

Mystery Solved: The Ashwell Receptor Reduces Mortality During Bacterial Infection

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In research that solves the longest-standing mystery in glycobiology – a field that studies complex sugar chains called glycans – researchers at the University of California, San Diego School of Medicine have discovered that a molecule in the liver of all animals, called the Ashwell receptor, is critical in helping the body fight off the abnormal and lethal blood clotting caused by bacterial infection. Until now, it was suspected that this receptor might serve to remove abnormal proteins from circulation, but it wasn't understood which proteins were affected or what biological purpose this receptor served.

The study, published online in advance of publication in the June issue of *Nature Medicine*, shows that the Ashwell receptor plays an essential role in reducing coagulation abnormalities during infection and sepsis, significantly improving the probability of survival.

Sepsis, a life-threatening complication of bacterial infection in the blood, remains a major cause of death worldwide, according to the study's principal investigator, Jamey Marth, Ph.D., UCSD Professor of Cellular and Molecular Medicine and Investigator with the Howard Hughes Medical Institute. One of the major factors contributing to death in patients with sepsis is a condition called disseminated intravascular coagulation, which accelerates blood clotting.

UCSD researchers discovered that a protective response, triggered by the Ashwell receptor in the liver, limits this lethal side effect by reducing the levels of circulating blood coagulation factors, including platelets.

The bacterial pathogen *Streptococcus pneumoniae* (pneumococcus) is a leading cause of sepsis, especially in the young, the elderly and the immuno-compromised. The pneumococcus makes an enzyme called sialidase, which removes sugar molecules called sialic acid from host cells, and helps facilitate spread of the pathogen through the body. Using a mouse model of sepsis, the researchers found that the pneumococcal sialidase also removes sialic acid from circulating host factors involved in blood coagulation, including platelets and a glycoprotein called von Willebrand Factor (vWF). When this occurs, the Ashwell receptor recognizes the change in the glycoprotein

structure and removes those pro-coagulation factors from circulation before they can cause increased blood coagulation.

The researchers made a breakthrough when they discovered that platelet counts and vWF that are reduced during pneumococcal infection remained high and unchanged in the absence of the Ashwell receptor. Pivotal results came when mice lacking the Ashwell receptor developed severe tissue and organ damage due to increased coagulation and died at significantly higher frequency and more rapidly than expected.

“This finding contradicts the prevailing notion that the low platelet count of sepsis is due to the consumption of coagulation factors caused by the pathogen and is therefore harmful,” said Marth. “Rather, this low platelet count is due an adaptive response by the Ashwell receptor that is beneficial by reducing tissue damage and organ failure and thereby improving the chance of survival.”

More than 35 years ago, researcher Gilbert Ashwell and colleagues discovered that the liver controls the removal of proteins in the bloodstream. The Ashwell receptor –also known as the hepatic asialoglycoprotein receptor – was the first glycan-binding receptor, or lectin, ever discovered in animals.

“The Ashwell receptor is ‘turned on’ after birth, and this was a clue that it is needed for environmental and pathogenic challenges,” said Marth.

“This research provides a whole new way of thinking about coagulation problems in sepsis produced by pneumococcus and related pathogens” said Victor Nizet, M.D., UCSD professor of pediatrics and pharmacy whose laboratory assisted in the study. “Drugs designed to support the normal capabilities of the Ashwell receptor in the liver would represent a new approach to limiting mortality in these life-threatening conditions.”

Additional and important contributors to the study include lead author Prabhjit K. Grewal, at the Howard Hughes Medical Institute and UCSD Department of Cellular and Molecular Medicine; as well as Satoshi Uchiyama, at the UCSD Department of Pediatrics; and David Ditto, Nissi Varki, and Dzung T. Le in the UCSD Department of Pathology.

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