

distinguish sepsis from widespread non-infectious inflammation based on genetic profiles of patients' blood. Testing this method in mice, researchers at Washington University School of Medicine in St. Louis found the profiles could accurately discriminate between the two conditions 94 percent of the time. The molecular profiles measure differences in patterns of gene expression that are unique to sepsis vs. non-infectious inflammation.

"Our findings hold out hope that scientists could develop a simple bedside blood test that would greatly speed the diagnosis of sepsis," says J. Perren Cobb, MD, director of Washington University's Center for Critical Illness and Health Engineering and a surgeon at Barnes-Jewish Hospital. "We could in a few hours determine if a patient had a blood infection and treat them right away."

Such a test could not only be used in intensive care units but also in emergency rooms and other settings where a timely diagnosis of infection is important, adds Cobb, who is also professor of surgery and associate professor of genetics. His team's research was published in the November issue of the Journal of the American College of Surgeons.

"If someone came into the hospital with a cough and had a working diagnosis of pneumonia or someone came in with abdominal pain with a suspicion of infection, wouldn't it be wonderful if we could run a blood test in the emergency department and more accurately triage patients so they could be treated earlier with the appropriate antibiotic," Cobb says.

The researchers used microarrays, also called gene chips, to analyze patterns of gene expression in the mice. The same technology is already used by doctors to diagnose breast cancer and predict a patient's response to various chemotherapy drugs, but this is the first time researchers have attempted to use gene chips to distinguish sepsis from non-infectious inflammation.

Early symptoms of sepsis and non-infectious systemic inflammation are subtle and similar - fever and an elevated white blood cell count - making it virtually impossible in many cases even for seasoned doctors to make a diagnosis based on symptoms alone. Non-infectious inflammation is common among ICU patients recovering from surgery, pancreatitis, or trauma from a car accident or fall. Because these patients are also hooked up to IV fluids, catheters or ventilators, they are also prone to bacterial infections, including pneumonia, that can quickly spiral out of control and lead to sepsis.

Although both conditions are life-threatening because of their threat to major organs, sepsis is more lethal. In the United States, about 750,000 cases occur annually, and one-third of patients die - a toll greater than deaths from breast, colon, pancreas and prostate cancer combined.

Currently, a diagnosis of sepsis or non-infectious systemic inflammation is made by sending cultures of patients' blood, sputum, or urine to the laboratory for analysis, which can take several days. Gene chips could cut the typical time needed for diagnosis to eight hours or less, Cobb says.

In the new research, Cobb and his colleagues mimicked sickness in four groups of mice: each of three groups had a varying severity of sepsis and a fourth had systemic non-infectious inflammation. Using gene chips, they created molecular profiles based on the abundance of messenger RNA expressed in immune cells taken from the blood of the sick mice. These profiles were compared with profiles from the blood of control mice.

The researchers looked at the activity of thousands of genes 24 hours after the onset of sickness with the goal of identifying all the genes that might be markers of inflammation and infection. They found small increases in gene expression among hundreds of genes, but it was not the

magnitude of change in gene expression that accurately distinguished sepsis from systemic inflammation. Instead, it was the pattern of changes in gene expression that proved to be important, Cobb says.

"Based on the profiles, we could easily distinguish mice who were sick with infection from mice who were really sick but did not have an infection," Cobb says. "We think this is an important first step to developing a similar test for human patients."

Nine of these genes turned out to be common responders to inflammation and infection in mice. Some of these genes also have been identified by other scientists studying infection and inflammation in humans but had not been identified as being central to the development of sepsis.

Five of the genes identified are linked to the activation or maturation of white blood cells called neutrophils. These cells are the immune system's first line of defense against invading organisms.

"At one level, we've found a suite of genes that are informative with regard to making a diagnosis," Cobb says. "But as biologists, we can also say these genes are major clues to the biology of infection and the host's response to it. If every type of infection activates these genes, then we know they must be important to the disease process, and may also be new treatment targets."

Cobb's current studies are focused on narrowing the number of genetic markers in patients to make it practical to develop a bedside test to screen for signs of infection. He is also exploring whether gene chips can identify the specific type of invading organism in the blood samples. Early findings suggest that the technology detects differences in molecular profiles based on the type of pathogen involved.

Citation: Chung TP, Laramie JM, Meyer DJ, Downey T, Tam LHY, Ding H, Buchman TG, Karl I, Stormo GD, Hotchkiss RS, Cobb JP. Molecular Diagnostics in Sepsis: from Bedside to Bench. *Journal of the American College of Surgeons* 2006 Nov;203(5):585-598.

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