Immune system foiled by a hairpin

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The innate immune system detects invasive pathogens and activates defense mechanisms to eliminate them. Pathogens, however, employ a variety of tricks to block this process. A new study shows how the measles virus thwarts the system, by means of a simple hairpin-like structure.

The innate immune system is the body's first line of defense against invasive pathogens and noxious chemicals. Essentially the system consists of an array of receptors that recognize particular molecular conformations which are characteristic of pathogenic organisms and viruses. Among the classes of molecules bound by these receptors are viral nucleic acids, which are bound specifically by so-called RIG-I-like receptors in the cytoplasm of infected cells. One of these is MDA5, which polymerizes into filaments on long double-stranded RNAs that indicate the presence of RNA viruses. RIG-I itself binds to shorter terminal segments of viral RNAs.

However, viruses have come up with a plethora of ways to avoid triggering immune defense measures. "The virus that causes measles, for instance, produces a so-called V protein, which binds specifically to MDA5 and one other RIG-I-like receptor, and thus impairs recognition of virus-infected cells by the adaptive immune system, although it does not inhibit RIG-I itself," says Professor Karl-Peter Hopfner of LMU's Gene Center. Indeed this kind of competition between viral and cellular proteins largely determines the distribution and - above all - the virulence of viral pathogens.

A hairpin opens up the receptor

"We have been able to crystallize the complex formed by the V protein and MDA5 for the first time, and have determined its three-dimensional structure in detail," Hopfner reports. This structure also permitted Hopfner's team, in collaboration with LMU virologist Professor Karl-Klaus Conzelmann, to clarify the mode of action of the V protein. The analysis revealed that it inserts a hairpin loop into the core secondary structure of MDA5, unfolding the protein and allowing V to bind to a segment that is normally buried in the interior of the molecule. This in turn prevents MDA5 from forming filaments and signaling the presence of viral RNA.

This finding was completely unexpected, and explains why MDA5, but not RIG-I, is inhibited by the V protein: This internal sequence is different in RIG-I and this is the reason why RIG-I is not targeted by the viral product. "Our work provides a detailed insight into the mechanisms viral proteins use to inhibit host protein function. It may also open opportunities for new therapeutic interventions," Hopfner concludes.

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