

Researchers learn why immune system's watch dogs howl

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Toll-like receptors are the guard dogs of the immune system, sniffing out bacteria and viruses then activating the body's immune system for an attack on these invaders.

Because of their ability to quickly activate the body's defenses, toll-like receptors have recently become a darling of drug makers. One of the proteins in this class, toll-like receptor 9 or TLR9, can pick up a very specific scent – a snippet of DNA common in bacteria and viruses.

The idea for drug makers is to create DNA-based drugs containing these snippets, called CpG DNA. The drugs would get the guard dogs howling, which, in turn, would trip a fast immune response, causing the body to attack cancerous tumors or, if used as an ingredient in vaccines, bolster the assault on infectious diseases such as hepatitis B and C. CpG DNA could even be used to treat immune system disorders such as asthma and allergies.

To make these pills or vaccines, however, it would be helpful to know what gets the guard dogs howling. New research led by Brown University immunologist Wen-Ming Chu, M.D., has uncovered one of these molecular mechanisms – high-mobility group box 1 protein, or HMGB1, a protein released when infection occurs, when cells are damaged or when tissue is injured.

Chu and his team found a direct interaction between HMGB1 and TLR9. When the invader's DNA is present, researchers found that TLR9 meets

up with HMGB1. The combination occurs inside tiny cellular cargo boxes, with a long name: endoplasmic reticulum-Golgi intermediate compartments or ERGIC. In these boxes, researchers found, the proteins bind to form a complex. Formation of this complex sets off a biochemical cascade that triggers the body's immune response.

When HMGB1 is absent from cells, researchers found, the body's immune response is significantly delayed.

“We found out that HMGB1 acts an accelerator, quickly activating the body's defenses,” Chu said. “What's exciting is that drug makers might be able to use this knowledge to treat disease. CpG DNA and HMGB1 could be used together in a vaccine.”

Source: Brown University

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