Cracking the interferon code

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(Medical Xpress) -- Interferons, protective chemicals produced by most cells in the body, live up to their name, hampering cancer and viral infections. It takes many different kinds of interferon molecules to get the job done, with each one activating a particular component of the body's defense systems. Researchers have long been puzzled by how interferons could call in such a wide range of cellular attacks if they all transmitted their messages to cells through the same molecular antenna, or receptor. A new study suggests that key may be in how tightly the interferons grip that receptor at each of their attachment points.

Interferons spur a cell to perform certain activities, such as switching on genes that help fight viruses, by latching onto a receptor molecule on the surface of the cell, forming a signaling complex that has a unique architecture. Type I interferons can curb the division of cancer cells, activate immune cells, and even soothe pain, and researchers have translated these natural abilities into treatments for a variety of conditions, including hairy cell leukemia and melanoma.

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Many researchers believe interferons hold an even broader therapeutic potential. According to K. Chris Garcia, a Howard Hughes Medical Institute investigator who specializes in studying receptors that recognize and bind to several different molecules, a first step toward designing better treatments is nailing down how each of the 16 varieties of type I interferon triggers a particular cellular action. But, he says, the interferon

system is “a unique structural conundrum” that structural biologists have puzzled over for decades.

Garcia says one of his first presentations when he was in graduate school was about how the interferons work. “There was real excitement about interferons, but the mechanism of action wasn’t known and this made a lasting impression on me,” he says. “It’s remained one of the fundamental problems in receptor biology.”

Garcia and his colleagues have solved this conundrum, offering an explanation for how each type I interferon triggers its own set of antiviral and anticancer functions while acting through the same receptor. They published their results in the August 19, 2011, issue of the journal *Cell*.

Christoph Thomas, a postdoctoral fellow in Garcia’s lab, used x-ray crystallography to deduce the three-dimensional structure of the receptor while it was linked to either of two kinds of type I interferons, IFNα and IFNω The researchers could then map out the points where the interferon molecules connect to the receptor.

The team revealed that the two interferon varieties they studied share most of these contact points, but the overall shape of the signaling complex is nearly identical. “That’s a big surprise,” Garcia says. Scientists had assumed that each kind of type I interferon would bind to the receptor in a unique way. The discovery also deepened the mystery of how an interferon molecule indicates its identity to the receptor. To answer that question, Garcia’s lab teamed up with researchers from the Weizmann Institute of Science in Israel and the University of Osnabruck in Germany.

By replacing amino acids at the contact points in the two kinds of interferons, the researchers partially deciphered the molecules’ code.

Although the locations of most contact points are constant from interferon to interferon, the strength of the bonds varies. Thus, the receptor can differentiate between interferon molecules based largely on how avidly they attach at certain positions. The researchers also found that the few contact points that are unique to each kind of interferon also play a part by "tuning" the receptor to stimulate an appropriate response.

Tampering with the code can blur the differences between the two interferon types, Garcia and his colleagues found. They analyzed mutant versions of both interferons that carry atypical amino acids at the contact points. In one IFNωmutant for example, a single amino acid had been replaced by the one found in the same position in IFNα. That change boosted the mutant IFNωs cancer-fighting ability, making it more like IFNα. "By manipulating the chemistry of the binding surfaces, we were able to endow one interferon with the functional properties of another," Garcia says.

"We've found a molecular and structural basis for understanding how interferons have differing activities," says Garcia. To discover how the molecules shape cellular activities, he notes, researchers still need to learn more about what happens after interferon and receptor combine. "We can't predict why a certain interferon will have a certain cellular function because the relationship between receptor signaling and gene activity is incredibly complex," he adds.

Garcia says that this complexity has so far limited interferons' success as cancer therapies. But if scientists can fill in more of the missing details, they might be able to synthesize large numbers of new interferons that could be medically useful. "This type of information will eventually work its way into a better way to use interferons clinically or to re-engineer them to have improved therapeutic properties."

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