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Activation by breakdown: Identifying molecular mechanisms that underlie immune response

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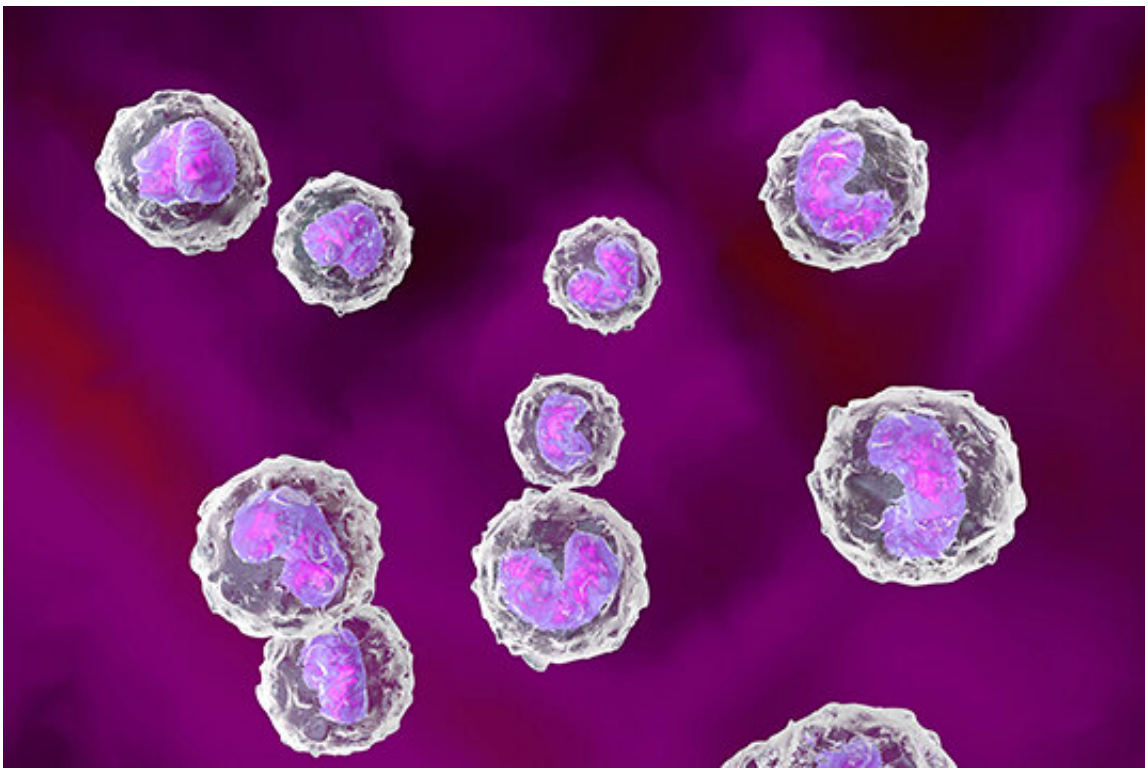

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LMU researchers report that a central component of the innate immune response is activated by two short RNAs which are produced by site-specific cleavage of a precursor RNA molecule—and both derivatives are generated by the same enzyme.

The innate immune system can be thought of as the frontline in the body's fight against invasive pathogens. Cells possess specialized receptors that can distinguish between RNAs derived from foreign cells—such as pathogenic bacteria and viruses—and "native" RNAs. Recognition of the former then activates the appropriate immune response to eliminate the invaders. However, the molecular mechanisms that underlies this mode of detection has remained obscure. Now LMU immunologist Professor Veit Hornung, in collaboration with LMU chemist Professor Thomas Carell, has discovered that the activation of one of these receptors, called TLR8, is mediated by the binding of two specific RNA fragments, generated by degradation of foreign RNA—and that both breakdown products are generated by a single enzyme called RNase T2. The new findings appear in the leading journal *Cell*.

"Earlier work had suggested that foreign RNA molecules are not recognized as a whole, but must first be cut into smaller fragments before they can be recognized by the innate immune system," says Hornung. To explore the recognition process further, he and his colleagues specifically deleted the genes for individual RNases in a human cell model. They then asked how the loss of each of the RNases affected the activation of TLR8, which is known to be an important sensor of bacterial RNA in human cells. "We chose to work with a human cell model in this case, because the version of the receptor found in mouse acts in a different way," explains Wilhelm Greulich of Veit Hornung's research group, who is joint first author of the new study.

The team found that only the cells that lacked the gene for RNase T2 failed to trigger the TLR8 mediated response to bacterial RNA, clearly pointing to a central role of this enzyme in the activation of the receptor. Notably, RNase T2 has been highly conserved over the course of evolution. The enzyme is found in virtually all classes of organisms and its structure has remained largely unchanged. This high degree of

conservation strongly indicates that it carries out an essential cellular function, and that this mechanism may also play a role in other species.

"We were able to identify the specific products of RNA cleavage by RNaseT2 using mass spectrometry," says Mirko Wagner, a member of Thomas Carell's team. These data revealed that the enzyme preferentially cleaves RNA molecules at defined nucleotide sequences leading to degradation products exclusively activating TLR8: uridine and a purine terminate RNA fragment. "Essentially, the receptor contains two distinct pockets, which have to be occupied for activation," Carell explains. One pocket accommodates uridine, and this interaction is ultimately responsible for receptor activation. However, in a physiological context, activation depends on prior binding of the purine-terminated RNA fragment, which then allows the uridine to bind. "Activation is a two-step process, and RNase T2 provides the keys that trigger both steps," says Hornung. "We believe that, in the course of its evolution, the receptor has adapted to specifically recognize the degradation products of this enzyme."

More information: Wilhelm Greulich et al. TLR8 Is a Sensor of RNase T2 Degradation Products, *Cell* (2019). DOI: 10.1016/j.cell.2019.11.001

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